IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNIVERSITY OF MASSACHUSETTS and CARMEL LABORATORIES, LLC, Plaintiffs, v. L'ORÉAL USA, INC., Defendant.	C.A. No. 17-cv-868-CFC-SRF

JOINT CLAIM CONSTRUCTION APPENDIX

JOINT APPENDIX OF EVIDENCE
University of Massachusetts, et al v. L'Oréal USA, Inc.
17-cv-868-CFC-SRF

TAB 01

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PATENT & TRADEMARK OFFICE

GP1615

Attorney Docket No.: 3,917-045001 / (UMMC 97-32)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : James G. Dobson et al. Art Unit : 1615
Serial No. : 09/179,006 Examiner : Channavajjala
Filed : October 26, 1998
Title : TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

Assistant Commissioner for Patents
Washington, D.C. 20231

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RESPONSE

In response to the action mailed December 22, 1999, please amend the application as follows:

In the Claims:

Cancel claims 9, 11-29, 37, 46 and 48-53.

Amend claims 1, 30 and 39 as follows:

1. (Amended) A method for [enhancing the condition] reducing wrinkling, roughness, dryness, laxity or sallowness of non-diseased, unbroken skin of a mammal, comprising [topically] applying a [therapeutically] patch comprising an effective amount of a composition comprising adenosine or an adenosine receptor agonist to the non-diseased, unbroken skin of said mammal.

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30. (Amended) A method for increasing protein synthesis in a [dermal cell of] fibroblast in non-diseased, unbroken skin of a mammal, comprising [topically administering] applying to a region of the skin containing the fibroblast a patch comprising an [a therapeutically] effective amount of adenosine or an adenosine receptor agonist [to a region of non-diseased skin of said

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mammal containing said dermal cell, wherein addition of said adenosine does not cause proliferation of said dermal cell].

39. (Amended) A method for increasing cell size [in a dermal cell] of fibroblast in non-diseased, unbroken skin of a mammal, comprising [topically administering] applying to a region of the skin containing the fibroblast a patch comprising an [a therapeutically] effective amount of adenosine or an adenosine receptor agonist [to a region of non-diseased skin of said mammal containing said dermal cell, wherein addition of said adenosine does not cause proliferation of said dermal cell].

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Remarks

Claims 1-10 and 30-47 are pending, claims 11-29 and 48-53 having been cancelled.

35 USC § 112

Claims 21, 30 and 39 stand rejected under 35 USC § 112, first paragraph, as allegedly nonenabled. More particularly, the Office action states:

> [T]he specification, while being enabling for treating fibroblasts with adenosine to increase DNA synthesis, protein synthesis and increase cell size does not reasonably provide enablement for other dermal cells as claimed. ... The instant claims are directed to increasing DNA synthesis, protein synthesis or cell size in dermal cells. However, the specification provides data only with fibroblasts from skin and not from any other cell types. ... [I]t is well known from the anatomical structure, skin comprises several types of cells ....

Applicant has clarified claims 30 and 39 by amending them to specify that the increased protein synthesis and increased cell size (respectively) occur in a "fibroblast" in the skin rather than "a dermal cell." This overcomes the rejection (Claim 21 having been cancelled).

Claims 1-53 stand rejected under 35 USC § 112, second paragraph for alleged lack of clarity. More particularly, the Office action states:

> Claims 1 and 48 recite "method of enhancing" skin condition, which is vague because it is not clear as to enhance from what and to achieve what effect. A correction and clarification is requested. From claims 1-53, it is unclear why a

therapeutically effective amount of adenosine is required when there is no disease being treated for.

Cancellation of claims 11-29 and 48-53 renders the rejection moot with respect to those claims.

Applicant has clarified claim 1 by amending it to recite "reducing wrinkling, roughness, dryness, laxity or sallowness" of the skin, instead of "enhancing the condition" of the skin. Support for this amendment appears in the specification, e.g., at page 4, lines 3-6 and 13-15. Therefore, the amendment does not introduce new matter. This amendment fully addresses the "enhancing the condition" aspect of the rejection.

Applicant has amended claims 1, 30 and 39 to recite "effective amount" instead of "therapeutically effective amount." This amendment merely deletes an unnecessary word, and does not change the meaning or scope of the claim. Therefore, the amendment does not introduce new matter. This amendment fully addresses the "therapeutically effective amount" aspect of the rejection.

The above amendments overcome the rejection.

35 USC § 102

Claims 1, 3-5 and 10 stand rejected under 35 USC § 102(b) as allegedly anticipated by Stramentinoli et al., U.S. Patent No. 4,454,122. More particularly, the Office action states:

> [Stramentinoli] '122 teaches adenosine or adenosine derivatives for the treatment of inflammation or as analgesic or antipyretic (see col. 1, 3). Although the reference does not explicitly mention skin treatment, the teaching of external use by topical application (col. 11 and 12) includes skin. Further, although the [reference] does not mention non-diseased skin, analgesia (defined as sense of pain) and inflammation (defined as local response to injury) are not always associated with a disease.

Applicant traverses this rejection. Contrary to the examiner's statement, *Stramentinoli* does not teach the use of adenosine for the treatment of inflammation or as an analgesic or antipyretic. The *Stramentinoli* disclosure is limited to *certain sulfur-containing derivatives* of adenosine. Moreover, *Stramentinoli* does not indicate that the disclosed, sulfur-containing

derivatives are agonists of any type of adenosine receptor. Consequently, Stramentinoli lacks relevance to the present claims. Therefore, the rejection should be withdrawn.

Claims 1, 3-8 and 10 stand rejected under 35 USC § 102(e) as allegedly anticipated by Manneth et al., U.S. Patent No. 5,998,423 or Cronstein et al., U.S. Patent No. 5,932,558. More particularly, the Office action states:

> [Manneth]'423 teaches compositions comprising adenosine, cyclohexyladenosine or cyclopentyladenosine and their use for the modulation of melanin production in the skin and hair and in enhancing the tanning process and providing protection for the skin against UV radiation (see col. 1, lines 7-13; col. 2, lines 44-63). ...
>
> [Cronstein] '558 teaches composition comprising adenosine agonists for the healing wounds, burns (abstract, lines bridging col. 3 and 4) by promoting influx of fibroblasts and epithelial cells (col. 4).

As presently amended, claim 1 requires "applying to the unbroken skin a patch comprising an effective amount of a composition comprising adenosine or an adenosine receptor agonist." Support for the amendment appears in the specification, e.g., at page 9, lines 29-31 (transdermal patch). Support for the amendment also appears in the specification at page 6, lines 22, 28 and 33, and page 7, line 1 ("adenosine *receptor* agonist," instead of "adenosine agonist"). The specification discloses using adenosine or an adenosine receptor agonist to enhance the condition of non-diseased skin, e.g., at page 2, lines7-9, and to decrease wrinkling or roughness, e.g., at page 13-15. This constitutes a clear disclosure of the use of these agents on unbroken skin, thereby fully supporting amendment of claim 1 to recite "unbroken" skin.

Manneth does not teach administering adenosine or an adenosine receptor agonist by incorporating it into a patch. Indeed, a person following the teaching of *Manneth* would be motivated *not* to administer adenosine or an adenosine receptor agonist by means of a patch, because melanin production, *i.e.*, tanning, because tanning only in isolated spots or areas of skin would be unsightly and undesirable. Therefore, *Manneth* lacks relevance to amended claim 1.

The *Cronstein* disclosure is limited to the use of an adenosine receptor agonist to promote healing of a wound or burn, *i.e.*, applying a composition containing an adenosine receptor agonist to *broken* skin. In contrast, claim 1 specifies applying a patch containing adenosine or an adenosine receptor agonist to *unbroken* skin. Therefore, *Cronstein* lacks relevance to amended claim 1.

Claims 1-20 stand rejected under 35 USC § 102(a) as allegedly anticipated by von Borstel et al., U.S. Patent No. 5,770,582. More particularly, the Office action states (emphasis added):

> [Von Borstel] '582 teaches **deoxy**ribonucleosides such as **2'-deoxy**adenosine for accelerating the healing of wounds, cuts, abrasions and ameliorate the effects of aging. '582 teaches angiogenic factors, growth factors such as fibroblast growth factor and other additives for topical application. ... [W]ounds, cuts, [and] abrasions involve broken skin.

Applicants traverse this rejection. The *von Borstel* teaching relates to **deoxy**ribonucleosides, ***not*** ribonucleosides. In contrast, applicant's claims require application of adenosine or an adenosine receptor agonist. Adenosine is a ribonucleoside, ***not*** a deoxyribonucleoside. The two classes of compounds differ structurally and are quite distinct in their chemical and biological properties. The structural difference is well known. *See, e.g.*, Lehninger, *Biochemistry* (2nd Ed.), Worth Publishers, New York (1975), at page 310 (copy enclosed). Deoxyribonucleosides would not be expected to bind to adenosine receptors so as to elicit a biological response, and thus, the deoxyriboncleosides taught by *von Borstel* are not adenosine receptor agonists. *See, e.g.*, Wolff et al., *Adv. Cyclic Nuc. Acids Res.* 14:199-214 (1981)(copy enclosed). While applicant's method claims involve the use of one class of compounds, *von Borstel* relates to a *different class of compounds*.[1] For this reason, and contrary to the examiner's contention, *von Borstel* clearly lacks relevance to applicants' claims. Therefore, the rejection should be withdrawn.

35 USC § 103(a)

Claims 1-8 and 10 stand rejected under 35 USC § 103(a) for alleged obviousness over *Stramentinoli*, *Manneth* or *Cronstein*. In particular, the Office action asserts that claim recitations regarding molar concentrations, failure to cause cell proliferation or inclusion of

[1] Applicant recognizes that at page 6, line 17 the specification refers to 2'-deoxyadenosine as an "agonist of adenosine." However, the pending claims specify use of an "adenosine *receptor* agonist," in contrast to an "adenosine agonist." The specification clearly gives those two terms distinct meanings. For example, at page 6, lines 12-16, those terms are listed as two separate subcategories under the more general category "adenosine analog." Thus, although the specification lists 2'-deoxyadenosine as an adenosine analog, the specification does not state or otherwise indicate that 2'-deoxyadenosine or any other deoxyribonucleoside is an "adenosine receptor agonist," which is what the claimed methods explicitly require.

angiogenic components do not suffice to distinguish the claimed invention over the cited references. These assertions are rendered moot by the present amendments and the resulting distinctions discussed above. Therefore, the rejection should be withdrawn.

Claims 1-20 and 48-53 stand rejected under 35 USC § 103(a) for alleged obviousness over *von Borstel*. For the reasons explained above, *von Borstel* lacks relevance to the claimed methods. Therefore, the rejection should be withdrawn.

Claims 21-47 stand rejected under 35 USC § 103(a) for alleged obviousness over *Stramentinoli*, *Manneth*, *Cronstein* or *von Borstel* in view of Ahmed et al., *Biochem. Biophys. Res. Commun.* 208:871-878, 1995. More particularly, the Office action states (emphasis added):

> Ahmed et al teaches adenosine stimulates DNA synthesis in human foreskin fibroblasts as measured by thymidine incorporation. Although *none of the references teach protein synthesis and increase in cell size with adenosine*, it is the position of the examiner that it is well known during in [sic] a cell cycle, typically a cell undergoes mitotic or resting phase and DNA synthesis occurs during resting phase. It is in the resting phase that a cell prepares for mitosis by increasing the process of translation, protein synthesis followed by increase in contents of cell (cell size), before entering the mitotic phase (proliferation).

Applicants traverse this rejection with respect to claims 30-47, which relate to increasing protein synthesis or increasing cell size. The Office action concedes that "none of the references teach [increase in] protein synthesis and increase in cell size with adenosine." There are at least two fatal flaws in the rejection.

First, the examiner's contention that increased protein synthesis and increased cell size *necessarily* follow from increased DNA synthesis is highly speculative, and unsupported by citation of any specific reference whatsoever from the prior art. A proper obviousness rejection must be based on more than such a mere unsupported conclusion by the examiner. Furthermore, the examiner's reasoning postulates mitotic activity, *i.e.*, *cell proliferation*, and applicant's specification explicitly states that the invention works *without* stimulation of cell proliferation (page 2, lines 31-33): "The adenosine or adenosine analog does not cause proliferation of the dermal cell."

Second, where the rejection is based on a combination of references, the examiner has the burden of showing a that a person of ordinary skill in the art would have been motivated to

combine the references so as to arrive at the invention -- with the motivation coming from the prior art – not applicant's own teaching. It is well established that hindsight reconstruction using the application as a template is improper and impermissible. *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991). Moreover, to the extent that the rejection rests on *von Borstel*, the rejection fails, because as applicant explains above, *von Borstel* teaches a class of compounds different from the genus of compounds specified by the pending claims.

For the foregoing reasons, the rejection of claims 30-47 is unsound and should be withdrawn. Cancellation of claims 21-29 renders the rejection moot with respect to those claims.

Conclusion

Applicant submits that all of the claims are now in condition for allowance, which action is requested. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 09 MARCH 2000

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TAB 02

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Attorney's Docke 07917-045002 / (UMMC 97-32)

APPLICATION

FOR

UNITED STATES LETTERS PATENT

09672348.092800

TITLE: TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

APPLICANT: James G. Dobson and Michael F. Ethier

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PATENT
ATTORNEY DOCKET NO: 07917/045002

TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

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Statement as to Federally Sponsored Research

Work on this invention was supported by funds from the United States government (Public Health Service Grants HL-22828 and AG-11491). The government therefore has certain rights in this invention.

Field of the Invention

This invention relates to dermatology and cell biology.

Background of the Invention

Skin includes a surface layer, known as the epidermis, and a deeper connective tissue layer, known as the dermis. The epidermis undergoes continuous turnover as the outermost cells are exfoliated and replaced by cells that arise from inner dermal layers. The dermis is composed of a variety of cell types, including fibroblasts.

Skin thickness begins to decline in humans after the age of 20 as the dermis becomes thinner and the number of skin fibroblasts declines. As skin ages, or is exposed to UV light and other environmental insults, changes in the underlying dermis can lead to the functional and morphological changes associated with damaged skin. Decreases in the abundance and function of products of the fibroblasts, which include collagen and proteoglycans, are believed to play major roles in wrinkled and damaged skin.

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Summary of the Invention

We have discovered that adenosine stimulates DNA synthesis, increases protein synthesis, and increases cell size in cultures of human skin fibroblasts. Based on this discovery, the invention provides methods and compositions for enhancing the condition of skin.

In general, the invention provides a method for enhancing the condition of non-diseased skin of a mammal, e.g., a human. The method includes topically applying a therapeutically effective amount of a composition including adenosine or an adenosine analog to non-diseased skin of the mammal.

The invention also provides a method for promoting healing of broken, non-diseased skin in a mammal by topically administering a composition including a therapeutically effective amount of adenosine or an adenosine analog to the mammal.

Also included in the invention is a method for increasing DNA synthesis in a dermal cell of non-diseased skin of a mammal. The method includes topically administering a therapeutically effective amount of adenosine or an adenosine analog to a region of non-diseased skin of the mammal containing dermal cell. The adenosine is added so that it does not cause proliferation of the dermal cell.

The invention also features a method of increasing protein synthesis in a dermal cell of non-diseased skin of a mammal. The method includes topically administering a composition including a therapeutically effective amount of adenosine or an adenosine analog to a region of skin of the mammal containing the dermal cell. The adenosine or adenosine analog does not cause proliferation of the dermal cell.

Also provided in the invention is a method of increasing cell size in a dermal cell in non-diseased skin of a mammal, e.g., a human. The method includes topically administering a composition including a therapeutically effective amount of adenosine to a region of skin of the mammal containing the dermal cell, wherein addition of the adenosine does not cause proliferation of the dermal cell, wherein addition of the adenosine does not cause proliferation of the dermal cell.

The invention also includes a method for enhancing skin condition in a mammal, e.g., a human. The method includes providing fibroblasts from the mammal *ex vivo*, culturing the fibroblasts in the presence of adenosine, and reintroducing the fibroblasts into the mammal.

The therapeutically effective amount of adenosine used in the above-described methods is preferably 10^{-3} M to 10^{-7} M, more preferably 10^{-4} M to 10^{-6} M, and most preferably about 10^{-4} M.

The composition used in the above-described methods can include a second agent in addition to adenosine. The second agent can be, e.g. an agent that promotes binding of adenosine or an adenosine analog to an adenosine receptor, an angiogenic factor such as vascular endothelial cell growth factor (VEGF), basic fibroblast growth factor (BFGF), an agent that itself enhances skin condition, such as tretoinin or another known conditioning agent such as an emollient, a humectant, or an occlusive agent.

In preferred embodiments of the invention, the adenosine or an adenosine analog does not promote skin cell proliferation.

The invention also provides a composition including about 10^{-3} M to about 10^{-7} M adenosine and a therapeutically effective amount of an angiogenesis factor. In some

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embodiments, the composition of the adenosine is about 10^{-4} M.

As used herein, "enhancement of skin condition" means a noticeable decrease in the amount of wrinkling, roughness, dryness, laxity, sallowness, or pigmentary mottling in skin.

As used herein, a "therapeutically effective amount" of adenosine or an adenosine analog means an amount that enhances skin condition when applied to skin.

As used herein, "non-diseased skin" means skin free of any proliferative disorder observable by visual inspection.

The present invention advantageously allows for enhancement of skin condition. This results in skin that shows a less wrinkled, rough, or dry complexion. For example, the invention provides for enhancing the condition of skin damaged due to exposure to the sun or skin whose condition has deteriorated due to normal aging.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

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Other features and advantages of this invention will be apparent from the following description of the preferred embodiments thereof, and from the claims.

Brief Description of the Drawings

Figs. 1A and 1B are histograms showing the effect of adenosine on [^{3}H]thymidine incorporation in cultures of normal human skin (Fig. 1A) and lung fibroblasts (Fig. 1B). After incubation in serum-free medium for 24 hours, cells were exposed to 10^{-4} M adenosine for 18 hours. Medium was replaced with serum-free medium without adenosine, and [^{3}H]thymidine was added. Results are expressed as percent [^{3}H]thymidine incorporation compared to control cultures without adenosine and are means ± SEM for 4-5 experiments. "*" denotes value was significantly different from control value without adenosine.

Figs. 2A and 2B are histograms showing concentration responses of adenosine-stimulated protein synthesis in human skin fibroblasts from a young (Fig. 2A) and aged (Fig. 2B) donor. Cells were grown to 75% confluence. Medium was then replaced with serum-free medium with or without adenosine. After 48 hours, [^{3}H]phenylalanine incorporation was determined as described. Results are expressed as % [^{3}H]phenylalanine incorporation compared to control cultures without adenosine and are means ±SEM for 6-25 experiments. "*" denotes value was significantly different from control value without adenosine.

Detailed Description

The invention is suitable for treating skin of a mammal, e.g., a human, for which promotion of fibroblast-associated dermal functions is desired. For example,

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promotion of fibroblast-associated functions is desirable in enhancing the condition of aged skin, which is associated with a decrease in dermal cell function and is characterized by increased dryness or roughness, or both. The method can also be used on subjects having otherwise damaged skin, *e.g.*, wrinkled skin and skin with a non-proliferative disorder. The method can may further be used prophylactically on a subject to minimize deterioration of skin condition associated with aging or environmental factors, such as photodamage.

Adenosine and suitable adenosine analogs are suitable for use in enhancing skin condition. Adenosine analogs such as adenosine agonists, adenosine receptor agonists, and compounds that increase intracellular or extracellular adenosine levels are suitable for use in the invention.

Agonists of adenosine include 2′-deoxyadenosine; 2′,3′-isopropoylidene adenosine; toyocamycin; 1-methyladenosine; N-6-methyladenosine; adenosine N-oxide; 6-methylmercaptopurine riboside; 6-chloropurine riboside, 5′-adenosine monophosphate, 5′-adenosine diphosphate, or 5′-adenosine triphosphate. Adenosine receptor agonists include phenylisopropyl-adenosine ("PIA"), 1-Methylisoguanosine, ENBA (S(-), N^6-Cyclohexyladenosine (CHA), N^6-Cyclopentyladenosine (CPA), 2-Chloro-N_6-cyclopentyladenosine, 2-chloroadenosine, and adenosine amine congener (ADAC), all of which are agonists for the adenosine A_1 receptor. Other receptor agonists include 2-p-(2-carboxy-ethyl) phenethyl-amino-5′-N-ethylcarboxamido-adenosine (CGS-21680), N-ethylcarboxamido-adenosine (NECA) and napthyl-substituted aralkoxyadenosine (SHA-082), 5′(N-Cyclopropyl)-carboxamidoadenosine, DPMA (PD 129,944), Metrifudil, which are agonists for the adenosine A_2

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receptor. Other adenosine receptor agonists include those which preferentially bind the A_1 receptor relative to the A_2 receptor, such as 2-Chloroadenosine, N^6-Phenyladenosine, and N^6-Phenylethyladenosine; and those which preferentially bind the A_2 receptor relative to the A_1 receptor, such as 2-Phenylaminoadenosine and MECA.

Also suitable for use are compounds that increase intracellular adenosine concentration by inhibiting the cellular uptake of adenosine or the breakdown of adenosine. One pathway of adenosine metabolism is the conversion of adenosine to inosine by adenosine deaminase. An example of an adenosine deaminase inhibitor is erythro-9-(2-hydroxy-3-nonyl) adenine ("EHNA"). Adenosine kinase inhibitors can also be used. Adenosine kinase converts adenosine to adenosine monophosphate by adenosine kinase. An example of an adenosine kinase inhibitor is iodotubercidin. Other suitable compounds include those that inhibit the dipyridamole-sensitive nucleoside transporter, which exports adenosine from the cytoplasm, and agents that promote the activity of a 5'-nucleotidase, e.g., the ATP-activated 5'-nucleotidase, which forms adenosine. Compounds that increase tissue adenosine and ATP levels include acadesine (AICA-riboside), which is described in Gruber et al., Circulation 80:1400-1411 (1989).

Adenosine can be also be administered with a second compound. The second compound can enhance the action of adenosine or the adenosine analog, e.g., by enhancing binding of adenosine or an adenosine analog to an adenosine receptor. An example of such a compound is PD 81,728, which is described in Kollias-Baker et al. J. Pharmacol. Exp. Ther. 281:761-68. Alternatively, the second agent can itself act to enhance skin condition. Examples of these types of agents include tretinoin, a recognized skin

8

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conditioning agent (see, e.g., Olsen et al., J. Amer. Acad. Dermatol. 37:217-26, 1997), an angiogenic factor such as vascular endothelial cell growth factor (VEGF) or basic fibroblast growth factor (BFGF), or a conditioning agent.

The second compound can also be a conditioning agent such as an emollient, humectant, or occlusive agent. Numerous examples of particular conditioning agents are provided in the CTFA Cosmetic Ingredient Handbook (Cosmetic Toiletries and Fragrances Association, Washington, D.D., 1988). Emollients help to maintain the soft, smooth, and pliable appearance of skin and function by remaining on the skin surface or in the stratum corneum to act as lubricants, to reduce flaking, and to improve the skin's appearance. Examples of emollients include acetyl trioctyl citrate, cetyl alcohol, butyl myristate, cetyl alcohol, and mineral oil.

Humectants act to increase the water content of the top layers of the skin. Humectants include, *e.g.*, acetamide MEA, fructose, and xylitol. Occlusive agents inhibit the evaporation of water from skin, thereby increasing the water contend of the skin. Acetylated castor oil, mineral oil, and lauryl stearate are examples of occlusive agents.

A subject can be treated by applying adenosine or an adenosine analog in a pharmaceutical composition in an effective amount and for a period of time sufficient to improve the condition of the skin.

The pharmaceutical composition may be formulated using conventional methods to prepare pharmaceutically useful compositions. Such compositions preferably include at least one pharmaceutically acceptable carrier, such as those described in Remington's Pharmaceutical Sciences (E.W. Martin). In addition, the compositions preferably include a pharmaceutically acceptable buffer, preferably phosphate

9

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buffered saline, together with a pharmaceutically acceptable compound for adjusting isotonic pressure, such as, for example, sodium chloride, mannitol, or sorbitol.

Adenosine or an adenosine agonist can also be provided in carriers and adjuvants such as ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances, such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances and polyethylene glycol. Adjuvants for topical or gel base forms of adenosine or adenosine analogs may, for example, be selected from the group consisting of sodium carboxymethylcellulose, polyacrylates, polyoxythylene-polyoxypropylene-block polymers, polyethylene glycol and wood wax alcohols. For all administrations, conventional depot forms may be used.

The adenosine or adenosine analog-containing compositions may be in any pharmaceutically acceptable dosage form. They are preferably applied by topical routes to exert local therapeutic effects. For topical application, the penetration of the adenosine into skin tissue may be enhanced by a variety of methods known to those of ordinary skill in the art. For example, adenosine may be applied directly and mechanically rubbed into the skin. Alternatively, adenosine or adenosine analogs may be incorporated into a transdermal patch that is applied to the skin. Preferably, the penetration resulting from these methods is enhanced with a chemical transdermal delivery agent such as dimethyl sulfoxide (DMSO) or the nonionic

10

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surfactant, n-decylmethyl sulfoxide (NDMS), as described in Choi et al., Pharmaceutical Res., 7(11):1099, 1990.

Other modes of administration include, e.g., oral, subdermal, intradermal, or intravenous. When oral administration is used, it is critical that the adenosine or adenosine analog be delivered to that it is not degraded prior to exiting the digestive system.

The most effective mode of administration and dosage regimen of adenosine or the adenosine analog will depend upon the skin condition, previous therapy, the subject's health status, response to the adenosine, the judgment of the treating physician and the mode in which the adenosine is applied. For example, dosages for a therapeutically effective amount for topical application would be in the range of 100 ng to 10 mg per treated surface area per day. The adenosine may be administered to the patient at one time or over a series of treatments. When adenosine or the adenosine analog is administered in conjunction with a second agent, they can be administered either concurrently or sequentially, and can be administered in the same mode or a different mode, e.g., topical or oral.

Adenosine or an adenosine analog enhances skin condition when there is a noticeable decrease in noticeable decrease in the amount of wrinkling, roughness, dryness, laxity, sallowness, or pigmentary mottling of the treated skin. Methods of measuring improvements in skin condition are well known in the art (see, e.g., Olsen et al., J. Amer. Acad. Dermatol. 26:215-24, 1992), and can include subjective evaluations by the patient or a second party, e.g., a treating physician. Objective methods can include skin topography measurements, such as those described in Grove et al., J. Amer. Acad. Dermatol. 21:631-37 (1989). In skin topography measurements, silicone rubber replicas are made

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of a small area of skin, e.g., a 1 cm diameter circular area. The silicone rubber replicas capture fine lines and wrinkles on the skin. These specimens are then analyzed using computerized digital image processing to provide an objective measurement of the skin's topography. Skin topography measurements generated following digital-image processing can be measured using the values R_a and R_z as described in Olsen et al., J. Amer. Acad. Dermatol. 37:217-26, 1997, where R_a represents the area of deviation of skin surface features above and below an average central line, and R_z represents the difference between the maximum and minimum heights in five equal segments of the skin surface profile. A statistically significant decline (e.g., $P < 0.05$) in R_a and R_z values in skin treated with adenosine or an adenosine analog compared to untreated skin indicates an enhancement of skin condition.

Fibroblasts treated with adenosine or adenosine analogs can also be incorporated into a matrix and implanted in the body, e.g., as part of a skin graft. In addition, fibroblasts can be genetically engineered ex vivo to increase the amount of intracellular adenosine levels and then re-introduced into a human patient. (See, for example, Anderson et al. U.S. Patent No. 5,399,349; and Mulligan & Wilson, U.S. Patent No. 5,460,959, each of which is incorporated by reference herein in its entirety).

Experimental Information

Cell Culture

Human skin fibroblasts and human lung fibroblasts were supplied by the N.I.A. Aging Culture Repository Center (Camden, NJ). For skin fibroblasts, primary cultures had been initiated from explants obtained from a 3 mm punch biopsy of the mesial aspect of the upper left arm. Human

12

lung fibroblasts (IMR-90) were established from a 16-week normal female fetus. All cells displayed a normal diploid karyotype and all cells tested negative for bacteria, fungi and mycoplasma contamination.

Cells were grown in Eagle's minimal essential medium (MEM) supplemented with 10% fetal bovine serum (FBS), 100 U/ml penicillin and 100 mg/ml streptomycin in a 37°C, 5% CO_2/95% air environment. After reaching confluence, cells were subcultivated with 0.25% trypsin in MEM with no added Ca^{2+} or Mg^{2+}.

Incorporation of [^{3}H]Thymidine

As an index of DNA synthesis incorporation of [^{3}H]thymidine was measured as described in Ethier et al., Am. J. Physiol. 272:H1470-79 (1997). Confluent monolayers of human skin fibroblasts in MEM plus 10% FBS were seeded into 16 mm diameter culture wells (24-well plates) at a density of 1 x 10^4 cells/cm^2. Cells were grown at 37°C under standard culture conditions (5% CO_2-95% air) until they were approximately 75% confluent. Medium was then removed and the cells were made "serum-free" by incubation in MEM with no FBS for 24 hours. Adenosine or vehicle (MEM) was added for an additional 18 hours. This medium was then replaced with fresh MEM, and the cells were pulsed with 1mCi/ml [^{3}H] thymidine (6.7 Ci/mmol). After a 2 hour incubation period, the medium was discarded and the cells were rinsed twice with cold (4°C) Hank's balanced salt solution (HBSS) and incubated for 5 minutes with 0.5 ml cold 10% (w/v) trichloroacetic acid (TCA). The wells were then rinsed with 8% TCA and the TCA-insoluble material was solubilized with 0.5 ml of a solution of 0.2M NaOH and 0.2% sodium decyl sulfate (SDS). The radioactivity of this

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fraction was determined by standard liquid scintillation spectrometric techniques.

Incorporation of [^{3}H] thymidine was expressed as counts per minute (cpm) of ^{3}H per culture. Data in each experiment was derived from 4 identically treated wells. Since the cpm/well exhibited variation between experiments, data representing combined experiments are expressed herein as a percent of their respective mean control value.

Incorporation of [^{3}H]phenylalanine

Incorporation of [^{3}H]phenylalanine was measured as an index of protein synthesis. Human skin fibroblasts were seeded into 24-well culture plates in MEM containing 10% FBS. When cells had grown to approximately 75% confluence the culture medium was replaced with serum-free MEM with or without adenosine. After 48 hours, 2μCi/ml [^{3}H]phenylalanine was added to the cultures. Unlabeled phenylalanine (0.36 mM) was also added to equalize concentrations of intracellular and extracellular phenylalanine. After 8 hours, medium was removed and the cells were washed twice with cold (4°C) HBSS and incubated for 20 minutes in cold 10% (w/v) TCA. Cells were then incubated 5 minutes in 95% ethanol (4°C) and the TCA-insoluble material was solubilized with a solution of 0.2M NaOH and 0.2% SDS. The radioactivity of this fraction was determined by standard liquid scintillation spectrometric techniques.

Incorporation of [^{3}H] phenylalanine was expressed as cpm of ^{3}H per culture well and data in each experiment were derived from six identically treated wells. Since the cpm/well exhibited variation between experiments, data representing combined experiments are expressed as a percent of their respective mean control value.

Determination of Cell Size

Human fibroblasts in MEM 10% FBS were seeded into 25 cm^2 culture flasks at a density of 1×10^4 cells/cm^2. When the cells had grown to approximately 80% confluence the culture medium was removed and the cells were incubated in serum-free MEM for 24 hours. Adenosine or vehicle (MEM) was added for 18 hours and cells were then washed twice with cold (4°C) HBSS. Cells were removed with 0.25% trypsin in calcium-and magnesium-free MEM and diluted in cold (4°C) HBSS for measurement of relative cell size with a fluorescence-activated cell sorter (FACS; Becton Dickinson Vantage). Cell size was determined by forward light scatter on a minimum of 1×10^4 cells per experiment.

Experimental Materials

MEM, FBS, penicillin, streptomycin, trypsin, and HBSS were obtained from GIBCO (Grand Island, NY), [^{3}H] thymidine (6.7 Ci/mmol) and phenylalanine, L-ring-2,3,4,5,6-^{3}H] (92 Ci/mmol) were obtained from Dupont NEN (Boston, MA). Adenosine was from Boehringer Mannheim, SDS was from National Diagnostics, (Highland Park, NJ) and TCA and ethanol were obtained from Fisher Scientific (Pittsburgh, PA).

Data Analysis

Analysis of variance (ANOVA) was used to determine statistical differences between means. The Dunett's test was applied for multiple comparisons as described in Zar, J.H., Biostatistical Analysis. Englewood Cliffs, N.J., Prentice Hall, Inc. pp. 150-153, 1984. In addition, the Wilcoxon test was employed to verify differences between values expressed as a percentage. Differences were considered statistically different when $P < 0.05$.

15

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DNA Synthesis

Exposure to 10^{-4}M adenosine increased [^{3}H]thymidine incorporation by 43 ±9% in five studies on cultures of human fibroblasts (AG607720B) made quiescent by serum removal. These results are summarized in Fig. 1A. In contrast, adenosine (10^{-4}M) had no effect on [^{3}H]thymidine incorporation in cultures of human lung fibroblasts (IMR-90) (Fig. 1B). Concentrations of adenosine ranging from 10-7 M to 10^{-3}M also failed to stimulate [^{3}H]thymidine incorporation in IMR-90 lung fibroblasts (data not shown).

The effect of adenosine on DNA synthesis was additionally determined on skin fibroblast cultures from six different human donors. Adenosine (10^{-4}M) stimulated DNA synthesis in all three cultures derived from young human donors (Table 1). Values shown are means ±SEM, where *n* is number of experiments. Exposure to adenosine and determination of [^{3}H] thymidine incorporation were as described above. The asterisk denotes a value significantly different from the corresponding control (100%).

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Table 1. Effect of adenosine on [^{3}H]thymidine incorporation into cultured human skin fibroblasts derived from young donors

Cell Strain	Adenosine (10^{-4} M)	Donor		[^{3}H]thymidine incorporation (% of control)	*n*
		Age	Sex		
AG07720B	-	24	F	100	24
	+			124±7*	24
AG07306A	-	28	F	100	6
	+			193±20*	6
AG09605	-	30	M	100	12
	+			133±15*	12

Peak stimulation of [^{3}H]thymidine incorporation (93±20%, n=6) was achieved in human skin fibroblast cultures derived from a 28 year old female (AG07306A).

Adenosine (10^{-4}M) stimulated DNA synthesis in 2 of 3 cultures derived from aged human donors (Table 2). As in Table 1, values are means ±SEM, and *n* is the number of experiments performed. The asterisk denotes a measurement significantly different from the corresponding control (100%). Adenosine exposure increased [^{3}H]thymidine incorporation by 53±31% and 54 ±22% in human skin fibroblast cultures derived from a 70 year-old male and a 84 year-old male, respectively. Adenosine had no effect on cultures derived from a 67-year old female.

Table 2. Effect of adenosine on [^{3}H]thymidine incorporation into cultured human skin fibroblasts derived from aged donors

Cell Strain	Adenosine (10^{-4} M)	Donor		[^{3}H]thymidine incorporation (% of control)	*n*
		Age	Sex		
AG11728	-	67	F	100	6
	+			91±6	6
AG12949	-	70	M	100	11
	+			150±31*	11
AG11730	-	84	M	100	10
	+			154±22*	10

Protein Synthesis

The effect of adenosine on protein synthesis was determined by measuring [^{3}H]phenylalanine incorporation into cultures of human fibroblasts from a young and aged donor. Cultures made quiescent by serum removal were exposed to adenosine (10^{-6}M to 10^{-4}M) for 48 hours and then pulsed with phenylalanine. In skin fibroblast cultures derived from a 28-year old female (AG073060A) and an 84-year old male (AG11730), adenosine(10^{-4}M) increased protein synthesis by 13 ± 4% (n=25) and 13 ± 6% (n=17), respectively (Fig. 2).

Cell Size

The effect of adenosine on cell size was determined on human skin fibroblasts from young and aged donors by measuring forward light scatter in a FACS analyzer. Cultures made quiescent by serum removal were exposed to adenosine for 18 hours, removed by trypsinization, and

diluted in 4°C HBSS. A minimum of 1×10^4 cells were measured for each experiment. The results are shown in Table 2. Values are mean ± SEM for relative cell size determined by forward light scatter (FLS) in a fluorescence-activated cell sorter, and *n* = number of cells measured. The asterisk denotes the measurement is significantly different from corresponding control.

In skin fibroblast cultures from a 28 year old female (AG073060A) adenosine (10^{-4}M) significantly increased cell size by 1.8 and 2.2% in two of three experiments (Table 3).

The effect of adenosine on cell size was also measured on skin fibroblasts from an aged donor. The results are shown in Table IV. Values are mean ± SEM for relative cell size determined by forward light scatter (FLS) in a fluorescence-activated cell sorter, where *n* is the number of cells measured. An asterisk indicates a value significantly different from corresponding control.

In cultures derived from an 84-year old male (AG11730), adenosine (10^{-4}M) significantly increased cell size by 2.7-4.9% in 3 of 3 experiments (Table 4).

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Table 3. Effect of adenosine on cell size in cultured human skin fibroblasts derived from young donors

Experiment Number	Adenosine (10^{-4} M)	Relative Size (FLS)	% increase	*n*
1	-	524±0.55	-	1.5×10^4
	+	526±0.55	0.4	1.5×10^4
2	-	319±1.24	-	1.0×10^4
	+	326±1.16*	2.2*	1.0×10^4
3	-	342±0.94	-	1.0×10^4
	+	348±0.95*	1.8*	1.0×10^4

Table 4. Effect of adenosine on cell size in cultured human skin fibroblasts derived from aged donors

Experiment Number	Adenosine (10^{-4} M)	Relative Size (FLS)	% increase	*n*
1	-	333±0.79	-	1.0×10^4
	+	342±0.75*	2.7*	1.0×10^4
2	-	323±1.01	-	1.0×10^4
	+	337±0.96*	4.3*	1.0×10^4
3	-	306±0.81	-	1.0×10^4
	+	321±0.81*	4.9*	1.0×10^4

Other Embodiments

While the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention. For example, while the

invention has been described using adenosine and adenosine agonists, other compounds structurally similar to adenosine can also be used, e.g., purine-containing compounds and compounds having a ribosyl moiety. Other aspects, advantages, and modifications of the invention are within the scope of the following claims.

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21

We claim:

Claims

1. A method for enhancing the condition of non-diseased skin of a mammal, comprising topically applying a therapeutically effective amount of a composition comprising adenosine or an adenosine agonist to non-diseased skin of said mammal.

2. The method of claim 1, wherein said composition further comprises an angiogenic factor.

3. The method of claim 1, wherein the therapeutically effective amount of adenosine is an adenosine concentration of 10^{-3} M to 10^{-7} M.

4. The method of claim 3, wherein said adenosine concentration is 10^{-4} M to 10^{-6} M.

5. The method of claim 4, wherein said adenosine concentration is about 10^{-4} M.

6. The method of claim 1, wherein said composition further comprises a conditioning agent.

7. The method of claim 6, wherein said conditioning agent is selected from the group consisting of a humectant, an emollient, and occlusive agent.

8. The method of claim 1, wherein addition of adenosine does not affect skin cell proliferation.

9. The method of claim 1, wherein said skin comprises a skin graft.

22

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10. The method of claim 1, wherein said mammal is a human.

11. A method for promoting healing of broken, non-diseased skin in a mammal, comprising topically administering a composition comprising a therapeutically effective amount of adenosine or an adenosine agonist to said mammal.

12. The method of claim 11, wherein said composition further comprises an angiogenic factor.

13. The method of claim 11, wherein the therapeutically effective amount of adenosine is an adenosine concentration of 10^{-3} M to 10^{-7} M.

14. The method of claim 13, wherein said adenosine concentration is 10^{-4} M to 10^{-6} M.

15. The method of claim 14, wherein said adenosine concentration is about 10^{-4} M.

16. The method of claim 11, wherein said composition further comprises a conditioning agent.

17. The method of claim 16, wherein said conditioning agent is selected from the group consisting of a humectant, an emollient, and occlusive agent.

18. The method of claim 11, wherein addition of adenosine does not affect skin cell proliferation.

19. The method of claim 11, wherein said region of skin comprises a skin graft.

20. The method of claim 11, wherein said mammal is a human.

21. A method for increasing DNA synthesis in a dermal cell of non-diseased skin of a mammal, comprising topically administering a therapeutically effective amount of adenosine to a region of non-diseased skin of said mammal containing said dermal cell, wherein addition of said adenosine does not cause proliferation of said dermal cell.

22. The method of claim 21, wherein said composition further comprises an angiogenic factor.

23. The method of claim 21, wherein the therapeutically effective amount of adenosine is an adenosine concentration of 10^{-3} M to 10^{-7} M.

24. The method of claim 23, wherein said adenosine concentration is 10^{-4} M to 10^{-6} M.

25. The method of claim 24, wherein said adenosine concentration is about 10^{-4} M.

26. The method of claim 21, wherein said composition further comprises a conditioning agent.

27. The method of claim 26, wherein said conditioning agent is selected from the group consisting of a humectant, an emollient, and occlusive agent.

28. The method of claim 21, wherein said region of skin comprises a skin graft.

29. The method of claim 21, wherein said mammal is a human.

30. A method of increasing protein synthesis in a dermal cell of non-diseased skin of a mammal, comprising topically administering a composition comprising a therapeutically effective amount of adenosine to a region of skin of said mammal containing said dermal cell, wherein addition of said adenosine does not cause proliferation of said dermal cell.

31. The method of claim 30, wherein said composition further comprises an angiogenic factor.

32. The method of claim 30, wherein the therapeutically effective amount of adenosine is an adenosine concentration of 10^{-3} M to 10^{-7} M.

33. The method of claim 32, wherein said adenosine concentration is 10^{-4} M to 10^{-6} M.

34. The method of claim 33, wherein said adenosine concentration is about 10^{-4} M.

35. The method of claim 30, wherein said composition further comprises a conditioning agent.

36. The method of claim 35, wherein said conditioning agent is selected from the group consisting of a humectant, an emollient, and occlusive agent.

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37. The method of claim 30, wherein said region of skin comprises a skin graft.

38. The method of claim 30, wherein said mammal is a human.

39. A method of increasing cell size in a dermal cell in non-diseased skin of a mammal, comprising topically administering a composition comprising a therapeutically effective amount of adenosine to a region of skin of said mammal containing said dermal cell, wherein addition of said adenosine does not cause proliferation of said dermal cell, wherein addition of said adenosine does not cause proliferation of said dermal cell.

40. The method of claim 39, wherein said composition further comprises an angiogenic factor.

41. The method of claim 39, wherein the therapeutically effective amount of adenosine is an adenosine concentration of 10^{-3} M to 10^{-7} M.

42. The method of claim 41, wherein said adenosine concentration is 10^{-4} M to 10^{-6} M.

43. The method of claim 42, wherein said adenosine concentration is about 10^{-4} M.

44. The method of claim 39, wherein said composition further comprises a conditioning agent.

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45. The method of claim 44, wherein said conditioning agent is selected from the group consisting of a humectant, an emollient, and occlusive agent.

46. The method of claim 39, wherein said region of skin comprises a skin graft.

47. The method of claim 39, wherein said mammal is a human.

48. A method for enhancing skin condition in a mammal, comprising

providing fibroblasts from said mammal *ex vivo*,

culturing said fibroblasts in the presence of adenosine; and

reintroducing said fibroblasts into said mammal.

49. The method of claim 48, wherein the adenosine concentration in said culturing step is from about 10^{-3} M to about 10^{-7} M.

50. A method for increasing protein synthesis in a cultured skin fibroblast, comprising culturing said fibroblast in a culture medium comprising about 10^{-3} M to about 10^{-7} M adenosine.

51. The method of claim 50, wherein the adenosine concentration is about 10^{-4} M.

52. A composition comprising 10^{-3} M to 10^{-7} M adenosine and an angiogenesis factor.

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53. The composition of claim 52, wherein the concentration of said adenosine is about 10^{-4} M.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : James G. Dobson et al. Art Unit : 1615
Serial No. : 09/672,348 Examiner : L. Channavajjala
Filed : September 28, 2000
Title : TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

Commissioner for Patents
Washington, D.C. 20231

RESPONSE TO OFFICE ACTION DATED APRIL 20, 2001

Please amend the application as indicated below and consider the following remarks.

In the Claims:

Please cancel claim 1.

Please add new claims 54 to 79 as follows:

54. A method for increasing DNA synthesis in a dermal cell of a mammal without increasing proliferation of the cell, the method comprising applying to the cell a concentration of about 10^{-3} M to 10^{-7} M of adenosine or an adenosine analog to increase DNA synthesis in the cell without increasing proliferation of the cell.

55. The method of claim 54, wherein the cell is a fibroblast cell.

56. The method of claim 54, wherein the cell is a skin cell, and the composition is applied topically to skin of the mammal.

57. The method of claim 54, wherein the cell is a skin cell within a skin graft.

58. The method of claim 54, wherein the adenosine concentration is 10^{-4} M to 10^{-6} M.

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, Washington, D.C. 20231.

July 20, 2001
Date of Deposit

Joanne D Boyle
Signature

JOANNE D. BOYLE
Typed or Printed Name of Person Signing Certificate

59. The method of claim 54, wherein the adenosine concentration is about 10^{-4} M.

60. The method of claim 54, wherein the mammal is a human.

61. The method of claim 54, further comprising an angiogenic factor.

62. The method of claim 54, wherein the adenosine analog is selected from the group consisting of 2'-deoxyadenosine; 2',3'-isopropoylidene adenosine; toyocamycin; 1-methyladenosine; N-6-methyladenosine; adenosine N-oxide; 6-methylmercaptopurine riboside; 6-chloropurine riboside; 5'-adenosine monophosphate; 5'-adenosine diphosphate; 5'-adenosine triphosphate; phenylisopropyl-adenosine ("PIA"); 1-methylisoguanosine; N6-cyclohexyladenosine ("CHA"); N6-cyclopentyladenosine ("CPA"); 2-chloro-N6-cyclopentyladenosine; 2-chloroadenosine; adenosine amine congener (ADAC); 2-p-(2-carboxy-ethyl) phenethyl-amino-5'-N-ethylcarboxamido-adenosine; N-ethylcarboxamido-adenosine ("NECA"); napthyl-substituted aralkoxyadenosine; 5'(N-cyclopropyl)-carboxamidoadenosine; 2-chloroadenosine; N6-phenyladenosine; N6-phenylethyladenosine; and 2-phenylaminoadenosine.

63. A method of increasing protein synthesis in a dermal cell of a mammal without increasing proliferation of the cell, the method comprising applying to the cell a concentration of about 10^{-3} M to 10^{-7} M of adenosine or an adenosine analog to increase protein synthesis in the cell without increasing proliferation of the cell.

64. The method of claim 63, wherein the cell is a fibroblast cell.

65. The method of claim 63, wherein the cell is a skin cell, and the composition is applied topically to skin of the mammal.

66. The method of claim 63, wherein the cell is a skin cell within a skin graft.

67. The method of claim 63, wherein the adenosine concentration is 10^{-4} M to 10^{-6} M.

68. The method of claim 63, wherein the adenosine concentration is about 10^{-4} M.

69. The method of claim 63, wherein the mammal is a human.

70. A method for enhancing the condition of unbroken skin of a mammal by reducing one or more of wrinkling, roughness, dryness, or laxity of the skin, without increasing dermal cell proliferation, the method comprising topically applying to the skin a composition comprising a concentration of adenosine in an amount effective to enhance the condition of the skin without increasing dermal cell proliferation.

71. The method of claim 70, wherein the composition further comprises an angiogenic factor.

72. The method of claim 70, wherein the adenosine concentration is 10^{-4} M to 10^{-6} M.

73. The method of claim 70, wherein the adenosine concentration is about 10^{-4} M.

74. The method of claim 70, wherein the composition further comprises a conditioning agent.

75. The method of claim 74, wherein the conditioning agent is a humectant, an emollient, or an occlusive agent.

76. The method of claim 70, wherein the mammal is a human.

77. The method of claim 70, wherein the skin comprises a skin graft.

78. The method of claim 70, wherein the composition further comprises a transdermal delivery agent.

79. The method of claim 70, wherein the composition is in a transdermal patch and the composition is topically applied by contacting the patch to the skin.

REMARKS

Claims 54 to 79 are pending in this application. Applicants have cancelled claim 1 without prejudice and added new claims 54 to 79. These new claims add no new matter. In particular, claims to specific concentrations are supported by the original claims and in the application, e.g., at page 3, lines 15-18. Claims to specific adenosine analogs are supported in the application, e.g., at page 6, line 17, to page 7, line 6. Claims to the use of transdermal patches and delivery agents are also described in the application, e.g., at page 9, line 30, to page 10, line 2.

These and all of the other new claims are supported by the claims filed in the original application. For example, independent claim 54 to a method for increasing DNA synthesis in a dermal cell of a mammal without increasing proliferation of the cell is supported by original claim 21. Independent claim 63 to a method of increasing protein synthesis in a dermal cell of a mammal without increasing proliferation of the cell is supported by original claim 30. Independent claim 70 to a method for enhancing the condition of unbroken skin of a mammal by reducing one or more of wrinkling, roughness, dryness, or laxity of the skin, without increasing dermal cell proliferation is supported by original claims 1 and 8.

The Invention

The invention is based on the discovery that adenosine stimulates DNA synthesis, increases protein synthesis, and increases cell size in cultures of human dermal cells, such as fibroblasts, all without increasing cell proliferation. Based on this discovery, the invention provides various methods for increasing DNA or protein synthesis in dermal cells using specific concentrations of adenosine or adenosine analogs (10^{-3} M to 10^{-7} M)(claims 54 to 69), and for enhancing the condition of the skin using an effective amount of adenosine applied topically (claims 70 to 79). In these methods, the adenosine, or in some methods, adenosine analogs, are applied to the cells or topically to the skin to increase the cell size, and the function and abundance of products produced by the dermal cells, such as fibroblasts, e.g., by increasing DNA synthesis and/or protein synthesis.

However in all of these methods, it is important to avoid increasing proliferation of the dermal cells, which could lead to scarring, keloids, and other effects of excess dermal proliferation that are detrimental to the complexion of the skin. This important aspect of avoiding increased cell proliferation is not considered or described in any of the references cited in the Office Action.

Applicants will now address the Office Action rejections in the order they were presented by the Examiner.

35 U.S.C. § 112, Second Paragraph

Claim 1 has been rejected as being allegedly indefinite for reciting a "method of enhancing" the skin condition, which the Office Action states to be "vague." This rejection is moot in view of the cancellation of claim 1. However, applicants submit that the rejection should not apply to new claim 70, which is based on claim 1, for the following reasons.

Applicants submit that this phrase is not vague, because it is defined in the specification at page 3, lines 3-6. However, in the interests of moving this application towards allowance, and not for any reason related to patentability, applicants have drafted new claim 70 to recite "a method for enhancing the condition of unbroken skin of a mammal by reducing one or more of wrinkling, roughness, dryness, or laxity of the skin." Support for this amendment appears in the specification, for example, at page 4, lines 3-6 and lines 13-15.

In addition, the phrase "unbroken skin" in claim 70 is supported in the application based on the overall intent and general nature of the claimed invention. Specifically, page 2, lines 7-8, describes one general method of the invention as "a method for enhancing the condition of non-diseased skin of a mammal." In the very next paragraph, the specification states, "[t]he invention also provides a method for promoting healing of broken, non-diseased skin in a mammal." Although applicants are not presently pursuing this second method in the present application, its recitation implies to one of skill in this field that the discussion in the previous paragraph in the application must relate to enhancing the condition of unbroken, non-diseased skin, even though the term "unbroken" is not expressly stated. Taken in the context of the application as a whole,

the concepts of enhancing the condition of unbroken skin, as well as treating broken skin, are both supported in the application as originally filed.

Applicants remind the Examiner that the courts have long held that amendments that merely render explicit what is implicitly disclosed in the specification do not to constitute new matter. See, e.g., In re Wright, 343 F.2d 761, 767 (C.C.P.A. 1965). In Wright, the court said:

> We feel that the amendments to the specification merely render explicit what had been implicitly disclosed originally, and, while new *language* has certainly been added, we are not prone to view all new "language" ipso facto as "new matter." (emphasis in original).

Therefore, applicants submit that new claim 70 is fully supported by the originally filed specification, and avoids the indefiniteness rejection of original claim 1.

35 U.S.C. § 102

Claim 1 has been rejected as being allegedly anticipated by Manneth, U.S. Patent No. 5,998,423 (Manneth) or Cronstein, U.S. Patent No. 5,932,558 (Cronstein). This rejection is moot in view of applicants' cancellation of claim 1. Applicants respectfully submit that these rejections do not apply to new claims 54 to 79 for the following reasons.

Applicants have claimed the invention in three independent claims, 54, 63, and 70, to cover variations on the overall method of using adenosine, or in some methods, adenosine or adenosine analogs, to affect dermal cells, e.g., fibroblasts, without increasing proliferation of the dermal cells. Claim 54 covers a method for increasing DNA synthesis in a dermal cell by applying to the cell a concentration of about 10^{-3} M to 10^{-7} M of adenosine or an adenosine analog to increase DNA synthesis in the cell without increasing proliferation of the cell. Claim 63 covers a method of increasing protein synthesis in a dermal cell by applying to the cell a concentration of about 10^{-3} M to 10^{-7} M of adenosine or an adenosine analog to increase protein synthesis in the cell without increasing proliferation of the cell. Claim 70 covers a method for enhancing the condition of unbroken skin of a mammal by reducing one or more of wrinkling, roughness, dryness, or laxity of the skin, without increasing cell proliferation, by topically applying to the skin a composition comprising a concentration of adenosine, but not adenosine

analogs, in an amount effective to enhance the condition of the skin without increasing cell proliferation.

These claims are distinguished from the cited prior art for the following reasons.

First, according to the Office Action, Manneth describes "compositions comprising adenosine, cyclohexyladenosine or cyclopentyladenosine and their use for the modulation of melanin production in the skin and hair and in enhancing the tanning process and providing protection for the skin against UV radiation" (Office Action at page 2). Manneth also discloses various formulations of the composition including topical formulation containing various thickeners, castor oil and other additives.

However, Manneth fails to describe increasing DNA or protein synthesis by using a specific concentration of 10^{-3} M to 10^{-7} M of adenosine or an adenosine analog to achieve increased DNA or protein synthesis while avoiding detrimental dermal cell proliferation. Thus, Manneth does not anticipate independent claims 54 and 63.

Furthermore, Manneth describes the use of specific adenosine-1 and adenosine-2 receptor agonists and antagonists that are required for his invention. Manneth requires compounds that will selectively activate the adenosine-2 (A2) receptor or inactivate the adenosine-1 (A1) receptor to increase melanin production (see column 4, lines 29-41), or selectively inactivate the A2 receptor and activate the A1 receptor to decrease melanin production. That is why Manneth describes useful compounds for his methods as "analogs or derivatives of adenosine" (at column 3, lines 11-12), but not adenosine. Manneth does not describe the use of adenosine itself for a simple reason - adenosine activates both the A2 and A1 receptors, and would thus negate the selective effect required to modulate melanin production. Compounds such as adenosine that activate both A1 and A2 receptors will not work in Manneth's method of modulating melanin production. Therefore, Manneth does not anticipate applicants' claim 70 to a method of enhancing the condition of skin by topically applying adenosine.

Next, according to the Office Action, Cronstein describes a composition comprising adenosine agonists for the healing wound and burns by promoting influx of fibroblasts and epithelial cells. Cronstein is further said to describe topical application of the composition containing various additives or carriers (Office Action at page 3).

As the Examiner correctly notes, Cronstein limits his application of adenosine receptor agonists to open wounds such as burns. Cronstein also describes that his invention promotes the migration of endothelial cells, fibroblasts, and epithelial cells to the wound site. However, Cronstein fails to describe increasing DNA or protein synthesis by using a specific concentration of 10^{-3} M to 10^{-7} M of adenosine or an adenosine analog to achieve increased DNA or protein synthesis while avoiding detrimental dermal cell proliferation. To the contrary, Cronstein would want the dermal cells to proliferate to repair the wound. Thus, independent claims 54 and 63 are not anticipated by Cronstein.

With respect to new claim 70, applicants submit that Cronstein is limited to treating wounds that naturally involve broken skin, whereas claim 70 recites enhancing the condition of unbroken skin. Cronstein simply does not describe or suggest that adenosine should be applied to unbroken skin. Applicants apply adenosine as a cosmetic approach to enhance the condition or complexion of the skin, whereas Cronstein describes a medical therapy for open wounds such as burns. Thus, Cronstein does not anticipate claim 70.

Next, claim 1 has been rejected as allegedly anticipated by von Borstel, U.S. Patent No. 5,770,582 (von Borstel). Applicants traverse this rejection with respect to the new claims.

According to the Office Action, the von Borstel patent describes "deoxyribonuclosides such as 2'-deoxayadenosine for accelerating the healing of wounds, cuts, abrasions and to ameliorate the effects of aging" (at page 3). The Office Action also states, "[s]kin aging does not involve any underlying disease process. Accordingly treating aged skin reads on enhancing non-diseased skin condition" (id.).

The independent claims all recite the use of "adenosine" or "adenosine or adenosine analogs." As the Examiner correctly points out, Von Borstel describes the use of **deoxy**ribonucleosides, not ribonucleosides. However, adenosine and adenosine analogs are ribonucleosides, **not** deoxyribonucleosides. The two classes of compounds differ structurally and are quite distinct in their chemical and biological properties. The structural difference is well known. Deoxyribonucleosides would not be expected to bind to adenosine receptors to elicit a biological response, and thus, the deoxyriboncleosides described by von Borstel are not

the same as applicants' claimed adenosine and adenosine analogs. For this reason, von Borstel cannot anticipate applicants' pending claims. Therefore, this rejection should be withdrawn.

35 U.S.C. § 103

Claim 1 has been rejected as being allegedly unpatentable over Manneth, Cronstein, or von Borstel. Applicants submit that this rejection is moot in view of the cancellation of claim 1, and that this rejection does not apply to the new claims.

As the Office Action concedes, these patents "do not explicitly state enhancing the condition of a non-diseased skin" (Office Action at page 4). Moreover, these references do not describe or even suggest that one can increase DNA or protein synthesis of dermal cells by using a specific concentration of 10^{-3} M to 10^{-7} M of adenosine or an adenosine analog to achieve beneficial results while avoiding detrimental dermal cell proliferation.

Based on the discussions above, applicants submit that the new claims are not rendered obvious by any of the cited patents, either singly or in combination.

CONCLUSION

Applicants submit that all of the new claims are in condition for allowance. Please apply

charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 07917-045002.

Respectfully submitted,

Date: July 20, 2001

J. Peter Fasse
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20290413.doc

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/672,348	09/28/00	DOBSON J	07917-045002

HM12/1010

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EXAMINER	
CHANNAVAJJALA, L	
ART UNIT	PAPER NUMBER
1615	8

DATE MAILED: 10/10/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev.11/00) 1- File Copy

Office Action Summary	Application No.	Applicant(s)	
	09/672,348	DOBSON ET AL.	
	Examiner	Art Unit	
	Lakshmi S. Channavajjala	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54-79* is/are pending in the application.

4a) Of the above claim(s) *54-69* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *70-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

U.S. Patent and Trademark Office
PTO-326 (Rev. 04-01) **Office Action Summary** Part of Paper No. 8

DETAILED ACTION

Receipt of amendment B, dated 7-30-01 is acknowledged.

Claim 1 is canceled and new claims 54-79 have been presented.

Response to Arguments

Applicant's arguments with respect to claim 1 have been considered but are moot in view of the new ground(s) of rejection.

Election/Restrictions

Newly submitted claims 54-69 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

The newly presented claims 54-62 are directed to a method of increasing DNA synthesis and new claims 63-69 are directed to a method of protein synthesis, which were not presented in the original claims. The original claims are directed to a method of enhancing the skin condition and is different from claims 54-69.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 54-69 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

However, instant claims 70-79 are considered for examination.

Claim Rejections - 35 USC § 112

Claims 70-79 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Instant claims recite the limitation " a concentration of adenosine in an amount effective to enhance the condition of the skin without increasing dermal cell proliferation". Applicants state that adenosine does not cause cell proliferation of dermal cells, in the instant specification. However, applicants does not show any experimental evidence if there is any increase or any absence of increase in the cell proliferation. On the other hand, it is well known in the art that adenosine stimulates proliferation of cells, such as endothelial cells or in particular cells in the skin. For instance, German patent, DE 19545107 discloses that adenosine is useful in treating skin aging and its sequelae by stimulating cell proliferation in skin.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 70, 74-76 and 78 are rejected under 35 U.S.C. 102(b) as being anticipated by DE 19545107 (DE).

DE discloses a cosmetic and dermatological preparation containing adenosine for the treatment of natural, chemical induced or UV-induced skin aging and its sequelae. While DE states that adenosine **stimulates** cell proliferation, DE does not state that adenosine **increases** cell proliferation. Also refer to the 35 USC 112, rejection, with respect to the claim limitation "increase cell proliferation". Accordingly, DE anticipates the instant method. At this time a complete document is not available and abstract is therefore relied upon. DE teaches other cosmetic ingredients in the composition such as glycerin, cyclomethicone etc., which read on the "conditioning agent" of the instant claims. Further, instant claim 78 merely states "a transdermal delivery agent", which is broad and can include any topical agent, unless otherwise shown on the contrary. Accordingly, isopropyl palmitate, glycerin or cyclomethicone of DE also meet the requirement of claim 78. It is also well known that aging of skin is associated with skin dryness, wrinkles or loss of elasticity etc. Accordingly, the method of DE, which employs adenosine as claimed, also reduces one or more conditions such as dryness, wrinkles etc.

Claims 70 and 76 are rejected under 35 U.S.C. 102(b) as being anticipated by Hartzshtark et al (Experentia, 1985).

Hartzshtark et al discloses that application of adenosine along with isoproterenol bitartarate, terbutaline sulfate, papaverine etc., reduced the degree of skin indentation, which is an indication of a firmer and younger skin. Hartzshtark et al does not teach the increase or decrease of cell proliferation or even stimulation of cell proliferation, with adenosine application. Absent showing evidence on the contrary, it is the position of the examiner that adenosine

treatment of Hartzshtark et al, does not increase the stimulation of dermal cell proliferation and therefore, Hartzshtark et al anticipates the instant method.

Claim Rejections - 35 USC § 103

Claims 70 and 72-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of DE 19545107 and Hartzshtark et al or DE in view of Hartzshtark et al.

DE and Hartzshtark et al, discussed above, teach adenosine for the treatment of aging and it sequelae. With respect to the limitation "without increasing the cell proliferation", see the explanation above. Neither reference discloses the exact amounts of adenosine. However, Hartzshtark et al states that the reduced skin indentation, which is an indication of firmer and younger skin, occurs at those concentrations of adenosine, which is known to increase the cAMP concentrations. Therefore it would have been obvious for a skilled artisan at the time of the instant invention to optimize the amounts of adenosine such that the cAMP levels of skin increase and thus contribute for the reduced skin indentation and hence a firmer skin.

Claim 71 is rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of DE 19545107 and Hartzshtark et al as applicable to claims 70 and 72-78 above, and further in view of US patent 5,618,544 to Brown.

DE and Hartzshtark et al, discussed above fails to teach angiogenic factors in their composition.

Brown teaches a method of decreasing cutaneous senescence in aging humans, which involves administering a cosmetic composition comprising a mixture of growth factors such epidermal growth factor, fibroblast growth factor (FGF), transforming growth factor etc., in a pharmaceutically acceptable carrier. Brown also teaches that the lifetime damaging effects of include wrinkling and hardening of the skin, with loss of elasticity (col. 1-2 and claims). Instant claim does not specify any angiogenic factor. However, FGF is known angiogenic factors in the art, as also described by applicants in the instant application. Therefore, it would have been obvious for a skilled artisan at the time of the instant invention to add FGF of Brown to the cosmetic composition containing adenosine of DE (or Hartzshtark et al), with an expectation to reduce or delay the cutaneous atrophy because Brown suggests that the reduced senescence in epidermal cells improves the youthful appearance of human skin.

Claims 78 and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of DE 19545107 and Hartzshtark et al as applicable to claims 70 and 72-78 above, and further in view of US patent 5,785,978 to Porter.

DE and Hartzshtark do not specifically teach a transdermal patch or a transdermal delivery agent of the instant claims. However, as explained in the 102 rejection above, DE teaches isopropyl palmitate, glycerin etc., which read on the transdermal agent.

Alternatively, Porter teaches a skin care composition for the improving the appearance of skin affected by aging, comprising antioxidant vitamins and moisturizers. The composition of Porter is applied in the form of a patch (cols.1, 4 & 6). Further, Porter suggests permeability enhancing agents such as isopropyl palmitate (also taught by DE) for the delivery of

antioxidant vitamins from the transdermal patch. Therefore, it would have been obvious for a skilled artisan at the time of the instant invention to administer adenosine containing cosmetic compositions of DE or Hartzshtark et al either as cosmetic cream (DE) or as a transdermal patch (Porter) and still achieve improvement in the appearance of aging skin.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S. Channavajjala whose telephone number is 703-308-2438. The examiner can normally be reached on 7.30 AM -4.00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on 703-308-2927. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-7921 for regular communications and 703-308-7921 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Lakshmi Channavajjala
October 2, 2001

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

PATENT & TRADEMARK OFFICE FEB 2 OIPE JC147

Attorney's Docket No. 07917-045002 / (UMMC 97-32)

RECEIVED MAR 07 2002 TECH CENTER 1600/2900

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : James G. Dobson, Jr. and Michael F. Ethier
Art Unit : 1615
Examiner : L. Channavajjala
Serial No. : 09/672,348
Filed : September 28, 2000
Title : TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

10/C w/att (RE) afm 2-11-02

BOX AF
Commissioner for Patents
Washington, D.C. 20231

RESPONSE TO FINAL OFFICE ACTION DATED OCTOBER 10, 2001

PURSUANT TO 37 C.F.R. 1.116(A)

Please amend the application as indicated below, and consider the following remarks.

In the claims

Cancel claims 54 to 69 without prejudice as directed to a non-elected invention. Bet 3-8-02

Amend claim 70 as follows.

~~70.~~ (Amended) A method for enhancing the condition of unbroken skin of a mammal by reducing one or more of wrinkling, roughness, dryness, or laxity of the skin, without increasing dermal cell proliferation, the method comprising topically applying to the skin a composition comprising a concentration of adenosine in an amount effective to enhance the condition of the skin without increasing dermal cell proliferation, wherein the adenosine concentration applied to the dermal cells is 10^{-4} M to 10^{-7} M.

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, Washington, D.C. 20231.

February 11, 2002
Date of Deposit

Lisa G. Gray
Signature

Lisa G. Gray
Typed or Printed Name of Person Signing Certificate

25

REMARKS

Claims 70 to 79 are pending in this application. Applicants propose canceling claims 54 to 69 as allegedly directed to a non-elected invention. Applicants also propose to amend claim 70. This amendment would add no new matter, as it merely includes a range of concentrations of adenosine recited in dependent claims and in the specification at page 3, lines 15-18.

In addition, the amendment set forth above would raise no new issues that would require further consideration and/or search. Applicants submit that this amendment would place the claims into condition for allowance, or at least present the rejected claims in better form for consideration on appeal, and should therefore be entered after the final rejection under 37 C.F.R. § 1.116 (a).

Restriction

Applicants disagree with the Examiner's conclusion that the present claims 54 to 69 are directed to a separate invention than that claimed in claims 70 to 79, because all are based on the application of certain concentrations of adenosine to the skin to achieve certain results. Nevertheless, applicants propose to cancel these claims as directed to a non-elected invention unless the Examiner reconsiders and withdraws this restriction. Thus, claims 70 to 79 would be pending.

35 U.S.C. § 112, First Paragraph

Claims 70 to 79 have been rejected as allegedly containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Applicants traverse this rejection in view of experimental test results as described in a declaration (attached hereto) by the two co-inventors of this application, Dr. James G. Dobson, Jr. and Dr. Michael F. Ethier ("the Declaration").

According to the Office Action, applicants state that adenosine does not cause cell proliferation of dermal cells, but the application provides no experimental evidence to show whether there is an increase or decrease in the cell proliferation. Applicants now provide that evidence. As described in the Declaration, applicants conducted tests of skin fibroblast cells,

which make up a significant portion of dermal cells, from two different donors (an 84 year-old man and 30 year-old female), with varying concentrations of adenosine (10^{-4} or 10^{-5} M). The added adenosine had no significant effect on cell proliferation over a 5 day period, i.e., the adenosine did not increase cell proliferation at concentrations of 10^{-4} or 10^{-5} M (see Declaration, paragraph 3).

Although applicants believe that claim 70 as written covers this result by functional language, in the interests of moving this application towards allowance, they have proposed to amend claim 70 to reflect this experimental result. Based on this new information, applicants request the Examiner to reconsider and withdraw this rejection under Section 112, first paragraph.

As for the Office's assertion that "it is well known in the art that adenosine stimulates proliferation of cells, such as endothelial cells or in particular cells in the skin" based on German patent DE 19545107, applicants will discuss this reference in more detail below in relation to the alleged anticipation.

35 U.S.C. § 102

Claims 70, 74 to 76, and 78 have been rejected as allegedly anticipated by DE 19545109 (the German patent application). Applicants traverse this rejection in view of the new data described in the enclosed Declaration.

According to the Office Action, the German patent application "discloses a cosmetic and dermatological preparation containing adenosine for the treatment of natural, chemical induced or UV-induced skin aging and its sequelae. While DE states that adenosine stimulates cell proliferation, DE does not state that adenosine increases cell proliferation. ... Accordingly, DE anticipates the instant method" (Office Action, page 4). Applicants submit that this rejection is based on information in the German patent application that contradicts applicants' test results, and request the Examiner to reconsider this rejection in view of applicants testing, the Declaration, and the following comments.

Applicants have obtained a translation of the German patent application, which is attached to the Declaration as Exhibit B. Applicants' comments in their Declaration and here are

based on this translation. As the Examiner has noted, the German patent application describes the use of adenosine for increasing cell proliferation in human skin (see, e.g., the title and claim 1). However, applicants' claims require no increase in dermal cell proliferation, because such excess cell proliferation can cause scarring, discoloration, and a variety of other skin anomalies associated with hyperplasia. See, Declaration at paragraph 2.

Furthermore, applicants' testing, as described above, has shown that low concentrations of adenosine do not increase dermal cell proliferation. Thus, when the German patent application states that concentrations of adenosine as low as 0.001% can be used for increasing cell proliferation, the German patent application must be mistaken in that adenosine was not likely actually administered at this low concentration. There is one paragraph in the German patent application that recites the 0.001% number, and this is in an extremely broad range from 0.001 to 10% by weight of a cosmetic composition (at page 9, 4th full paragraph). Other sections of the German patent application recite higher concentrations for a lower limit of adenosine. For example, the claims, recite 0.01 to 10%, with a preferred concentration of 0.1 to 6%. More importantly, each of the six Examples at pages 9 to 12 in the translation lists a relatively high concentration of 0.1% adenosine. See also the Declaration at paragraph 5.

Thus, based on applicants' test results, applicants submit that the extremely broad range of adenosine concentrations listed in the German patent application is not supported by reality. The low end of this unsupported range is 0.001%, which corresponds to 3.8×10^{-5} M adenosine. This is between the 10^{-4} M and 10^{-5} M concentrations recited in the claims of the present application. However, the presently claimed invention is based on the demonstration that the recited concentrations of adenosine do not increase cell proliferation. This is the exact opposite of the assertions in the German patent application. It is for these reasons that the German patent application recitation of adenosine concentrations less than 10^{-4} M (0.00265%) cannot be valid, and thus the German patent application does not disclose the same invention as the proposed claims in the present application. See Declaration, paragraph 5.

In addition, applicants submit that the dependent claims 74 to 76, and 78 are also not anticipated for the same reasons discussed above for independent claim 70. Thus, applicants

respectfully request that the Examiner reconsider and withdraw the rejection of the claims in view of the German patent application.

Next, claims 70 and 76 have been rejected as being allegedly anticipated by Hartzshtark et al. (Experentia, 1985). Applicants disagree for the following reasons.

According to the Office Action, Hartzshtark discloses that the application of adenosine along with isoproterenol bitartarate, terbutaline sulfate, papavarine etc., reduced the degree of skin indentation, which is an indication of a firmer and younger skin (Office Action, page 4). The Examiner concedes that Hartzshtark does not discuss whether the addition of adenosine increases or decreases cell proliferation, but states, "[a]bsent showing evidence on the contrary, it is the position of the examiner that adenosine treatment of Hartzshtark et al, does not increase the stimulation of dermal cell proliferation and therefore, Hartzshtark et al. anticipates the instant method" (Office Action, pages 4-5).

As discussed above, applicants have demonstrated that certain low concentrations of adenosine do not increase cell proliferation. In the enclosed Declaration, applicants describe their review of the two main prior art references, and the testing they have done that supports the present claims.

Hartzshtark states that certain concentrations of various agents, including adenosine, increase skin cyclic-AMP content and thus cause a decrease in skin indentation. Specifically, Hartzshtark indicates in the Table on page 379 that the adenosine concentration effective to reduce indentation was 0.1% (3.8×10^{-3} M), but also notes that they tested adenosine "at one-third of the concentrations shown in the table [e.g., about 1.27×10^{-3} M], and at this level [adenosine was] ineffective" (bottom of page 378 to top of page 379). Applicants discuss these results of Hartzshtark in their Declaration, at paragraph 4.

The proposed amended claims would recite a maximum concentration of adenosine of 10^{-4} M. The results in Hartzshtark indicate that a concentration of adenosine of 10^{-4} M or lower would be even less effective than one-third of 0.1% (1.27×10^{-3} M), which was ineffective in their testing. See Declaration, paragraph 4. Thus, Hartzshtark does not anticipate claim 70 as amended, and does not anticipate dependent claim 76, which depends from claim 70.

35 U.S.C § 103

Claims 70 and 72 to 78 have been rejected as allegedly obvious over the combination of the German patent application and Hartzshtark. Applicants traverse this rejection for the reasons stated above and as follows.

The Office Action states that "[n]either reference discloses the exact amounts of adenosine," but concludes that "it would have been obvious for a skilled artisan at the time of the instant invention to optimize the amounts of adenosine such that the cAMP levels of skin increase and thus contribute for the reduced skin indentation and hence a firmer skin" (Office Action, page 5).

As discussed above, Hartzshtark indicates that adenosine was effective at a concentration of 0.1%, which is 3.8×10^{-3} M. However, when they tested adenosine at a lower concentration, at one-third of 0.1%, there was no effect. Thus, applicants submit that one skilled in this field would not have "optimized" the concentrations described in Hartzshtark to lower them even further. Thus, there would have been no suggestion or motivation in any of the cited references for one of skill in this field to use **a maximum** concentration of 10^{-4} M adenosine as recited in applicants' claim 70. Thus, claim 70, and dependent claims 72 to 78, are not obvious in view of the cited prior art.

Claim 71 has been rejected as being allegedly unpatentable over a combination of the German patent application of DE 1955107 and Hartzshtark in view of Brown, U.S. Patent No. 5,618,544 ("Brown"). Similarly, claims 78 and 79 have been rejected as obvious over the combination of the German patent application and Hartzshtark in view of Porter, U.S. Patent No. 5,785,978 ("Porter").

Claims 71, 78, and 79 depend from claim 70, which is patentable for all the reasons discussed above. Thus, these dependent claims are also patentable. However, applicants note further that Brown's suggestion to apply epidermal and fibroblast growth factors to the skin would not lead one of skill in the art to avoid an increase in cell proliferation, as recited in applicants' claims, because these growth factors are known to increase cell proliferation (Brown notes that these factors increase "the rate of cellular replication," at column 3, lines 25-26). Thus, applicants see no suggestion or motivation to combine Brown with any of the other cited

references, and even if such a combination were made, one would not have achieved the claimed invention.

As for Porter, if one of skill in the art were to use the transdermal patch that this patent describes, the dosage of adenosine would, according to the cited prior art, cause an increase in skin cell proliferation and/or provide a higher concentration of adenosine than recited in applicants' claims. Thus, applicants submit that even if Porter were combined with the German patent application or Hartzshtark, the result would not be the presently claimed invention.

CONCLUSION

Attached is a marked-up version of the changes being made by the current amendment.

Applicants request that the proposed claim amendment be entered and that all pending claims then be allowed. No excess claims fee is required. Applicants enclose a $55.00 check and a Petition for Extension of Time. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 07917-045002.

Respectfully submitted,

Date: 02-11-02

J. Peter Fasse
Reg. No. 32,983

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70021823.doc

Version with Markings to Show Changes Made

In the claims:

Claims 54 to 69 have been cancelled as directed to a non-elected invention.

Claim 70 has been amended as follows.

70. (Amended) A method for enhancing the condition of unbroken skin of a mammal by reducing one or more of wrinkling, roughness, dryness, or laxity of the skin, without increasing dermal cell proliferation, the method comprising topically applying to the skin a composition comprising a concentration of adenosine in an amount effective to enhance the condition of the skin without increasing dermal cell proliferation, wherein the adenosine concentration applied to the dermal cells is 10^{-4} M to 10^{-7} M.

(19) Federal Republic of Germany
DPMA German Patent Office

(12) **Application Published Unexamined**
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A 61 K 31/70

DE 195 45 107 A1

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The following documents are to be considered in the determination of patentability:

(56)

DE	34 47 618 C2
DE	43 23 615 A1
DE	33 19 282 A1
DE	26 17 919 A1
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Derwent abstract, 84-227814/37 relating to J5 9134-707-A; JP Patents Abstracts of Japan: 63-152309 A., C-541, Nov. 8, 1988, Vol. 12, N° 421; 6-80564 A., C-1217, June 27, 1994, Vol. 18, N° 337;

(54) Use of an Effective Adenosine Concentration in Cosmetic or Dermatological Preparations.

(57) Use of Adenosine for Increasing Cell Proliferation in Human Skin.

DE 195 45 1 107 A1

The following information has been taken from the documents submitted by the applicant.

National Printing Office 04.97 702 023/445 9/24

DESCRIPTION

The present invention relates to the use of adenosine in cosmetic and dermatological preparations.

In a separate embodiment, the present invention relates to cosmetic and dermatological preparations for the prevention and therapy of cosmetic or dermatological skin changes such as, for example, skin aging.

The skin ages because of endogenous, genetically determined influences. Exogenous factors, such as UV-light and chemical irritants, can have cumulative effects and accelerate the natural aging processes. This produces a number of degenerative processes whose results include the following structural changes and insult in the dermis and epidermis (dermatoheliosis), depending on the magnitude of the factors:

a) Involution of the microvascular system.

b) Loosening and formation of wrinkles in part due to the reduction and cross-linking of collagen and accumulation of glucosaminoglycans (basic substance).

c) Flattening of the reticular plugs. In conjunction with this is the surface reduction between dermis and epidermis, through which substances for the nourishment and cleansing of the skin are exchanged.

d) Limited regenerative turnover in the epidermis in conjunction with abnormal formation of the horny layer (hornification) that leads to drying out of the skin.

e) Abnormal regulation of cell division (proliferation) and cell maturation (differentiation) in the epidermis resulting in atypical cells and polarity loss.

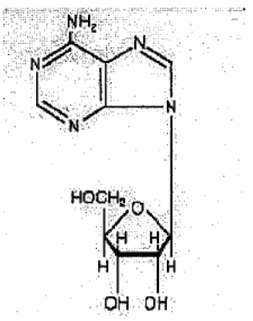
f) Local hyper-, hypo-, and abnormal pigmentations (age spots).

Accordingly, the present invention relates to products for the care and prevention of aged skin and for the therapy of the damage resulting from skin aging, in particular those phenomena listed in a) to f).

It was surprising and unforeseeable by the specialist that for enhancement of cell proliferation in human skin, preferably in cosmetics or dermatological preparations, remedies the drawbacks of the prior art [sic].

In one particular embodiment, the present invention accordingly relates to the use of adenosine for the care and prevention of aged skin and for the therapy of the damage resulting from skin aging, in particular those phenomena listed in a) to f).

Adenosine is characterized by the structural formula:



DE-OS 24 01 450 discloses pharmaceutical preparations for the relief of proliferative skin diseases containing of an active adenosine component. Furthermore, several prior art documents are known that deal with the cosmetic or dermatological use of adenosine phosphates (cyclic adenosine-3'5'-monophosphate = cAMP, adenosine monophosphate = AMP, adenosine diphosphate = ADP, adenosine triphosphate = ATP), for example US patent 4,702,913, in which the use of ATP and cAMP as substances enhancing skin moisture is discussed. The prior art does not, however, provide an indication of the use according to this invention.

According to the use as described in the invention, cosmetic or dermatological formulations can be composed as usual and used for the treatment, care and cleansing of the skin and/or hair, and as a make-up product in decorative cosmetics. They contain preferably 0.001 percent by weight to 10 percent by weight, in particular 0.01 percent by weight to 6 percent by weight, of the active substance combinations relative to the total weight of the product.

For use according to the invention, the cosmetic and dermatological preparations are applied in sufficient quantity to the skin and/or hair in the manner conventional for cosmetics.

The cosmetic and dermatological preparations can be in various forms for use according to the invention. For example, they can be a solution, a non-aqueous preparation, a water-in-oil (W/O) or oil-in-water (O/W) emulsion or microemulsion, a multiple emulsion such as a water-in-oil-in-water (W/O/W) emulsion, a gel, a solid stick, a salve or even an aerosol. Adenosine can also be advantageously administered in an encapsulated form according to the invention, for example in collagen matrices and other conventional encapsulation materials, for example as cellulose encapsulations, in gelatins, wax matrices or encapsulated in liposomes. In particular, wax matrices as disclosed in DE-OS 43 08 282 have been shown to be advantageous.

The addition of adenosine to aqueous systems or tenside preparations for cleansing the skin and the hair is also possible and advantageous according to the present invention.

In keeping with the use according to the invention, cosmetic and dermatological preparations can contain cosmetic adjuvants as conventionally used in such preparations, for example preservatives, bactericides, fragrances, anti-foaming agents, dyes, pigments having a coloring effect, thickeners, surfactants, emulsifiers, softening , wetting , and/or moisture-retaining substances, fats, oils, waxes or other conventional components of cosmetic or dermatological formulations like alcohols, polyols, polymers, foam stabilizers, electrolytes, organic solvents or silicone derivates.

In particular, adenosine can also be combined with antioxidants.

According to the invention, all antioxidants suitable or usable in cosmetic and/or dermatological applications can be used advantageously as antioxidants.

It is advantageous to select the antioxidants from the group comprised of the amino acids (for example, glycine, histidine, tyrosine, tryptophan) and their derivatives, imidazole (for example, urocanic acid) and their derivatives, peptides like D,L-carnosine, D-carnosine, L-carnosine and their derivatives (for example, anserine); carotenoids, carotene (for example, α-carotene, β-carotene, lycopine) and their derivatives; chlorogenic acid and its derivatives, liponic acid and its derivatives (for example, dihydroliponic acid), aurothioglucose, propylthiouracil and other thiols (for example, thioredoxin, glutathion, cysteine, cystine, cystamine, and their glycosyl-, N-acetyl-, methyl-, ethyl-, propyl-, amyl-, butyl-, and lauryl-, palmitoyl-, oleyl-, γ-linoleyl-, cholesteryl-, and glyceryl esters) and their salts, dilaurylthiodipropionate, distearylthiodipropionate, thiodipropionic acid and their derivatives (esters, ethers, peptides, lipids, nucleotides, nucleosides, and salts) and sulfoximine compounds (for example, buthionine sulfoximine, homocysteine sulfoximine, buthionine sulfone, penta-, hexa-, heptathionine sulfoximine) in very low, tolerable doses (for example, pmol to μmol/kg); in addition, (metal) chelators (for example, α-hydroxy fatty acids, palmitic acid, phytinic acid, lactoferrin), α-hydroxy acids (for example, citric acid, lactic acid, malic acid), humic acid, bile acid, bile extracts, bilirubin, biliverdin, EDTA, EGTA and their derivatives; unsaturated fatty acids and their derivatives (such as γ-linoleic acid, linolic acid, oleic acid), folic acid and its derivatives, ubiquinone and ubiquinol and their derivatives; vitamin C and its derivatives (for example, ascorbyl palmitate, Mg-ascorbyl phosphate, ascorbyl acetate), tocopherols and derivatives (for example, vitamin E acetate), vitamin A and derivatives (for example, vitamin A palmitate) and coniferyl benzoate of benzoic resin, rutic acid and its derivatives; butylhydroxytoluene, butylhydroxyanisol, nor-dihydroguaiac resin acid, nordihydroguaiaretic acid, trihydroxybutyrophenone, uric acid and its derivates, mannose and its derivatives, sesamol, sesamolin, zinc and its derivatives (for example, ZnO, $ZnSO_4$), selenium and its derivatives (for example, selenium methionine), stilbene and its derivatives (for example, stilbene oxide, trans-stilbene oxide) and the suitable derivatives according to the inventions (salts, esters, ethers, sugars, nucleotides, nucleosides, peptides, and lipids) of said active substances.

The quantity of the above antioxidants (one or a plurality of compounds) in the preparations is advantageously preferably 0.001 to 30 percent by weight, particularly preferred 0.05 – 20 percent by weight relative to the total weight of the formulation.

In so far as vitamin E and/or its derivatives represent the antioxidant or antioxidants, it is advantageous if their respective concentrations are chosen from the range of 0.001 – 10 percent by weight relative to the total weight of the formulation.

Insofar as vitamin A or vitamin A derivatives, or carotene or its derivatives are the antioxidant(s), it is advantageous if their respective concentrations are chosen from the range of 0.001 – 10 percent by weight relative to the total weight of the formulation.

Emulsions according to the invention are advantageous and contain, for example, the said fats, oils, waxes and other aliphatics, water and an emulsifier as it is conventionally used for such a formulation.

The lipid phase can thus be advantageously selected from the following group of substances:

- natural, synthetic and/or semi-synthetic oils like triglycerides of capric or caprylic acid, preferably castor oil;
- fats, waxes and other natural, synthetic and/or semi-synthetic aliphatics, preferably esters of fatty acids with low-carbon alcohols, for example with isopropanol, propylene glycol or glycerin, or esters of fatty alcohols with low-carbon alkanoic acids or with fatty acids;
- silicone oils like dimethylpolysiloxane, diethylpolysiloxane, diphenylpolysiloxane, and mixed forms of same;
- saturated compounds like hydrocarbons of natural or synthetic origin (vaseline, squalane).

The aqueous phase of the preparations according to the invention may advantageously contain low-carbon alcohols, diols or polyols and their ethers, preferably ethanol, isopropanol, propylene glycol, glycerin, ethylene glycol, ethylene glycol monoethyl or monobutyl ether, propylene glycol monomethyl, monoethyl or monobutyl ether, diethylene glycol monomethyl or monoethyl ether and analog products, further low-carbon alcohols such as ethanol, isopropanol, 1,2-propane diol, glycerin and particularly one or a plurality of thickeners which can be advantageously selected from the group of silicon dioxide, aluminum silicates, polysaccharides or their derivatives such as hyaluronic acid, xanthan gums, hydroxypropylmethyl cellulose, particularly advantageously from the polyacrylate group, preferably a polyacrylate from the group of so-called carbopols, for example type 980, 981, 1382, 2984, 5984 carbopols, or even the ETD (easy-to-disperse) 2001, 2020, 2050 types, either singly or in any combinations.

In particular, mixtures of the solvents mentioned above are used. When alcoholic solvents are used, water can be a further component.

According to the invention, emulsions are advantageous and contain, for example, the mentioned fats, oils, waxes and other aliphatics, and water and an emulsifier as are conventionally used for such formulations.

Gels according to the invention conventionally contain low-carbon alcohols, for example ethanol, isopropanol, 1,2-propane diol, glycerin and water or one of the above-named oils in the presence of a thickening agent, which in the case of oil-alcohol gels is preferably silicon dioxide or an aluminum silicate, or in the case of aqueous-alcoholic or alcoholic gels is preferably a polyacrylate.

As a propellant for sprayable preparations in aerosol containers according to the invention, the conventionally known highly-volatile, liquidized propellants, for example hydrocarbons (propane, butane, isobutane) are suitable and can be used alone or in mixtures with each other. Compressed air can also be used advantageously.

Preparations according to the invention can furthermore advantageously contain substances that absorb UV-rays in the UVB range, whereby the total quantity of filter substance, for example 0.1 percent by weight to 30 percent by weight, preferably 0.5 to 10 percent by weight, in particular 1.0 to 6.0 percent by weight relative to the total weight of the preparations, in order to provide cosmetic preparations that protect the hair or the skin against the entire range of ultraviolet radiation. They can also be used as sun screens for the hair or the skin.

If the emulsions according to the invention contain UVB filtering agents, they can be oil-soluble or water-soluble. Advantageous oil-soluble UVB filters according to the invention include, for example:

- 3-benzylidene camphor derivatives, preferably 3-(4-methylbenzylidene) camphor, 3-benzylidene camphor;
- 4-amino benzoic acid derivatives, preferably 4-(dimethylamino)- benzoic acid (2-ethylhexyl) ester, 4-(dimethylamino) benzoic acid amyl ester;
- Esters of cinnamic acid, preferably 4-methoxycinnamic acid (2-ethylhexyl) ester, 4-methoxycinnamic acid isopentyl ester
- Esters of salicylic acid, preferably salicylic acid (2-ethylhexyl) ester, salicylic acid (4-isopropylbenzyl) ester, salicylic acid homomenthyl ester;
- Derivatives of benzophenone, preferably 2-hydroxy-4-methoxybenzophenone, 2-hydroxy-4-methoxy-4'-methlylbenzophenone, 2,2'-dihydroxy-4-methoxybenzophenone;
- Esters of benzalmalonic acid, preferably 4-methoxybenzalmalonic acid di(2-ethylhexyl)ester, -2,4,6-trianilinio-(p-carbo-2'-ethyl-1'-hexyloxy)-1,3,5 triazine.

Advantageous water-soluble UVB filters are, for example:

- Salts of 2-phenylbenzimidazol-5-sulfonic acid like its sodium, potassium, or its triethanol ammonium salt, and sulfonic acid itself;
- Sulfonic acid derivates of benzophenones, preferably 2-hydroxy-4-methoxybenzophenone-5-sulfonic acid and its salts;
- Sulfonic acid derivatives of 3-benzylidene camphor such as 4-(2-oxo-3-bornylidene methyl) benzene sulfonic acid, 2-methyl-5-(2-oxo-3-bornylidene methyl) sulfonic acid and its salts.

The list of cited UVB filters that can be used together with the active substance combinations according to the invention is, of course, not restricted.

The subject of the invention is also the use of a combination of adenosine with at least one UVB filter as an antioxidant, or the use of adenosine with at least one UVB filter as an antioxidant in a cosmetic or dermatological preparation.

It can also be advantageous if adenosine is combined with UVA filters that are conventionally contained in cosmetic preparations. These substances are preferably derivatives of dibenzoyl methane, in particular 1-(4'-tert.-butylphenyl)-3-(4'-methoxyphenyl) propane-1,3-dione and 1-phenyl-3-(4'-isopropylphenyl) propane-1,3-dione. The combinations or preparations that contain these combinations, are also the object of the invention. Those quantities used for the UVB combination can be used.

A subject of the invention is also the use of combinations of adenosine with at least one UVA filter as an antioxidant, or the use of a combination of adenosine with at least one UVA filter as an antioxidant in a cosmetic or dermatological preparation.

A subject of the invention is also the use of a combination of adenosine with at least one UVA filter and at least one UVB filter as an antioxidant, or the use of a combination of adenosine with at least one UVA filter and at least one UVB filter as an antioxidant in a cosmetic or dermatological preparation.

Cosmetic and dermatological preparations having an active adenosine content can also contain inorganic pigments that are conventionally used in cosmetics for the purpose of protecting the skin against UV rays. These are oxides of titanium, zinc, iron, zirconium, silicon, manganese, aluminum, cerium and mixtures thereof as well as alterations in which the oxides are the active substances.

Titanium-dioxide-based pigments are particularly preferred.

The cosmetic and dermatological preparations for the protection of hair against UV rays pursuant to the invention, are for example, shampoos, preparations applied when rinsing the hair before or after shampooing, before or after permanent waving, before or after dying or bleaching the hair, preparations for blow drying or setting the hair, preparations for dying or bleaching, hairdressing and treatment lotion, hair lacquer, or permanent waving agents.

The cosmetic and dermatological [preparations] contain active ingredients and adjuvants as in conventional preparations of this type for hair care and hair treatment. The adjuvants that are used are preservatives, surfactants, foam inhibiting substances, thickeners, emulsifiers, fats, oils, waxes, organic solvents, bactericides, perfumes, dyes or pigments whose purpose is to color the hair or the cosmetic or dermatological preparation itself, electrolytes, and substances against oily hair.

According to the present invention, electrolytes are understood to be water-soluble alkali, ammonia, alkaline earth (including magnesium) and zinc salts of inorganic anions and a variety of mixtures of said salts, whereby it must be assured that said salts are pharmaceutically and cosmetically safe.

The anions according to the invention are preferably chosen from the group of chlorides, sulfates and hydrogen sulfates, phosphates, hydrogen phosphates and linear and cyclic oligophosphates as well as carbonates and hydrogen carbonates.

Cosmetic preparations as represented by skin cleansing agents or shampoos preferably contain at least one anionic, non-ionic or amphoteric surface-active substance or also a mixture of said substances, adenosine in aqueous medium and an adjuvant as are conventionally used. The surface-active substances or the mixtures of said substances can be used at a concentration between 1 percent by weight and 60 percent by weight in the shampoo.

If the cosmetic and dermatological preparations are in the form of a lotion that is rinsed out, for example before or after bleaching, before or after shampooing, between two shampoo applications, before or after permanent wave treatment, then aqueous or water-alcohol solutions are used that may contain surface-active substances whose concentration can be between 0.1 and 10 percent by weight, preferably between 0.2 and 5 percent by weight

Said cosmetic or dermatological preparations can also be aerosols having the conventional adjuvants.

A cosmetic preparation in the form of a lotion that is not rinsed out, in particular a hair setting lotion, a lotion that is used when blow-drying hair, a hairdressing and treatment lotion

generally is an aqueous, alcoholic or water-alcohol solution and contains at least one cationic, anionic, non-ionic, or amphoteric polymer, or their mixture as well as adenosine in an effective concentration. The quantity of the polymers used is, for example, between 0.1 and 10 percent by weight, preferably between 01. and 3 percent by weight

Cosmetic preparations for the treatment and care of hair that contain adenosine can be non-ionic or anionic type emulsions. Along with water, non-ionic emulsions contain oils or fatty alcohols that can be also polyethoxylated or polypropoxylated, for example, or mixtures comprised of both organic components. Said emulsions may contain cationic surface-active substances.

According to the invention, cosmetic preparations for the treatment and care of the hair can be gels that, along with an effective concentration of adenosine and conventional solvents, preferably contain water, organic thickening agents such as gum arabic, xanthan gum, sodium alginate; derivatives of cellulose, preferably methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose or inorganic thickening agents like aluminum silicates such as bentonite, or a mixture of polyethylene glycol and polyethylene glycol stearate or distearate. The gel contains the thickening agent in a quantity e.g. between 0.1 and 30 percent by weight, and preferably between 0.5 and 15 percent by weight.

Preferably, the quantity of adenosine in a particular product for the hair is 0.05 percent by weight to 10 percent by weight, in particular 0.5 percent by weight to 5 percent by weight, relative to the total weight of the product.

According to the invention, aqueous cosmetic cleansing agents or low-water or anhydrous cleansing concentrates used for aqueous cleansing can contain anionic, non-ionic and/or amphoteric tensides, such as:

- conventional soaps, for example sodium salts of fatty acids
- alkyl sulfates, alkyl ether sulfates, alkane and alkylbenzene sulfonates
- sulfoacetate
- sulfobetaine
- sarcosinate
- amidosulfobetaine
- sulfosuccinate
- butanedioic acid half-ester
- alkylether carboxylate
- protein-fatty acid condensates
- alkyl betaine and amidobetaine
- fatty acid alkanolamide
- polyglycol ether derivatives

Cosmetic preparations that are cosmetic cleansing preparations for the skin can be in liquid or solid form. Along with adenosine, they preferably contain at least one anionic, non-

ionic or amphoteric surface-active substance or mixtures thereof, and one or a plurality of conventional electrolytes as desired. The surfactants can be present in the cleansing preparation at a concentration between 1 and 94% by weight relative to the total weight of the preparation.

Along with an effective concentration of adenosine, cosmetic preparations that are shampoos contain preferably at least one anionic, non-ionic or amphoteric surface-active substance or a mixture thereof, or possibly a conventional electrolyte and adjuvant according to the invention. The surface-active substance can be in a concentration between 1% by weight and 94% by weight in the shampoo.

In addition to the above-cited tensides, the preparations according to the invention contain water and possibly the conventional cosmetic additives such as fragrance, thickeners, dyes, deodorants, antimicrobial substances, moisturizing agents, complexing and sequestration agents, pearl luster agents, plant extracts, vitamins, active substances, and the like.

The present invention also includes a cosmetic process for protection of the skin and hair against oxidative or photoxidative processes which is characterized in that a cosmetic agent containing an effective adenosine concentration is applied in sufficient quantity to the skin or hair.

The adenosine content in said preparations is preferably 0.001% to 10 % by weight, and especially 0.01 to 6 percent by weight relative to the total weight of the preparations.

The subject of the invention is also the method for manufacturing the cosmetic products according to the invention and is characterized in that adenosine is incorporated into cosmetic and dermatological formulations in a manner known per se.

The following examples are intended to clarify the invention but not restrict it. All indications of quantities, portions and percentages, unless otherwise indicated, refer to the weight and the total quantity or to the total weight of the preparation.

Example 1

O/W Sunscreen Lotion

	Wt. %
Cetearyl alcohol	2.50
PEG-40 castor oil / sodium cetearyl sulfate	
Caprylic / capric triglyceride	4.00
Octyl stearate	4.00
Octyl methoxycinnamate	5.50
Butyl methoxydibenzolyl methyl	0.70
Cyclodimethicone	1.00
Carbomer	0.27
NaOH (45%)	0.22
Na_3 HEDTA	1.00

Butylene glycol	5.00
Adenosine	0.10
Preservative / fragrance	q.s.
Water, add until	100.00

Example 2

O/W After-Sun Lotion

	Wt.-%
Stearic acid	2.00
Glyceryl stearate	1.00
Isopropyl palmitate	6.00
Caprylic / capric triglyceride	5.00
Buxus chinensis	2.00
Carbomer	0.20
NaOH (45%)	0.20
Glycerin	5.00
Ethanol	5.00
Adenosine	0.10
Preservative / fragrance	q.s.
Water, add until	100.00

Example 3

O/W Sun Cream

	Wt.-%
Stearic acid	3.50
Octyl dodecanol	1.00
Isopropyl palmitate	5.00
Cyclomethicone	4.00
Methylbenzylidene camphor	1.00
Butyl methoxy dibenzoyl methane	3.00
Cetyl alcohol	1.00
Na_3 HEDTA	5.00
NaOH (45%)	1.00

Glycerin	0.40
Adenosine	0.10
Preservative / fragrance	q.s.
Water, add until	100.00

Example 4

O/W Cream

	Wt.-%
Trilaureth-4-phosphate	2.00
Cera microcristallina, paraffinum liquidum	5.00
Isopropyl palmitate	5.00
Cetyl alcohol	5.00
Adenosine	0.10
Glycerin	5.00
Preservative / fragrance	q.s.
Water, add until	100.00

Example 5

O/W Cream

	Wt.-%
Glyceryl stearate	3.00
Behenyl alcohol	5.00
Isopropylene palmitate	3.00
Octyl dodecanol	3.00
Glycerin	5.00
Adenosine	0.10
Preservative / fragrance	q.s.
Water, add until	100.00

Example 6

O/W Cream

	Wt.-%
Polyglyceryl-3-diisostearate	2.50

Paraffin oil	15.00
Ceresin	3.00
Magnesium stearate	3.00
Magnesium sulfate	0.70
Adenosine	0.10
Glycerin	3.00
Preservative / fragrance	q.s.
Water, add until	100.00

PATENT CLAIMS

1. The use of adenosine for enhancing cell proliferation in human skin.
2. The use of adenosine for combating and relief of the symptoms of exogenous aging of the skin, preferably in cosmetic or dermatological preparations.
3. The use of adenosine according to Claim 1 or 2, characterized in that the adenosine in cosmetic or dermatological preparations is present in concentrations of 0.01% by weight to 10% by weight but particularly 0.1% by weight to 6% by weight relative to the total weight of the preparations.

Table 1. Adenosine Does Not Stimulate Human Skin Fibroblast Proliferation

Skin Fibroblast Cell Strain	Age	Sex	Adenosine	Cell Number (% of control)	
AG09605	30	F	control	100	7
AG09605	30	F	10μM	104±14	7
AG11730	84	M	control	100	7
AG11730	84	M	10μM	102±9	7
AG09605	30	F	control	100	6
AG09605	30	F	100μM	102±7	6
AG11730	84	M	control	100	7
AG11730	84	M	100μM	93±13	7

Values are mean ± SEM. n=number of experiments. There was no significant difference in adenosine-treated cells compared to controls.

Attorney's Docket No. 7917-045002 / (UMMC 97-32)

11/declaration 1.132

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : James G. Dobson, Jr. and Michael F. Ethier
Art Unit : 16415
Examiner : L. Channavajjala
Serial No. : 09/672,348
Filed : September 28, 2000
Title : TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

Bet 3-15-02

Commissioner for Patents
Washington, D.C. 20231

DECLARATION UNDER 37 C.F.R. § 1.132

We, James G. Dobson, Jr., Ph.D. and Michael F. Ethier, declare that:

1. We are the co-inventors of the subject matter claimed in the patent application captioned above ("the present application").

2. The present application claims methods of enhancing the condition of unbroken skin of a mammal, but without increasing dermal cell proliferation. Excess skin cell proliferation can cause scarring, discoloration, and a variety of other skin anomalies associated with hyperplasia. The method claims recite applying to the skin a composition including a concentration of adenosine in an amount effective to enhance the condition of the skin without increasing dermal cell proliferation. These claims have been rejected by the U.S. Patent & Trademark Office Examiner in a Final Office Action dated October 10, 2001, as allegedly anticipated by German Patent No. DE 195 45 107 A1 ("the German patent application) and by Hartzshtark et al., Experentia, 41:378-379 (1985) ("Hartzshtark et al.). We have reviewed these two references, and based on a careful review of the references and our experimental test results, we believe that they do not disclose the methods claimed in our present application.

3. We have conducted testing to show that an important feature of our claimed methods is correct, i.e., that concentrations of adenosine recited in the pending claims do not increase

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I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, Washington, D.C. 20231.

February 13, 2002
Date of Deposit

Signature

Jeanine Mecherikanty
Typed or Printed Name of Person Signing Certificate

proliferation of a major type of dermal cells, i.e., skin fibroblasts. In this testing, we cultured skin fibroblasts from two subjects, a 30 year-old female and an 84 year-old male. For each experiment, we used 35 mm culture dishes plated with fibroblasts at a density of 1×10^4 cells/cm^2. Adenosine was added to dishes the following day. For each adenosine-treated dish, a matching control dish was treated with vehicle. After 5 days in culture, we counted the total number of cells in the control dish, and then in the test dish. For each pair of culture dishes, the number of cells in the control dish was designated as 100% and the number of cells in the adenosine-treated dish was expressed as a percentage of the control dish. In each experiment, the mean and standard error for adenosine-treated dishes was generated from the total number of samples (n = 6 or 7) for each test and expressed as a percent of the control. The adenosine concentrations and results are listed in Table 1 attached to this declaration as Exhibit A. As shown, adenosine concentrations of both 10 ☒M (10^{-5} M) and 100 ☒M (10^{-4} M) caused no significant change in cell proliferation, i.e., the number of cells did not change. Based on these results, we believe that lower adenosine concentrations, e.g., 10^{-6} M and 10^{-7} M, would also not increase cell proliferation.

4. Hartzshtark et al. states that certain concentrations of various agents, including adenosine, increase skin cyclic-AMP content and thus cause a decrease in skin indentation. More specifically, Hartzshtark et al. indicates in a Table on page 379 that the adenosine concentration effective to reduce indentation was 0.1% (3.8×10^{-3} M). In addition, they note that they also tested adenosine "at one-third of the concentrations shown in the table [e.g., about 1.27×10^{-3} M], and at this level [adenosine was] ineffective" (bottom of page 378 to top of page 379). The presently pending claims recite a maximum concentration of adenosine of 10^{-4} M, and require that there is no increase in dermal cell proliferation. The results in Hartzshtark indicate that a concentration of adenosine of 10^{-4} M or lower would be even less effective than one-third of 0.1% (1.27×10^{-3} M), which was ineffective in their testing.

5. We have obtained a translation of the German patent application, which is attached to this declaration as Exhibit B. Our comments are based on this translation. The German patent application describes the use of adenosine for increasing cell proliferation in human skin (see, e.g., the title and claim 1). However, our testing, as described above, has shown that low

concentrations of adenosine do not increase dermal cell proliferation. Thus, when the German patent application states that concentrations of adenosine as low as 0.001% are useful for increasing cell proliferation, we believe that the German patent application must be mistaken. There is one paragraph in the German patent application that states the 0.001% number, and this is in a very broad range from 0.001 to 10% by weight of a cosmetic composition (at page 9, 4th full paragraph). Other sections of the German patent application recite higher concentrations. For example, the claims, recite 0.01 to 10%, with a preferred concentration of 0.1 to 6%. More importantly, each of the six Examples lists a relatively high concentration of 0.1% adenosine. Thus, based on our own testing of skin fibroblasts, which make up a large part of the dermis, we believe that the extremely broad range of adenosine concentrations listed in the German patent application is not supported by reality. The low end of this unsupported range is 0.001%, which corresponds to 3.8×10^{-5} M adenosine. This is between the 10^{-4} M and 10^{-5} M concentrations recited in the claims of the present application. However, our claimed invention is based on the demonstration that the recited concentrations of adenosine do not increase cell proliferation. This is the exact opposite of the assertions in the German patent application. It is for these reasons that we believe the German patent application recitation of adenosine concentrations less than 10^{-4} M (0.00265%) cannot be valid, and thus the German patent application does not disclose the same invention as the claims in the present application.

We further declare that all statements made herein of our knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Applicant : James G. Dobson, and Michael F. Ethier
Serial No. : 09/672,348
Filed : September 28, 2000
Page : 4

Attorney's Docket 07917-045002 / (UMMC 97-32)

Date: 02/11/02

James G. Dobson, Jr., Ph.D

Date: 2/11/02

Michael F. Ethier, Ph.D

20387642.doc

Notice of Allowability	Application No.	Applicant(s)	
	09/672,348	DOBSON ET AL.	
	Examiner	Art Unit	
	Lakshmi S. Channavajjala	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *2-27-02 and 3-12-02*.
2. ☒ The allowed claim(s) is/are *70-79*.
3. ☐ The drawings filed on _____ are accepted by the Examiner.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____.
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.
5. ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
   (a) ☐ The translation of the foreign language provisional application has been received.
6. ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application. **THIS THREE-MONTH PERIOD IS NOT EXTENDABLE**

7. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

8. ☒ CORRECTED DRAWINGS must be submitted.
   (a) ☒ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☒ hereto or 2) ☐ to Paper No. ____.
   (b) ☐ including changes required by the proposed drawing correction filed _____, which has been approved by the Examiner.
   (c) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No. _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the top margin (not the back) of each sheet. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

9. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1☐ Notice of References Cited (PTO-892)
2☐ Notice of Informal Patent Application (PTO-152)
3☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
4☐ Interview Summary (PTO-413), Paper No.____.
5☐ Information Disclosure Statements (PTO-1449), Paper No. ____.
6☐ Examiner's Amendment/Comment
7☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
8☒ Examiner's Statement of Reasons for Allowance
9☐ Other

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

U.S. Patent and Trademark Office
PTO-37 (Rev. 04-01) **Notice of Allowability** Part of Paper No. 12

DETAILED ACTION

Receipt of request for extension of time & amendment, dated 2-27-02 and declaration dated 3-12-02 is acknowledged.

Allowable Subject Matter

Claims 70-79 are allowed.

The following is an examiner's statement of reasons for allowance:

Instant claims are directed to a method of enhancing the condition of unbroken skin by reducing wrinkling or dryness or laxity of skin, without increasing dermal cell proliferation, where the method comprises administering adenosine at a concentration of 10^{-4} M to 10^{-7} M, to the skin. The prior art of record teaches administering adenosine to skin for treating aging. However, the art of record utilizes concentrations much higher than claimed and also require that the amounts of adenosine used stimulate cell proliferation for the treatment. Whereas, instant claims are directed to treating skin without increasing the dermal cell proliferation. While the prior art does not recognize that increased cell proliferation result in adverse effects on skin such as discoloration, scarring etc., applicants have shown that using adenosine at the claimed concentrations do not result in adverse affects but still provide skin conditioning effects.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S. Channavajjala whose telephone number is 703-308-2438. The examiner can normally be reached on 7.30 AM -4.00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on 703-308-2927. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-7924 for regular communications and 703-308-7924 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Lakshmi S Channavajjala
Examiner
Art Unit 1615

March 18, 2002

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

#13
CK
6-17-02

OIPE JC174 JUN 03 2002 PATENT & TRADEMARK OFFICE

Attorney's Docket No.: 07917-045002 / (UMMC 97-32)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: James G. Dobson, Jr. and Michael F. Ethier	Art Unit	: 1615
Serial No.	: 09/672,348	Examiner	: L. Channavajjala
Filed	: September 28, 2000	Confirmation No.:	7733
Title	: TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG	Notice of Allowance Date:	March 21, 2002

BOX ISSUE FEE
Commissioner for Patents
Washington, D.C. 20231

COMMENTS ON STATEMENT OF REASONS FOR ALLOWANCE

These comments are submitted with applicants' Response to Notice of Allowance and payment of the issue fee in this application.

Applicants submit that the claims are allowable for at least all of the reasons of record in applicants' responses, and applicants do not concede that the Examiner's Statement of Reasons for Allowance is the only reason for which claims 70 to 79 are allowable. Futhermore, applicants note that the claimed concentration of adenosine is applied to the dermal cells.

No fees are believed due, however, please apply any charges or credits to our Deposit Account No. 06-1050, referencing Attorney Docket Number 07917-045002.

Respectfully submitted,

Date: May 17, 2002

J. Peter Fasse
Reg. No. 32,983

Fish & Richardson P.C.
225 Franklin Street
Boston, Massachusetts 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

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I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, Washington, D.C. 20231.

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Janet S. O'Connor
Typed or Printed Name of Person Signing Certificate

O I P E
JUN 0 3 2002
PATENT & TRADEMARK OFFICE

(2) 09/672,348

Attorney's Docket No.: 07917-045002 / (UMMC 97-32)

#13 $

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Dobson et al.	Art Unit :	1615
Serial No.	: 09/672,348	Examiner :	L. Channavajjala
Filed	: September 28, 2000	Confirmation No.:	7733
		Notice of Allowance Date: March 21, 2002	

Title : TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

BOX ISSUE FEE
Commissioner for Patents
Washington, D.C. 20231

RESPONSE TO NOTICE OF ALLOWANCE

In response to the Notice of Allowance mailed March 21, 2002, enclosed are a completed issue fee transmittal form PTOL-85b, transmittal of 2 sheets of formal drawings, Applicants' Comments on Statement of Reasons for Allowance, and a check for $670 for the required fee, including patent copies.

Please apply any additional charges or credits to our Deposit Account No. 06-1050, referencing attorney docket number 07917-045002.

Respectfully submitted,

Date: May 17, 2002

J. Peter Fasse
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Janet S. O'Connor
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TAB 03

10184810.062802

Attorney's Docket N. 7917-045003 / UMMC 97-32

APPLICATION

FOR

UNITED STATES LETTERS PATENT

TITLE: TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

APPLICANT: JAMES G. DOBSON AND MICHAEL F. ETHIER

CERTIFICATE OF MAILING BY EXPRESS MAIL

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6/28/02
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Signature

Leroy Jenkins
Typed or Printed Name of Person Signing Certificate

9/95

10184810.062802

PATENT
ATTORNEY DOCKET NO: 07917/045002

TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

Statement as to Federally Sponsored Research

Work on this invention was supported by funds from the United States government (Public Health Service Grants HL-22828 and AG-11491). The government therefore has certain rights in this invention.

Field of the Invention

This invention relates to dermatology and cell biology.

Background of the Invention

Skin includes a surface layer, known as the epidermis, and a deeper connective tissue layer, known as the dermis. The epidermis undergoes continuous turnover as the outermost cells are exfoliated and replaced by cells that arise from inner dermal layers. The dermis is composed of a variety of cell types, including fibroblasts.

Skin thickness begins to decline in humans after the age of 20 as the dermis becomes thinner and the number of skin fibroblasts declines. As skin ages, or is exposed to UV light and other environmental insults, changes in the underlying dermis can lead to the functional and morphological changes associated with damaged skin. Decreases in the abundance and function of products of the fibroblasts, which include collagen and proteoglycans, are believed to play major roles in wrinkled and damaged skin.

Summary of the Invention

We have discovered that adenosine stimulates DNA synthesis, increases protein synthesis, and increases cell size in cultures of human skin fibroblasts. Based on this discovery, the invention provides methods and compositions for enhancing the condition of skin.

In general, the invention provides a method for enhancing the condition of non-diseased skin of a mammal, e.g., a human. The method includes topically applying a therapeutically effective amount of a composition including adenosine or an adenosine analog to non-diseased skin of the mammal.

The invention also provides a method for promoting healing of broken, non-diseased skin in a mammal by topically administering a composition including a therapeutically effective amount of adenosine or an adenosine analog to the mammal.

Also included in the invention is a method for increasing DNA synthesis in a dermal cell of non-diseased skin of a mammal. The method includes topically administering a therapeutically effective amount of adenosine or an adenosine analog to a region of non-diseased skin of the mammal containing dermal cell. The adenosine is added so that it does not cause proliferation of the dermal cell.

The invention also features a method of increasing protein synthesis in a dermal cell of non-diseased skin of a mammal. The method includes topically administering a composition including a therapeutically effective amount of adenosine or an adenosine analog to a region of skin of the mammal containing the dermal cell. The adenosine or adenosine analog does not cause proliferation of the dermal cell.

Also provided in the invention is a method of increasing cell size in a dermal cell in non-diseased skin of a mammal, e.g., a human. The method includes topically administering a composition including a therapeutically effective amount of adenosine to a region of skin of the mammal containing the dermal cell, wherein addition of the adenosine does not cause proliferation of the dermal cell, wherein addition of the adenosine does not cause proliferation of the dermal cell.

The invention also includes a method for enhancing skin condition in a mammal, e.g., a human. The method includes providing fibroblasts from the mammal *ex vivo*, culturing the fibroblasts in the presence of adenosine, and reintroducing the fibroblasts into the mammal.

The therapeutically effective amount of adenosine used in the above-described methods is preferably 10^{-3} M to 10^{-7} M, more preferably 10^{-4} M to 10^{-6} M, and most preferably about 10^{-4} M.

The composition used in the above-described methods can include a second agent in addition to adenosine. The second agent can be, e.g. an agent that promotes binding of adenosine or an adenosine analog to an adenosine receptor, an angiogenic factor such as vascular endothelial cell growth factor (VEGF), basic fibroblast growth factor (BFGF), an agent that itself enhances skin condition, such as tretoinin or another known conditioning agent such as an emollient, a humectant, or an occlusive agent.

In preferred embodiments of the invention, the adenosine or an adenosine analog does not promote skin cell proliferation.

The invention also provides a composition including about 10^{-3} M to about 10^{-7} M adenosine and a therapeutically effective amount of an angiogenesis factor. In some

embodiments, the composition of the adenosine is about 10^{-4} M.

As used herein, "enhancement of skin condition" means a noticeable decrease in the amount of wrinkling, roughness, dryness, laxity, sallowness, or pigmentary mottling in skin.

As used herein, a "therapeutically effective amount" of adenosine or an adenosine analog means an amount that enhances skin condition when applied to skin.

As used herein, "non-diseased skin" means skin free of any proliferative disorder observable by visual inspection.

The present invention advantageously allows for enhancement of skin condition. This results in skin that shows a less wrinkled, rough, or dry complexion. For example, the invention provides for enhancing the condition of skin damaged due to exposure to the sun or skin whose condition has deteriorated due to normal aging.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

Other features and advantages of this invention will be apparent from the following description of the preferred embodiments thereof, and from the claims.

Brief Description of the Drawings

Figs. 1A and 1B are histograms showing the effect of adenosine on [^{3}H]thymidine incorporation in cultures of normal human skin (Fig. 1A) and lung fibroblasts (Fig. 1B). After incubation in serum-free medium for 24 hours, cells were exposed to 10^{-4} M adenosine for 18 hours. Medium was replaced with serum-free medium without adenosine, and [^{3}H]thymidine was added. Results are expressed as percent [^{3}H]thymidine incorporation compared to control cultures without adenosine and are means ± SEM for 4-5 experiments. "*" denotes value was significantly different from control value without adenosine.

Figs. 2A and 2B are histograms showing concentration responses of adenosine-stimulated protein synthesis in human skin fibroblasts from a young (Fig. 2A) and aged (Fig. 2B) donor. Cells were grown to 75% confluence. Medium was then replaced with serum-free medium with or without adenosine. After 48 hours, [^{3}H]phenylalanine incorporation was determined as described. Results are expressed as % [^{3}H]phenylalanine incorporation compared to control cultures without adenosine and are means ±SEM for 6-25 experiments. "*" denotes value was significantly different from control value without adenosine.

Detailed Description

The invention is suitable for treating skin of a mammal, e.g., a human, for which promotion of fibroblast-associated dermal functions is desired. For example,

promotion of fibroblast-associated functions is desirable in enhancing the condition of aged skin, which is associated with a decrease in dermal cell function and is characterized by increased dryness or roughness, or both. The method can also be used on subjects having otherwise damaged skin, *e.g.*, wrinkled skin and skin with a non-proliferative disorder. The method can may further be used prophylactically on a subject to minimize deterioration of skin condition associated with aging or environmental factors, such as photodamage.

Adenosine and suitable adenosine analogs are suitable for use in enhancing skin condition. Adenosine analogs such as adenosine agonists, adenosine receptor agonists, and compounds that increase intracellular or extracellular adenosine levels are suitable for use in the invention.

Agonists of adenosine include 2'-deoxyadenosine; 2',3'-isopropoylidene adenosine; toyocamycin; 1-methyladenosine; N-6-methyladenosine; adenosine N-oxide; 6-methylmercaptopurine riboside; 6-chloropurine riboside, 5'-adenosine monophosphate, 5'-adenosine diphosphate, or 5'-adenosine triphosphate. Adenosine receptor agonists include phenylisopropyl-adenosine ("PIA"), 1-Methylisoguanosine, ENBA (S(-), N^6-Cyclohexyladenosine (CHA), N^6-Cyclopentyladenosine (CPA), 2-Chloro-N_6-cyclopentyladenosine, 2-chloroadenosine, and adenosine amine congener (ADAC), all of which are agonists for the adenosine A_1 receptor. Other receptor agonists include 2-p-(2-carboxy-ethyl) phenethyl-amino-5'-N-ethylcarboxamido-adenosine (CGS-21680), N-ethylcarboxamido-adenosine (NECA) and napthyl-substituted aralkoxyadenosine (SHA-082), 5'(N-Cyclopropyl)-carboxamidoadenosine, DPMA (PD 129,944), Metrifudil, which are agonists for the adenosine A_2

receptor. Other adenosine receptor agonists include those which preferentially bind the A_1 receptor relative to the A_2 receptor, such as 2-Chloroadenosine, N^6-Phenyladenosine, and N^6-Phenylethyladenosine; and those which preferentially bind the A_2 receptor relative to the A_1 receptor, such as 2-Phenylaminoadenosine and MECA.

Also suitable for use are compounds that increase intracellular adenosine concentration by inhibiting the cellular uptake of adenosine or the breakdown of adenosine. One pathway of adenosine metabolism is the conversion of adenosine to inosine by adenosine deaminase. An example of an adenosine deaminase inhibitor is erythro-9-(2-hydroxy-3-nonyl) adenine ("EHNA"). Adenosine kinase inhibitors can also be used. Adenosine kinase converts adenosine to adenosine monophosphate by adenosine kinase. An example of an adenosine kinase inhibitor is iodotubercidin. Other suitable compounds include those that inhibit the dipyridamole-sensitive nucleoside transporter, which exports adenosine from the cytoplasm, and agents that promote the activity of a 5'-nucleotidase, e.g., the ATP-activated 5'-nucleotidase, which forms adenosine. Compounds that increase tissue adenosine and ATP levels include acadesine (AICA-riboside), which is described in Gruber et al., Circulation 80:1400-1411 (1989).

Adenosine can be also be administered with a second compound. The second compound can enhance the action of adenosine or the adenosine analog, e.g., by enhancing binding of adenosine or an adenosine analog to an adenosine receptor. An example of such a compound is PD 81,728, which is described in Kollias-Baker et al. J. Pharmacol. Exp. Ther. 281:761-68. Alternatively, the second agent can itself act to enhance skin condition. Examples of these types of agents include tretinoin, a recognized skin

conditioning agent (see, e.g., Olsen et al., J. Amer. Acad. Dermatol. 37:217-26, 1997), an angiogenic factor such as vascular endothelial cell growth factor (VEGF) or basic fibroblast growth factor (BFGF), or a conditioning agent.

The second compound can also be a conditioning agent such as an emollient, humectant, or occlusive agent. Numerous examples of particular conditioning agents are provided in the CTFA Cosmetic Ingredient Handbook (Cosmetic Toiletries and Fragrances Association, Washington, D.D., 1988). Emollients help to maintain the soft, smooth, and pliable appearance of skin and function by remaining on the skin surface or in the stratum corneum to act as lubricants, to reduce flaking, and to improve the skin's appearance. Examples of emollients include acetyl trioctyl citrate, cetyl alcohol, butyl myristate, cetyl alcohol, and mineral oil.

Humectants act to increase the water content of the top layers of the skin. Humectants include, *e.g.*, acetamide MEA, fructose, and xylitol. Occlusive agents inhibit the evaporation of water from skin, thereby increasing the water contend of the skin. Acetylated castor oil, mineral oil, and lauryl stearate are examples of occlusive agents.

A subject can be treated by applying adenosine or an adenosine analog in a pharmaceutical composition in an effective amount and for a period of time sufficient to improve the condition of the skin.

The pharmaceutical composition may be formulated using conventional methods to prepare pharmaceutically useful compositions. Such compositions preferably include at least one pharmaceutically acceptable carrier, such as those described in Remington's Pharmaceutical Sciences (E.W. Martin). In addition, the compositions preferably include a pharmaceutically acceptable buffer, preferably phosphate

buffered saline, together with a pharmaceutically acceptable compound for adjusting isotonic pressure, such as, for example, sodium chloride, mannitol, or sorbitol.

Adenosine or an adenosine agonist can also be provided in carriers and adjuvants such as ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances, such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances and polyethylene glycol. Adjuvants for topical or gel base forms of adenosine or adenosine analogs may, for example, be selected from the group consisting of sodium carboxymethylcellulose, polyacrylates, polyoxythylene-polyoxypropylene-block polymers, polyethylene glycol and wood wax alcohols. For all administrations, conventional depot forms may be used.

The adenosine or adenosine analog-containing compositions may be in any pharmaceutically acceptable dosage form. They are preferably applied by topical routes to exert local therapeutic effects. For topical application, the penetration of the adenosine into skin tissue may be enhanced by a variety of methods known to those of ordinary skill in the art. For example, adenosine may be applied directly and mechanically rubbed into the skin. Alternatively, adenosine or adenosine analogs may be incorporated into a transdermal patch that is applied to the skin. Preferably, the penetration resulting from these methods is enhanced with a chemical transdermal delivery agent such as dimethyl sulfoxide (DMSO) or the nonionic

surfactant, n-decylmethyl sulfoxide (NDMS), as described in Choi et al., Pharmaceutical Res., 7(11):1099, 1990.

Other modes of administration include, e.g., oral, subdermal, intradermal, or intravenous. When oral administration is used, it is critical that the adenosine or adenosine analog be delivered to that it is not degraded prior to exiting the digestive system.

The most effective mode of administration and dosage regimen of adenosine or the adenosine analog will depend upon the skin condition, previous therapy, the subject's health status, response to the adenosine, the judgment of the treating physician and the mode in which the adenosine is applied. For example, dosages for a therapeutically effective amount for topical application would be in the range of 100 ng to 10 mg per treated surface area per day. The adenosine may be administered to the patient at one time or over a series of treatments. When adenosine or the adenosine analog is administered in conjunction with a second agent, they can be administered either concurrently or sequentially, and can be administered in the same mode or a different mode, e.g., topical or oral.

Adenosine or an adenosine analog enhances skin condition when there is a noticeable decrease in noticeable decrease in the amount of wrinkling, roughness, dryness, laxity, sallowness, or pigmentary mottling of the treated skin. Methods of measuring improvements in skin condition are well known in the art (see, e.g., Olsen et al., J. Amer. Acad. Dermatol. 26:215-24, 1992), and can include subjective evaluations by the patient or a second party, e.g., a treating physician. Objective methods can include skin topography measurements, such as those described in Grove et al., J. Amer. Acad. Dermatol. 21:631-37 (1989). In skin topography measurements, silicone rubber replicas are made

of a small area of skin, e.g., a 1 cm diameter circular area. The silicone rubber replicas capture fine lines and wrinkles on the skin. These specimens are then analyzed using computerized digital image processing to provide an objective measurement of the skin's topography. Skin topography measurements generated following digital-image processing can be measured using the values R_a and R_z as described in Olsen et al., J. Amer. Acad. Dermatol. 37:217-26, 1997, where R_a represents the area of deviation of skin surface features above and below an average central line, and R_z represents the difference between the maximum and minimum heights in five equal segments of the skin surface profile. A statistically significant decline (e.g., $P < 0.05$) in R_a and R_z values in skin treated with adenosine or an adenosine analog compared to untreated skin indicates an enhancement of skin condition.

Fibroblasts treated with adenosine or adenosine analogs can also be incorporated into a matrix and implanted in the body, e.g., as part of a skin graft. In addition, fibroblasts can be genetically engineered ex vivo to increase the amount of intracellular adenosine levels and then re-introduced into a human patient. (See, for example, Anderson et al. U.S. Patent No. 5,399,349; and Mulligan & Wilson, U.S. Patent No. 5,460,959, each of which is incorporated by reference herein in its entirety).

Experimental Information

Cell Culture

Human skin fibroblasts and human lung fibroblasts were supplied by the N.I.A. Aging Culture Repository Center (Camden, NJ). For skin fibroblasts, primary cultures had been initiated from explants obtained from a 3 mm punch biopsy of the mesial aspect of the upper left arm. Human

lung fibroblasts (IMR-90) were established from a 16-week normal female fetus. All cells displayed a normal diploid karyotype and all cells tested negative for bacteria, fungi and mycoplasma contamination.

Cells were grown in Eagle's minimal essential medium (MEM) supplemented with 10% fetal bovine serum (FBS), 100 U/ml penicillin and 100 mg/ml streptomycin in a 37°C, 5% CO_2/95% air environment. After reaching confluence, cells were subcultivated with 0.25% trypsin in MEM with no added Ca^{2+} or Mg^{2+}.

Incorporation of [^{3}H]Thymidine

As an index of DNA synthesis incorporation of [^{3}H]thymidine was measured as described in Ethier et al., Am. J. Physiol. 272:H1470-79 (1997). Confluent monolayers of human skin fibroblasts in MEM plus 10% FBS were seeded into 16 mm diameter culture wells (24-well plates) at a density of 1 x 10^4 cells/cm^2. Cells were grown at 37°C under standard culture conditions (5% CO_2-95% air) until they were approximately 75% confluent. Medium was then removed and the cells were made "serum-free" by incubation in MEM with no FBS for 24 hours. Adenosine or vehicle (MEM) was added for an additional 18 hours. This medium was then replaced with fresh MEM, and the cells were pulsed with 1mCi/ml [^{3}H] thymidine (6.7 Ci/mmol). After a 2 hour incubation period, the medium was discarded and the cells were rinsed twice with cold (4°C) Hank's balanced salt solution (HBSS) and incubated for 5 minutes with 0.5 ml cold 10% (w/v) trichloroacetic acid (TCA). The wells were then rinsed with 8% TCA and the TCA-insoluble material was solubilized with 0.5 ml of a solution of 0.2M NaOH and 0.2% sodium decyl sulfate (SDS). The radioactivity of this

fraction was determined by standard liquid scintillation spectrometric techniques.

Incorporation of [^{3}H] thymidine was expressed as counts per minute (cpm) of ^{3}H per culture. Data in each experiment was derived from 4 identically treated wells. Since the cpm/well exhibited variation between experiments, data representing combined experiments are expressed herein as a percent of their respective mean control value.

Incorporation of [^{3}H]phenylalanine

Incorporation of [^{3}H]phenylalanine was measured as an index of protein synthesis. Human skin fibroblasts were seeded into 24-well culture plates in MEM containing 10% FBS. When cells had grown to approximately 75% confluence the culture medium was replaced with serum-free MEM with or without adenosine. After 48 hours, 2μCi/ml [^{3}H]phenylalanine was added to the cultures. Unlabeled phenylalanine (0.36 mM) was also added to equalize concentrations of intracellular and extracellular phenylalanine. After 8 hours, medium was removed and the cells were washed twice with cold (4°C) HBSS and incubated for 20 minutes in cold 10% (w/v) TCA. Cells were then incubated 5 minutes in 95% ethanol (4°C) and the TCA-insoluble material was solubilized with a solution of 0.2M NaOH and 0.2% SDS. The radioactivity of this fraction was determined by standard liquid scintillation spectrometric techniques.

Incorporation of [^{3}H] phenylalanine was expressed as cpm of ^{3}H per culture well and data in each experiment were derived from six identically treated wells. Since the cpm/well exhibited variation between experiments, data representing combined experiments are expressed as a percent of their respective mean control value.

Determination of Cell Size

Human fibroblasts in MEM 10% FBS were seeded into 25 cm^2 culture flasks at a density of 1×10^4 cells/cm^2. When the cells had grown to approximately 80% confluence the culture medium was removed and the cells were incubated in serum-free MEM for 24 hours. Adenosine or vehicle (MEM) was added for 18 hours and cells were then washed twice with cold (4°C) HBSS. Cells were removed with 0.25% trypsin in calcium-and magnesium-free MEM and diluted in cold (4°C) HBSS for measurement of relative cell size with a fluorescence-activated cell sorter (FACS; Becton Dickinson Vantage). Cell size was determined by forward light scatter on a minimum of 1×10^4 cells per experiment.

Experimental Materials

MEM, FBS, penicillin, streptomycin, trypsin, and HBSS were obtained from GIBCO (Grand Island, NY), [^{3}H] thymidine (6.7 Ci/mmol) and phenylalanine, L-ring-2,3,4,5,6-^{3}H] (92 Ci/mmol) were obtained from Dupont NEN (Boston, MA). Adenosine was from Boehringer Mannheim, SDS was from National Diagnostics, (Highland Park, NJ) and TCA and ethanol were obtained from Fisher Scientific (Pittsburgh, PA).

Data Analysis

Analysis of variance (ANOVA) was used to determine statistical differences between means. The Dunett's test was applied for multiple comparisons as described in Zar, J.H., Biostatistical Analysis. Englewood Cliffs, N.J., Prentice Hall, Inc. pp. 150-153, 1984. In addition, the Wilcoxon test was employed to verify differences between values expressed as a percentage. Differences were considered statistically different when $P < 0.05$.

DNA Synthesis

Exposure to 10^{-4}M adenosine increased [^{3}H]thymidine incorporation by 43 ±9% in five studies on cultures of human fibroblasts (AG607720B) made quiescent by serum removal. These results are summarized in Fig. 1A. In contrast, adenosine (10^{-4}M) had no effect on [^{3}H]thymidine incorporation in cultures of human lung fibroblasts (IMR-90) (Fig. 1B). Concentrations of adenosine ranging from 10-7 M to 10^{-3}M also failed to stimulate [^{3}H]thymidine incorporation in IMR-90 lung fibroblasts (data not shown).

The effect of adenosine on DNA synthesis was additionally determined on skin fibroblast cultures from six different human donors. Adenosine (10^{-4}M) stimulated DNA synthesis in all three cultures derived from young human donors (Table 1). Values shown are means ±SEM, where *n* is number of experiments. Exposure to adenosine and determination of [^{3}H] thymidine incorporation were as described above. The asterisk denotes a value significantly different from the corresponding control (100%).

Table 1. Effect of adenosine on [^{3}H]thymidine incorporation into cultured human skin fibroblasts derived from young donors

Cell Strain	Adenosine (10^{-4} M)	Donor		[^{3}H]thymidine incorporation (% of control)	*n*
		Age	Sex		
AG07720B	-	24	F	100	24
	+			124±7*	24
AG07306A	-	28	F	100	6
	+			193±20*	6
AG09605	-	30	M	100	12
	+			133±15*	12

Peak stimulation of [^{3}H]thymidine incorporation (93±20%, n=6) was achieved in human skin fibroblast cultures derived from a 28 year old female (AG07306A).

Adenosine (10^{-4}M) stimulated DNA synthesis in 2 of 3 cultures derived from aged human donors (Table 2). As in Table 1, values are means ±SEM, and *n* is the number of experiments performed. The asterisk denotes a measurement significantly different from the corresponding control (100%). Adenosine exposure increased [^{3}H]thymidine incorporation by 53±31% and 54 ±22% in human skin fibroblast cultures derived from a 70 year-old male and a 84 year-old male, respectively. Adenosine had no effect on cultures derived from a 67-year old female.

Table 2. Effect of adenosine on [^{3}H]thymidine incorporation into cultured human skin fibroblasts derived from aged donors

Cell Strain	Adenosine (10^{-4} M)	Donor		[^{3}H]thymidine incorporation (% of control)	*n*
		Age	Sex		
AG11728	-	67	F	100	6
	+			91±6	6
AG12949	-	70	M	100	11
	+			150±31*	11
AG11730	-	84	M	100	10
	+			154±22*	10

Protein Synthesis

The effect of adenosine on protein synthesis was determined by measuring [^{3}H]phenylalanine incorporation into cultures of human fibroblasts from a young and aged donor. Cultures made quiescent by serum removal were exposed to adenosine (10^{-6}M to 10^{-4}M) for 48 hours and then pulsed with phenylalanine. In skin fibroblast cultures derived from a 28-year old female (AG073060A) and an 84-year old male (AG11730), adenosine(10^{-4}M) increased protein synthesis by 13 ± 4% (n=25) and 13 ± 6% (n=17), respectively (Fig. 2).

Cell Size

The effect of adenosine on cell size was determined on human skin fibroblasts from young and aged donors by measuring forward light scatter in a FACS analyzer. Cultures made quiescent by serum removal were exposed to adenosine for 18 hours, removed by trypsinization, and

diluted in 4°C HBSS. A minimum of 1×10^4 cells were measured for each experiment. The results are shown in Table 2. Values are mean ± SEM for relative cell size determined by forward light scatter (FLS) in a fluorescence-activated cell sorter, and *n* = number of cells measured. The asterisk denotes the measurement is significantly different from corresponding control.

In skin fibroblast cultures from a 28 year old female (AG073060A) adenosine (10^{-4}M) significantly increased cell size by 1.8 and 2.2% in two of three experiments (Table 3).

The effect of adenosine on cell size was also measured on skin fibroblasts from an aged donor. The results are shown in Table IV. Values are mean ± SEM for relative cell size determined by forward light scatter (FLS) in a fluorescence-activated cell sorter, where *n* is the number of cells measured. An asterisk indicates a value significantly different from corresponding control.

In cultures derived from an 84-year old male (AG11730), adenosine (10^{-4}M) significantly increased cell size by 2.7-4.9% in 3 of 3 experiments (Table 4).

Table 3. Effect of adenosine on cell size in cultured human skin fibroblasts derived from young donors

Experiment Number	Adenosine (10^{-4} M)	Relative Size (FLS)	% increase	*n*
1	-	524±0.55	-	1.5×10^4
	+	526±0.55	0.4	1.5×10^4
2	-	319±1.24	-	1.0×10^4
	+	326±1.16*	2.2*	1.0×10^4
3	-	342±0.94	-	1.0×10^4
	+	348±0.95*	1.8*	1.0×10^4

Table 4. Effect of adenosine on cell size in cultured human skin fibroblasts derived from aged donors

Experiment Number	Adenosine (10^{-4} M)	Relative Size (FLS)	% increase	*n*
1	-	333±0.79	-	1.0×10^4
	+	342±0.75*	2.7*	1.0×10^4
2	-	323±1.01	-	1.0×10^4
	+	337±0.96*	4.3*	1.0×10^4
3	-	306±0.81	-	1.0×10^4
	+	321±0.81*	4.9*	1.0×10^4

Other Embodiments

While the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention. For example, while the

invention has been described using adenosine and adenosine agonists, other compounds structurally similar to adenosine can also be used, e.g., purine-containing compounds and compounds having a ribosyl moiety. Other aspects, advantages, and modifications of the invention are within the scope of the following claims.

We claim:

Claims

1. A method for enhancing the condition of non-diseased skin of a mammal, comprising topically applying a therapeutically effective amount of a composition comprising adenosine or an adenosine agonist to non-diseased skin of said mammal.

2. The method of claim 1, wherein said composition further comprises an angiogenic factor.

3. The method of claim 1, wherein the therapeutically effective amount of adenosine is an adenosine concentration of 10^{-3} M to 10^{-7} M.

4. The method of claim 3, wherein said adenosine concentration is 10^{-4} M to 10^{-6} M.

5. The method of claim 4, wherein said adenosine concentration is about 10^{-4} M.

6. The method of claim 1, wherein said composition further comprises a conditioning agent.

7. The method of claim 6, wherein said conditioning agent is selected from the group consisting of a humectant, an emollient, and occlusive agent.

8. The method of claim 1, wherein addition of adenosine does not affect skin cell proliferation.

9. The method of claim 1, wherein said skin comprises a skin graft.

10. The method of claim 1, wherein said mammal is a human.

11. A method for promoting healing of broken, non-diseased skin in a mammal, comprising topically administering a composition comprising a therapeutically effective amount of adenosine or an adenosine agonist to said mammal.

12. The method of claim 11, wherein said composition further comprises an angiogenic factor.

13. The method of claim 11, wherein the therapeutically effective amount of adenosine is an adenosine concentration of 10^{-3} M to 10^{-7} M.

14. The method of claim 13, wherein said adenosine concentration is 10^{-4} M to 10^{-6} M.

15. The method of claim 14, wherein said adenosine concentration is about 10^{-4} M.

16. The method of claim 11, wherein said composition further comprises a conditioning agent.

17. The method of claim 16, wherein said conditioning agent is selected from the group consisting of a humectant, an emollient, and occlusive agent.

18. The method of claim 11, wherein addition of adenosine does not affect skin cell proliferation.

19. The method of claim 11, wherein said region of skin comprises a skin graft.

20. The method of claim 11, wherein said mammal is a human.

21. A method for increasing DNA synthesis in a dermal cell of non-diseased skin of a mammal, comprising topically administering a therapeutically effective amount of adenosine to a region of non-diseased skin of said mammal containing said dermal cell, wherein addition of said adenosine does not cause proliferation of said dermal cell.

22. The method of claim 21, wherein said composition further comprises an angiogenic factor.

23. The method of claim 21, wherein the therapeutically effective amount of adenosine is an adenosine concentration of 10^{-3} M to 10^{-7} M.

24. The method of claim 23, wherein said adenosine concentration is 10^{-4} M to 10^{-5} M.

25. The method of claim 24, wherein said adenosine concentration is about 10^{-4} M.

26. The method of claim 21, wherein said composition further comprises a conditioning agent.

27. The method of claim 26, wherein said conditioning agent is selected from the group consisting of a humectant, an emollient, and occlusive agent.

28. The method of claim 21, wherein said region of skin comprises a skin graft.

29. The method of claim 21, wherein said mammal is a human.

30. A method of increasing protein synthesis in a dermal cell of non-diseased skin of a mammal, comprising topically administering a composition comprising a therapeutically effective amount of adenosine to a region of skin of said mammal containing said dermal cell, wherein addition of said adenosine does not cause proliferation of said dermal cell.

31. The method of claim 30, wherein said composition further comprises an angiogenic factor.

32. The method of claim 30, wherein the therapeutically effective amount of adenosine is an adenosine concentration of 10^{-3} M to 10^{-7} M.

33. The method of claim 32, wherein said adenosine concentration is 10^{-5} M to 10^{-6} M.

34. The method of claim 33, wherein said adenosine concentration is about 10^{-4} M.

35. The method of claim 30, wherein said composition further comprises a conditioning agent.

36. The method of claim 35, wherein said conditioning agent is selected from the group consisting of a humectant, an emollient, and occlusive agent.

37. The method of claim 30, wherein said region of skin comprises a skin graft.

38. The method of claim 30, wherein said mammal is a human.

39. A method of increasing cell size in a dermal cell in non-diseased skin of a mammal, comprising topically administering a composition comprising a therapeutically effective amount of adenosine to a region of skin of said mammal containing said dermal cell, wherein addition of said adenosine does not cause proliferation of said dermal cell, wherein addition of said adenosine does not cause proliferation of said dermal cell.

40. The method of claim 39, wherein said composition further comprises an angiogenic factor.

41. The method of claim 39, wherein the therapeutically effective amount of adenosine is an adenosine concentration of 10^{-3} M to 10^{-7} M.

42. The method of claim 41, wherein said adenosine concentration is 10^{-4} M to 10^{-6} M.

43. The method of claim 42, wherein said adenosine concentration is about 10^{-4} M.

44. The method of claim 39, wherein said composition further comprises a conditioning agent.

45. The method of claim 44, wherein said conditioning agent is selected from the group consisting of a humectant, an emollient, and occlusive agent.

46. The method of claim 39, wherein said region of skin comprises a skin graft.

47. The method of claim 39, wherein said mammal is a human.

48. A method for enhancing skin condition in a mammal, comprising

providing fibroblasts from said mammal *ex vivo*,

culturing said fibroblasts in the presence of adenosine; and

reintroducing said fibroblasts into said mammal.

49. The method of claim 48, wherein the adenosine concentration in said culturing step is from about 10^{-3} M to about 10^{-7} M.

50. A method for increasing protein synthesis in a cultured skin fibroblast, comprising culturing said fibroblast in a culture medium comprising about 10^{-3} M to about 10^{-7} M adenosine.

51. The method of claim 50, wherein the adenosine concentration is about 10^{-4} M.

52. A composition comprising 10^{-3} M to 10^{-7} M adenosine and an angiogenesis factor.

53. The composition of claim 52, wherein the concentration of said adenosine is about 10^{-4} M.

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#6 B 1615 2-4-03

Attorney's Docket No.: 07917-045003 / (UMMC 97-7)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : James G. Dobson et al. Art Unit : 1615
Serial No. : 10/184,810 Examiner : L. Channavajjala
Filed : June 28, 2002
Title : TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

Commissioner for Patents
Washington, D.C. 20231

RESPONSE TO OFFICE ACTION DATED OCTOBER 28, 2002

Please amend the application as indicated below and consider the following remarks.

In the Claims:

Please cancel claims 1 to 10, 52 and 53 without prejudice.

Please add new claims 54 to 63 as follows:

1 54. A method for enhancing the condition of unbroken skin of a mammal by reducing one or more of wrinkling, roughness, dryness, or laxity of the skin, without increasing dermal cell proliferation, the method comprising topically applying to the skin a composition comprising a concentration of adenosine in an amount effective to enhance the condition of the skin without increasing dermal cell proliferation, wherein the adenosine concentration applied to the dermal cells is 10^{-3} M to 10^{-7} M.

B1 2 55. The method of claim 1 54, wherein the composition further comprises an angiogenic factor.

3 1 56. The method of claim 1 54, wherein the adenosine concentration is 10^{-3} M to 10^{-6} M.

4 1 57. The method of claim 1 54, wherein the adenosine concentration is about 10^{-3} M.

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, Washington, D.C. 20231.

1/9/03
Date of Deposit

Dawn Marie Class
Signature

Dawn Marie Class
Typed or Printed Name of Person Signing Certificate

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58. The method of claim 54, wherein the composition further comprises a conditioning agent.

59. The method of claim 58, wherein the conditioning agent is a humectant, an emollient, or an occlusive agent.

60. The method of claim 59, wherein the mammal is a human.

61. The method of claim 54, wherein the skin comprises a skin graft.

62. The method of claim 54, wherein the composition further comprises a transdermal delivery agent.

63. The method of claim 54, wherein the composition is in a transdermal patch and the composition is topically applied by contacting the patch to the skin.

REMARKS

Claims 54 to 63 are pending in this application. Applicants have cancelled claims 1 to 10, 52, and 53 without prejudice and have added new claims 54 to 63. All of these new claims are supported by the claims filed in the original application. For example, new independent claim 54 is supported by original claims 1 and 8. The recitation of specific concentrations of adenosine in claims 54, 56, and 57 are supported by the original claims and in the application, e.g., at page 3, lines 15-18. Claims to the use of transdermal patches and delivery agents are also described in the application, e.g., at page 9, line 30, to page 10, line 2. Thus, the new claims add no new matter.

35 U.S.C. § 112, Second Paragraph

Claims 1 to 10 have been rejected as allegedly indefinite for reciting, "applying a therapeutically effective amount." Applicants have cancelled claim 1, and the phrase has not been repeated in the new claims. Thus, this rejection is moot.

Double Patenting

Claims 1 to 10, 52, and 53 have been rejected as unpatentable over claims 1 to 10 of U.S. Patent No. 6,423,327, which is the patent that issued in the "parent" of the present application. Without admitting the correctness of the double-patenting rejection, applicants will submit a terminal disclaimer in the present application upon notification of allowable subject matter.

35 U.S.C. § 102

Claims 1 and 3 to 10 have been rejected as allegedly anticipated by Manneth, U.S. Patent No. 5,998,423 (Manneth). This rejection is moot in view of applicants' cancellation of claims 1 to 10, and applicants respectfully submit that this rejection does not apply to new claims 54 to 63 for the following reasons.

Claim 54 covers a method for enhancing the condition of unbroken skin of a mammal by reducing one or more of wrinkling, roughness, dryness, or laxity of the skin, without increasing dermal cell proliferation, by topically applying to the skin a composition including a concentration of adenosine in an amount effective to enhance the condition of the skin without

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increasing dermal cell proliferation, where the adenosine concentration applied to the dermal cells is 10^{-3} M to 10^{-7} M. This claim is distinguished from the cited prior art for the following reasons.

According to the Office Action, Manneth describes "compositions comprising adenosine, cyclohexyladenosine or cyclopentyladenosine and their use for the modulation of melanin production in the skin and hair and in enhancing the tanning process and providing protection for the skin against UV radiation" (Office Action at page 4). Manneth also discloses various formulations of the composition including topical formulations containing various thickeners, castor oil, and other additives.

Applicants respectfully disagree with this characterization of Manneth, because this patent does not describe the use of "adenosine" in any of the described methods, but instead describes only the use of adenosine analogs or derivatives. In particular, Manneth requires compounds that will selectively activate the adenosine-2 (A2) receptor or inactivate the adenosine-1 (A1) receptor to increase melanin production (see column 4, lines 29-41), or selectively inactivate the A2 receptor and activate the A1 receptor to decrease melanin production. That is why Manneth describes useful compounds for his methods as "analogs or derivatives of adenosine" (at column 3, lines 11-12), but not adenosine.

Manneth does not describe the use of adenosine itself for a simple reason - adenosine activates both the A2 and A1 receptors, and would thus negate the selective effect required to modulate melanin production. Compounds such as adenosine that activate both A1 and A2 receptors will not work in Manneth's method of modulating melanin production. Thus, Manneth fails to anticipate the method of claim 54, which recites applying adenosine to the skin.

Furthermore, the Office Action states that Manneth describes "preferred amounts of adenosine receptor antagonists …., in the range of 100nM or 10nM, which is within the claimed range (10-4 M = 10nM)" (Office Action at page 4). Applicants respectfully submit that these statements are in error. First, what Manneth describes at column 4, lines 7-17, are the K_i values of adenosine receptor A1 antagonists and A2 agonists. These values of K*i* are inhibition constants for these compounds, not concentrations to be administered. The K*i* is the concentration at which the antagonist will inhibit 50% of the maximum response at a given receptor (technically, when Manneth refers to the A2 receptor agonists he should use K*a*, the

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concentration at which the agonist will activate 50% of the maximum response). The K*i* and K*a* values are used to express the potency of compounds. The more potent the antagonist or agonist is at a given receptor, the lower the K*i* or K*a* will be. This is useful to Manneth in comparing the relative potency of a group of agonists or antagonists, but is certainly not the same as stating a concentration to be administered. Thus, the K*i* values are not relevant to the claimed invention.

Second, the Office Action statement that 10^{-4} M is = 10 nM is simply wrong. Applicants respectfully submit that 10^{-4} M is 0.1 mM (or 100 μM, which is 100,000 nM). Thus, the numbers that Manneth recites for K*i* values are far removed from applicants' claimed concentrations.

Claims 1, 6, 7, and 10 have been rejected as allegedly anticipated by von Borstel et al., U.S. Patent No. 5,770,582 (von Borstel). This rejection is moot in view of applicants' cancellation of claims 1 to 10, and applicants respectfully submit that this rejection does not apply to new claims 54 to 63 for the following reasons.

According to the Office Action, von Borstel describes, "deoxyribonuclosides [sic] such as 2'-deoxayadenosine for accelerating the healing of wounds, cuts & abrasions and to ameliorate the effects of aging" (at page 5). The Office Action also states, "[s]kin aging does not involve any underlying disease process. Accordingly treating aged skin reads on enhancing non-diseased skin condition" (id.).

The present claims all recite the use of "adenosine." As the Examiner correctly points out, von Borstel describes the use of **deoxy**ribonucleosides, not ribonucleosides. However, adenosine is a ribonucleoside, **not** a deoxyribonucleosides. The two classes of compounds differ structurally and are quite distinct in their chemical and biological properties. The structural differences are well known. Deoxyribonucleosides would not be expected to bind to adenosine receptors to elicit a biological response, and thus, the deoxyribonucleosides described by von Borstel are not the same as applicants' claimed adenosine. For this reason, von Borstel cannot anticipate applicants' pending claims. Therefore, this rejection should be withdrawn.

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35 U.S.C. § 103

Claims 2 to 5, 9, 52, and 53 have been rejected as being allegedly unpatentable over von Borstel. Applicants submit that this rejection is moot in view of the cancellation of claims 1 to 10, 52, and 53, and that this rejection does not apply to the new claims.

As the Office Action concedes, von Borstel "do not teach the exact claimed amounts of adenosine or its analogs. However, optimizing the amount of adenosine in the composition of '582 [von Borstel], with an expectation to achieve [an] enhanced and quick wound healing effect would have been obvious for one of an ordinary skill in the art at the time of the instant invention" (id. at page 6). Applicants respectfully disagree for the following reasons.

Von Borstel does not describe the use of adenosine at all, and thus it cannot have been obvious to "optimize" the amount of adenosine for use in von Borstel's methods. One of skill in the art would not have thought to use adenosine based on the von Borstel patent, much less known what amount to apply to skin. Moreover, von Borstel fails to describe or even suggest that one can enhance the condition of unbroken skin of a mammal without increasing dermal cell proliferation. This is an unexpected result of the presently claimed methods, and rebuts any alleged *prima facie* case of obviousness.

Based on these discussions, applicants submit that the new claims are not rendered obvious by von Borstel.

CONCLUSION

The claim amendments are recited in the attached Version with Markings to Show Changes Made. Applicants submit that all of the new claims are in condition for allowance, and

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request such action. No fees are believed due. However, please apply any charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 07917-045003.

Respectfully submitted,

Date: January 9, 2003

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Version with Markings to Show Changes Made

In the claims:

Claims 1 to 10, 52, and 53 have been cancelled.

Claims 54 to 63 have been newly added.

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Notice of Allowability	Application No.	Applicant(s)	
	10/184,810	DOBSON ET AL.	
	Examiner	Art Unit	
	Laksnmi S Channavajjala	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *1-14-03 & 4-16-03*.
2. ☒ The allowed claim(s) is/are *54-63*.
3. ☒ The drawings filed on *28 June 2002* are accepted by the Examiner.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.
5. ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
   (a) ☐ The translation of the foreign language provisional application has been received.
6. ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application. **THIS THREE-MONTH PERIOD IS NOT EXTENDABLE**

7. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

8. ☐ CORRECTED DRAWINGS must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No. ____.
   (b) ☐ including changes required by the proposed drawing correction filed _____, which has been approved by the Examiner.
   (c) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No. _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the top margin (not the back) of each sheet. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

9. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1☒ Notice of References Cited (PTO-892)
2☐ Notice of Informal Patent Application (PTO-152)
3☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
4☐ Interview Summary (PTO-413), Paper No.____ .
5☐ Information Disclosure Statements (PTO-1449), Paper No. ____.
6☐ Examiner's Amendment/Comment
7☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
8☒ Examiner's Statement of Reasons for Allowance
9☐ Other

Allowable Subject Matter

Claims 54-63 are allowed.

The following is an examiner's statement of reasons for allowance:

Instant claims are directed to a method of enhancing the condition of unbroken skin by reducing wrinkling or dryness or laxity of skin, without increasing dermal cell proliferation, where the method comprises administering adenosine at a concentration of 10^{-3} M to 10^{-7} M, to the skin. The closest prior art of record teaches administering adenosine in skin care compositions. However, the art of record utilizes concentrations much higher than claimed and also require the presence of epidermal growth factor to stimulate cell proliferation. Whereas, instant claims are directed to treating skin without increasing the dermal cell proliferation. Further, prior art of record does not teach or suggest any reason for the addition of adenosine in skin care compositions, in particular, in amounts as low as those claimed.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S Channavajjala whose telephone number is 703-308-2438. The examiner can normally be reached on 7.30 AM -4.00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on 703-308-2927. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-7924 for regular communications and 703-308-7924 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Lakshmi S Channavajjala
Examiner
Art Unit 1615
April 19, 2003

#9
10/2/03
SP

Attorney's Docket No.: 07917-045003 / UMMC 97-32

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Dobson et al.	Art Unit :	1615
Serial No.	: 10/184,810	Examiner :	L. Channavajjala
Filed	: June 28, 2002	Confirmation No.:	5640
		Notice of Allowance Date: April 22, 2003	

Title : TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

MAIL STOP ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

COMMENTS ON STATEMENT OF REASONS FOR ALLOWANCE

Applicants submit that in addition to the reasons stated by the Examiner in the Notice of Allowability mailed April 22, 2003, claims 54 to 63 are allowable for the reasons of record in this application.

Respectfully submitted,

Date: July 7, 2003

J. Peter Fasse
Reg. No. 32,983

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225 Franklin Street
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Facsimile: (617) 542-8906

20685766.doc

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

July 7, 2003
Date of Deposit

Signature

Mary Elizabeth Jacoby
Typed or Printed Name of Person Signing Certificate

83/95

TAB 04

Attorney's Docket No.: 07917-045004 / UMMC 97-32

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Dobson et al. Art Unit : 1617
Serial No. : 10/680,370 Examiner : Unknown
Filed : October 7, 2003
Title : TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT IN REPLY TO ACTION OF DECEMBER 8, 2004

Please amend the above-identified application as follows:

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

June 8, 2005
Date of Deposit

Lisa G. Gray
Signature

Lisa G. Gray
Typed or Printed Name of Person Signing Certificate

Amendments to the Claims:

This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1. – 53. (Canceled)

54. (Amended) A method for enhancing the condition of unbroken skin of a mammal by reducing one or more of wrinkling, roughness, dryness, or laxity of the skin without increasing proliferation of dermal cells in the skin, the method comprising topically applying to the skin a composition comprising ~~adenosine or~~ a concentration of an adenosine analog in an amount effective to enhance the condition of the skin without increasing dermal cell proliferation, wherein the adenosine analog concentration applied to the dermal cells is about 10^{-4} M to 10^{-7} M.

55. (Canceled)

56. (Currently Amended) The method of claim 54 ~~55~~, wherein the adenosine analog concentration is about 10^{-4} M.

57. (Canceled)

58. (Canceled)

59. (Previously Presented) The method of claim 54, wherein the composition further comprises a conditioning agent.

60. (Previously Presented) The method of claim 59, wherein the conditioning agent is a humectant, an emollient, or an occlusive agent.

61. (Previously Presented) The method of claim 54, wherein the mammal is a human.

62. (Previously Presented) The method of claim 54, wherein the skin comprises a skin graft.

63. (Previously Presented) The method of claim 54, wherein the composition further comprises a transdermal delivery agent.

64. (Previously Presented) The method of claim 54, wherein the composition is in a transdermal patch and the composition is topically applied by contacting the patch to the skin.

65. (Previously Presented) The method of claim 54, wherein the adenosine analog is selected from the group consisting of 2'-deoxyadenosine; 2',3'-isopropoylidene adenosine; toyocamycin; 1-methyladenosine; N-6-methyladenosine; adenosine N-oxide; 6-methylmercaptopurine riboside; 6-chloropurine riboside; 5'-adenosine monophosphate; 5'-adenosine diphosphate; 5'-adenosine triphosphate; phenylisopropyl-adenosine; 1-Methylisoguanosine; N6-cyclohexyladenosine; N6-cyclopentyladenosine; 2-chloro-N6-cyclopentyladenosine; 2-chloroadenosine; adenosine amine congener; 2-p-(2-carboxy-ethyl) phenethyl-amino-5'-N-ethylcarboxamido-adenosine; N-ethylcarboxamido-adenosine; napthyl-substituted aralkoxyadenosine; 5'(N-cyclopropyl)-carboxamidoadenosine; 2-chloroadenosine; N6-phenyladenosine; N6-phenylethyladenosine; and 2-phenylaminoadenosine.

66. (Previously Presented) The method of claim 54, wherein the adenosine analog is 5'-adenosine monophosphate; 5'-adenosine diphosphate; or 5'-adenosine triphosphate.

67 to 73. (Canceled)

REMARKS

Claims 54 to 56, and 59 to 66 are pending in this application. Applicants have amended claims 54 and 71 and canceled claims 57, 58, and 67 to 73, without prejudice to applicants' right to pursue any one or more of these claims in a subsequent continuation application. These amendments add no new matter. In particular, applicants have amended the claims to remove references to adenosine and to focus the invention on the use of adenosine analogs to enhance the condition of unbroken skin without increasing dermal cell proliferation, and compositions comprising adenosine analogs and an angiogenesis factor. These concepts were already in the claims, and are described throughout the application.

Claim Objections

The Office Action notes that claims 57 and 58 are substantial duplicates of claims 55 and 56. Applicants disagree, because claims 57 and 58 relate to adenosine, and claims 55 and 56 relate to adenosine **analogs**, but by the present amendment, applicants have cancelled claims 57 and 58 rendering this rejection moot.

Double Patenting

Claims 55-59 have been rejected under U.S.C. § 101 as allegedly claiming the same invention as that of claims 1 and 4 of prior U.S. Patent No. 6,423,327 ("the '327 patent").

Applicants respectfully disagree, because the pending claims now focus on the use of adenosine **analogs**, whereas the claims in the '327 patent recite methods using adenosine, not adenosine analogs. Thus, the present claims do not claim the same invention as any of the claims in the '327 patent.

Claims 54-73 have been rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1-10 of U.S. Patent No. 6,645,513 ("the '513 patent"). The Office Action admits that "the conflicting claims are not identical," but alleges that "they are not patentably distinct from each other because both the sets of claims are directed to a method of enhancing the skin condition by topically applying

adenosine or adenosine analog in an amount effective to enhance the condition of the skin" (at page 3). Applicants again respectfully disagree, because the '513 patent does not recite the use of adenosine analogs, and all pending claims in the present application recite adenosine analogs. Thus, the present claims do not recite the same invention, or even an obvious variation of the invention, claimed in the '513 patent.

35 U.S.C. § 102

Claims 54-62, 65, 67, and 69 have been rejected under 35 U.S.C. 102(e) as being allegedly anticipated by U.S. Patent No. 5,998,423 to Manneth et all ("the '423 patent"). Applicants respectfully disagree and traverse this rejection for the following reasons.

According to the Office Action, the '423 patent describes compositions comprising adenosine, cyclohexyladenosine, or cyclopentyladenosine and their use for the modulation of melanin production in the skin and hair and in enhancing the tanning process and providing protection for the skin against UV radiation (see col. 1, lines 7-13; col. 2, lines 44-63; col. 5, lines 10-18). The Office Action assumes, without any factual support, that "enhancing the tanning process on the skin, taught by '423, reads on the enhancing the condition for non-diseased skin" (Office Action at page 4). Applicants disagree, because nowhere does the '423 patent state that its compositions or methods reduce one or more of wrinkling, roughness, dryness, or laxity of the skin without increasing proliferation of dermal cells in the skin. Instead, the '423 patent merely describes that its methods can be used to modulate melanin production and protect against UV rays. In fact, the '423 patent does not even use the terms wrinkle (or wrinkling), roughness, dryness, or laxity anywhere in its text (based on an electronic word search). Thus, enhancing the tanning process (i.e., getting a better tan) and protecting the skin against UV rays is not the same as enhancing the condition of unbroken skin as presently claimed.

Furthermore, the Office Action alleges that "with respect to claimed amounts of adenosine agonists, '423 discloses preferred amounts of adenosine receptor antagonists (which is same as adenosine agonists), in the range of 100nM or 10nM, which is within the claimed range

(col. 3, lies [sic, lines] 8-12 and col. 4, lines 7-17). Applicants again respectfully disagree, because the numbers recited in the '423 patent at column 4, lines 7 to 17 are in fact K_i values, which are measures of activity level with respect to an adenosine receptor binding assay, and not concentrations to be administered.

Next, the Office Action alleges that the '423 patent does not show that the adenosine agonists show any increase in cell proliferation, and thus assumes that this is a fact. Applicants submit that the '423 patent is silent on the issue, and thus the Office cannot merely assume that the '423 patent methods do not cause an increase in dermal cell proliferation. To the contrary, the Office Action provides no evidence whatsoever to support the rejection. Unless the Examiner provides some evidence to support the conjecture that the '423 patent compounds will not increase cell proliferation (which as far as applicants understand has nothing to do with improving a tan), the burden of proof does not shift to applicants.

As the Examiner is no doubt aware, "[a]nticipation under Section 102 requires 'the presence in a single prior art disclosure of all elements of a claimed invention arranged as in that claim,'" Carella v. Starlight Archery and Pro Line Co., 804 F.2d 135, 138 (Fed. Cir. 1986), and "[t]he identical invention must be shown in as complete detail as is contained in the ... claim," Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). The present Office Action does not meet these requirements, and thus, for all of these reasons, applicants submit that the '423 patent fails to anticipate the instant claims. As a result, applicants request that the Examiner reconsider and withdraw this rejection.

Next, claims 54, 59-61, and 66 have been rejected under 35 U.S.C. 102(e) as being allegedly anticipated by U.S. Patent No. 5,256,649 to Le Fur et al ("the '649 patent"). Applicants respectfully disagree and traverse this rejection for the following reasons.

According to the Office Action, the '649 patent discloses a cosmetic composition for treating aging skin that includes ATP or an ATP generating system and cosmetic additives such as emollients and humectants. The Office Action also states that the '649 patent recites that the composition slows down aging by maintaining optimum fluidity of the skin cell membrane and improves the condition of the skin, but does not mention cell proliferation. Again, the Examiner

merely alleges that silence in the patent indicates that the recited formulations do not increase cell proliferation. Applicants disagree, and note that the Examiner has no factual evidence or support for his conclusions.

More importantly, the '649 patent does not disclose the same concentrations of ATP as recited in applicants' amended claims to the use of adenosine analogs. The '649 patent recites percentages of ATP of 0.045 to 4.5 percent by weight of the composition. Given ATP's molecular weight, this concentration range is far higher than applicants' claimed range of concentrations. Applicants' highest claimed concentration is now 10^{-4} M, which corresponds to an ATP concentration of about 0.006 percent. This upper concentration of 0.006 percent is far lower that the 0.045 percent lower level that the '649 patent discloses, and there is no suggestion in the '649 patent that a lower concentration of ATP could work in the claimed methods.

Based on these reasons, the '649 patent does not anticipate the presently amended claims, and applicants request that the Examiner reconsider and withdraw this rejection.

35 U.S.C. § 103

Claims 55-58, 67, 68, and 70 have been rejected as being allegedly unpatentable over the '649 patent. Applicants traverse for the reasons discussed above and for the following reasons.

The Office Action notes that while the '649 patent "does not specify the amounts of ATP in terms of molar percentages, '649 suggests ATP at 0.45 to 4.5% (col. 3 table)," and concludes that "it would have been obvious for one of an ordinary skill in the art at the time of the instant invention to choose an optimum amount of ATP in the cosmetic composition of '649 with an expectation to achieve the desired effect of combating the external factors so as to prevent premature aging of the skin because '649 suggests that ATP or ATP generating system in the composition slows down aging by maintaining optimum fluidity of the skin cell membrane and improving the condition of the skin (col. 5) (Office Action, at pages 5-6)."

Applicants respectfully disagree. As noted above, the concentration range of the '649 patent now varies from the claimed concentration range by about an order of magnitude, and there is simply no suggestion in the '649 patent that either the claimed methods or the '649

methods would work at such low concentrations as applicants are now claiming. Furthermore, as best understood by applicants, the purpose of the ATP in the '649 patent is to supply energy for betaine to generate ademetionine, which in turn has the anti-aging effect (see, e.g., col. 1, lines 36-43 and lines 48-49). This is an intracellular process intended to increase membrane fluidity. These intracellular actions of the betaine/ATP mixture are unrelated to the ATP receptor activity addressed by applicants' claimed methods using applicants' claimed low concentrations of adenosine analogs. Applicants' claimed methods are believed to stimulate receptor-mediated physiological responses on the skin cells to enhance protein synthesis, cell size, etc., to enhance the condition of the skin. These are entirely different effects than the betaine/ATP mixture proposed in the '649 patent to increase membrane fluidity.

Thus, applicants submit that it would not have been obvious to one of skill in the art upon reading the '649 patent to lower the concentration of the ATP by almost an order of magnitude, much less to carry out the presently claimed methods. Based on these reasons, applicants request the Examiner to reconsider and withdraw this rejection.

Next, claims 62, 71, 72, and 73 have been rejected as being allegedly unpatentable over the '649 patent and further in view of U.S. Patent No. 5,770,582 to von Borstel et al. ("the '582 patent"). Applicants have cancelled claims 71 to 73, without prejudice, thereby rendering this rejection moot with respect to these claims. With respect to claim 62, that claim depends from claim 54, and is thus patentable for at least the same reasons as claim 54 as discussed above.

Claims 71, 72, and 73 have been rejected as being allegedly unpatentable over the '423 patent in view of the '582 patent. Applicants have cancelled claims 71 to 73, without prejudice, thereby rendering this rejection moot.

Claims 63 and 64 have been rejected as being allegedly unpatentable over the '423 patent or the '649 patent in view of U.S. Patent No. 5,785,978 to Porter. Applicants submit that claims 63 and 64 are patentable for at least the same reasons that claim 54, from which these claims depend, is patentable.

CONCLUSION

Applicants request that the Examiner reconsider and withdraw the rejections of the pending claims, and send a Notice of Allowance.

No excess claim fees are required. Applicants enclose a $510 check for the extension fee along with a Petition for Extension of Time for Three Months. Please apply any other charges or credits to deposit account 06-1050, referring to attorney docket 07917-045004.

Respectfully submitted,

Date: June 8, 2005

J. Peter Fasse
Reg. No. 32,983

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/680,370	10/07/2003	James G. Dobson JR.	07917-045004	4664

26161 7590 09/23/2005

FISH & RICHARDSON PC
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
VU, JAKE MINH	
ART UNIT	**PAPER NUMBER**
1618	

DATE MAILED: 09/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

Office Action Summary	Application No.	Applicant(s)	
	10/680,370	DOBSON ET AL.	
	Examiner	Art Unit	
	Jake M. Vu	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54,56 and 59-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54, 56, and 59-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of Applicant's Amendment and Response filed on 06/13/05. Applicants have amended claim 54 and 56 and cancelled claims 55, 57, 58, and 67-73. Claims 54, 56, and 59-66 are pending in the instant application.

Claim Objections

Previously, claims 57 and 58 were objected as being duplicates of claims 55 and 56. However, Applicants have cancelled claims 57 and 58 rendering this objection moot. Thus, the claims objection is withdrawn.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double

patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 54, 56, and 59-66 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,645,513. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the sets of claims are directed to a method of enhancing the skin condition by topically applying adenosine or adenosine analog in an amount effective to enhance the condition of the skin. The patented claims recite the effective amount of adenosine or its analogs between 10^{-3} to 10^{-7} M. The application claims recite the amount of adenosine analog from 10^{-4} to 10^{-7}, which falls within the claimed range of the patented. Further, instant dependent claim 65 recite specific adenosine analogs, whereas the patent does not. However, because the amount of adenosine and its analogs are being employed for achieving the same end result i.e., a method of enhancing the condition of an unbroken skin by reducing one or more of wrinkling, roughness, dryness or laxity of skins it would have been obvious for a skilled artisan at the time of the instant invention to practice the claimed method by employing the composition of patented claims. Therefore, this is an obviousness double patenting rejection.

Applicants' arguments have been fully considered, but are not found to be persuasive. Applicants argued that the '513 patent does not recite the use of adenosine analogs or even an obvious variation of the invention claimed in the '513 patent. The Examiner finds this argument unpersuasive, because the use of adenosine analogs is obviously disclosed in the '513 patent. The use of "adenosine analogs" are disclosed in the abstract, more than ten times in the specification, and the title of the '513 patent is "Treatment of Skin with Adenosine or Adenosine Analog".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 54, 56, 59-62, and 65 are rejected under 35 U.S.C. 102(e) as being anticipated by US 5,998,423 to Manneth et al (hereafter '423).

'423 teaches compositions comprising adenosine, cyclohexyladenosine or cyclopentyladenosine and their use for the modulation of melanin production in the skin and hair and in enhancing the tanning process and providing protection for the skin against UV radiation (see col. 1, lines 7-13, col. 2, lines 44-63,' col. 5, lines 10-18). Enhancing the tanning process on the skin, taught by '423, reads on the enhancing the

condition of non-diseased skin. With respect to claimed amounts of adenosine agonists, '423 discloses preferred amounts of adenosine receptor antagonists (which is same as adenosine agonists), in the range of 100nM or 10nM, which is within the claimed range (col. 3, lies 8-12 and col. 4, lines 7-17).

'423 discloses various formulations of the composition including topical formulation containing various thickeners, castor oil and other additives (Co1s. 5 and 6 and examples 2 and 3) that read on the claimed conditioning agents. With respect to the skin graft claimed, '423 tested the adenosine agonists in neonatal foreskins (col. 7, example 1, lines 5-37), which are nothing but skin grafts. Further, '423 disclose that increased cAMP causes increase in tyrosinase activity, which in turn increases melanogenesis. However, '423 do not show that their adenosine agonists show any increase in cell proliferation. Thus, the instant claims are anticipated by '423.

Applicants' arguments have been fully considered, but are not found to be persuasive. Applicants argued that enhancing the tanning process (i.e., increasing melanin) and protecting the skin against UV rays are not the same as enhancing the condition of broken skin by reducing wrinkles, roughness, dryness or laxity. However, in Bilia et al (US 5,486,353), this prior art disclosed "with the formation of melanin and thickening of the horny cell layer, the skin builds up its own natural protection against the sun's rays. In healthy skin and in healthy cells, these reactions proceed in an optimal fashion. In prematurely aged skin, which is damaged as a consequence of repeated exposure to the sun, they are reduced. The skin's capability of withstanding external environmental factors such as water and wind is also reduced. Stressed skin

shows symptoms such as wrinkles, dry, rough and tanned farmer's skin as well as lentigo senilis." Thus, not only does the melanin beautify (enhance) the skin by tanning, the melanin would also protect the skin from wrinkles, dryness, and roughness.

Applicants further argued that the "numbers recited in the '423 patent at column 4, lines 7 to 17 are in fact K_i values, which are measures of activity level with respect to adenosine receptor binding assay, and not concentrations to be administered." On closer examination, the Examiner finds that Applicants are correct regarding the numbers on column 4 represented K_i values. However, the numbers in the '423 patent at column 5, lines 48 to 56 recited the correct concentrations to be administered is 0.001% to 20%, which encompass Applicants' concentration of 0.006% as asserted by Applicant on page 7.

Additionally, Applicants asserted that the Examiner cannot merely assume that the '423 patent methods do not cause an increase in dermal cell proliferation when the '423 patent does not show if the adenosine agonists caused any increase in cell proliferation. Examiner finds Applicants argument unpersuasive, because the Applicants' pending claims and patent '423 both incorporate adenosine analogs to enhance the skin. Any reasonable person would recognize that the same chemical compounds would have the same chemical properties (or mechanism of actions). For example, at sea level, the chemical compound H_2O has the chemical property of boiling at 100°C. If a prior art does not disclosed that a chemical compound H_2O boils at 100°C at sea level, a reasonable person could apply the logical reasoning described

above and correctly deduce that the prior art's chemical compound H_2O would also boil at 100°C.

In this case, if an adenosine or adenosine analog could enhance the skin without increasing dermal cell proliferation, a reasonable person could deduce that another adenosine or adenosine analog could enhance the skin without increasing dermal cell proliferation. Nevertheless, Applicants contend this is not enough. Applicants have suggested that more proof is needed and that the burden of proof should be placed on the Patent Office. However, it would be too costly and burdensome for the Patent Office, which has limited resources, to have the burden of proving on every application that the same chemical compounds would have the same chemical properties. If Applicants disagree with this logical and scientific reasoning, then the burden of proof should be on the Applicants to prove why the logical and scientific reasoning is incorrect.

Thus, the 102(e) rejection still stands for claims 54, 56, 59-62, and 65.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 54, 56 and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,256,649 to Le Fur ('649).

'649 discussed above teach a method of treating aged skin by applying a composition comprising ATP or an ATP generating system, betaine, magnesium and potassium salt. The composition further comprises the claimed conditioners. While '649 does not specify the amounts of ATP in terms of molar percentages, '649 suggests ATP at 0.45 to 4.5% (col. 3 table), it would have been obvious for one of an ordinary skill in the art at the time of the instant invention to choose an optimum amount of ATP in the cosmetic composition of '649 with an expectation to achieve the desired effect of combating the external factors so as to prevent premature aging of the skin because '649 suggests that ATP or ATP generating system in the composition slows down aging by maintaining optimum fluidity of the skin cell membrane and improving the condition of the skin (col.5).

Applicants' arguments have been fully considered, but are not found to be persuasive. Applicants argue that "there is simply no suggestion in the '649 patent that either the claimed methods or the '649 methods would work at such low concentrations as Applicants are now claiming." However, the amount of adenosine analog in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of adenosine analog to best achieve the desired results. Furthermore, the '423 patent disclosed that the concentrations could typically be in the range from about 0.001% to 20% (col. 5, lines 48-56). Therefore, an ordinary person skilled in the art would have been

motivated to experiment with concentrations lower than 0.001%, because the less amount of adenosine analog used, the cheaper the product. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of adenosine analog concentration would have been obvious at the time of Applicant's invention.

Applicants further argue that the "the Applicants' claimed methods are believed to stimulate receptor-mediated physiological responses on the skin cells to enhance protein synthesis, cell size, etc., to enhance the condition of the skin. These are entirely different effects than the betaine/ATP mixture proposed in the '649 patent to increase membrane fluid. Examiner finds this argument unpersuasive, because as stated above the same chemical compound would have the same chemical properties and mechanism of actions. If a prior art states water boil at 100°C and another prior art states water freezes at 0°C, an ordinary person skilled in the art could logically deduce water has both of these properties. ATP has many mechanisms of action and functions in the human body. The prior art and Applicants' invention method comprise of topically apply an ATP or adenosine analog composition on the skin; therefore, an ordinary person skilled in the art could logically deduce this ATP or adenosine analog composition has both mechanisms of action.

Claims 62 is rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,256,649 to Le Fur as applied to claims 54, 56 and 66 above, and further in view of US 5,770,582 to von Borstel et al (hereafter '582) OR

'649 fail to teach angiogenic factor and the skin graft as claimed.

'582 teach deoxyribonuclosides such as 2'-deoxyadenosine for accelerating the healing of wounds, cuts, and abrasions and to ameliorate the effects of aging (see abstract, col. 1, field of the invention, col. 5, 6). '582 teaches angiogenic factors (col. 8, lines 24), growth factors such as fibroblast growth factor (col.7 and 8) and other additives for topical application (col. 7, lines 19 - 65 and col. 8). '582 teaches that glycosaminoglycans, angiogenic factors, peptide growth factors such as, bFGF, PDGF etc., may be added to the compositions containing 2-deoxyribonucleosides (col. 8, lines 24-31). Accordingly, it would have been obvious for one of an ordinary skill in the art at the time of the instant invention to incorporate peptide growth factors or glycosaminoglycans, all of which read on angiogenic factors of the instant claims, in the skin treating composition of '649 with an expectation to enhance skin condition and also achieve quick wound healing effect on the skin.

Applicants' arguments have been fully considered, but are not found to be persuasive. Applicants argue that claim 62 depends from claim 54, and is thus patentable for at least the same reasons as claim 54 as argued by Applicants. However, claim 54 is still unpatentable as discussed above by Examiner.

Claims 63 and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,998,423 to Manneth et al (hereafter '423) as applied to claims 54, 56 and 66 above, and further in view of US 5,785,978 to Porter ('978).

'423 fail to teach a transdermal patch. '978 teach transdermal patches comprising skin care compositions wherein the compositions comprise active agents such as vitamins or moisturizers for applying and protecting skin from wrinkling, yellowing, dryness or other aging conditions (col. 1 and col. 6). '978 do not specifically teach the claimed active agents. However, it would have been obvious for one for one of an ordinary skill in the art at the time of the instant invention to prepare the composition of '423 containing adenosine analogs in the form of a transdermal patch and apply it to skin, because '978 suggests that patches can be conveniently applied to the desired target site, improve the oxygen supply to the applied site and also that the evaporation of the composition is minimal from the patch. Accordingly, a skilled artisan would have expected to achieve the added advantages of improved oxygen supply and minimal evaporation with the patches containing the composition of '423, while treating skin dryness, wrinkles, etc.

Applicants' arguments have been fully considered, but are not found to be persuasive. Applicants argue that claims 63 and 64 are patentable for at least the same reasons as claim 54, from which these claims depend. However, claim 54 is still unpatentable as discussed above.

Claims 63 and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,256,649 to Le Fur as applied to claims 54 and 56 above, and further in view of US 5,785,978 to Porter ('978).

'649 fail to teach a transdermal patch. '978 teach transdermal patches comprising skin care compositions wherein the compositions comprise active agents such as vitamins or moisturizers for applying and protecting skin from wrinkling, yellowing, dryness or other aging conditions (col. 1 and col. 6). '978 do not specifically teach the claimed active agents. However, it would have been obvious for one for one of an ordinary skill in the art at the time of the instant invention to prepare the composition of 1649 containing ATP in the form of a transdermal patch and apply it to skin, because '978 suggests that patches can be conveniently applied to the desired target site, improve the oxygen supply to the applied site and also that the evaporation of the composition is minimal from the patch. Accordingly, a skilled artisan would have expected to achieve the added advantages of improved oxygen supply and minimal evaporation with the patches containing the composition of '649, while treating skin dryness, wrinkles, etc.

Applicants' arguments have been fully considered, but are not found to be persuasive. Applicants argue that claims 63 and 64 are patentable for at least the same reasons as claim 54, from which these claims depend. However, claim 54 is still unpatentable as discussed above.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Telephonic Inquiries

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jake M. Vu whose telephone number is (571) 272-8148. The examiner can normally be reached on Mon-Fri 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Paper No. 9
Entered: September 7, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

L'ORÉAL USA, INC.
Petitioner,

v.

UNIVERSITY OF MASSACHUSETTS
Patent Owner.

Case IPR2018-00778
Patent 6,423,327 B1

Before CHRISTOPHER G. PAULRAJ, ROBERT A. POLLOCK, and DAVID COTTA, *Administrative Patent Judges*.

COTTA, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 314(a)

I. INTRODUCTION

L'Oréal USA, Inc. ("Petitioner" or "L'Oréal") filed a petition requesting an *inter partes* review of claims 1–7 and 9 of U.S. Patent No. 6,423,327 B1 (Ex. 1001, "the '327 patent"). Paper 2 ("Pet."). The University of Massachusetts ("Patent Owner" or "UMass") filed a Preliminary Response to the Petition. Paper 7 (Prelim. Resp.).

Institution of an *inter partes* review is authorized by statute when "the information presented in the petition . . . and any response . . . shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314; *see* 37 C.F.R. §§ 42.4, 42.108. Upon considering the Petition, the Preliminary Response, and the cited evidence, we conclude that Petitioner has not satisfied its burden under 35 U.S.C. § 314(a) to show that there is a reasonable likelihood that it would prevail with respect to at least one of the challenged claims.

A. Related Proceedings

Petitioner and Patent Owner identify the following district court proceeding as relating to the '327 patent: *University of Massachusetts Medical School and Carmel Laboratories, LLC v. L'Oréal S.A. and L'Oréal USA, Inc.*, No. 1:17-cv-00868 (D. Del.). Pet. 8–9; Paper 5, 2. Petitioner and Patent Owner identify the following *inter partes* review proceeding as related to the '327 patent: IPR2018-00779, which challenges the patentability of U.S. Patent No. 6,645,513 ("the '513 patent"). *Id*. The '327 patent is the parent of the '513 patent. *Id.*

B. The '327 Patent (Ex. 1001)

The '327 patent issued July 23, 2002, identifying James G. Dobson, Jr. and Michael F. Ethier as co-inventors. Ex. 1001. The patent discloses "methods and compositions for enhancing the condition of skin." *Id.* at 1:40–41.

The '327 patent teaches that "[s]kin includes a surface layer, known as the epidermis, and a deeper connective tissue layer, known as the dermis." *Id.* at 1:19–20. "The dermis is composed of a variety of cell types, including fibroblasts." *Id.* at 1:24–25. "As skin ages, or is exposed to UV light and other environmental insults, changes in the underlying dermis can lead to the functional and morphological changes associated with damaged skin." *Id.* at 1:28–31. According to the '327 patent, "[d]ecreases in the abundance and function of products of the fibroblasts, which include collagen and proteoglycans, are believed to play major roles in wrinkled and damaged skin." *Id.* at 1:31–34.

The '327 patent discloses that the inventors "discovered that adenosine stimulates DNA synthesis, increases protein synthesis, and increases cell size in cultures of human skin fibroblasts." *Id.* at 1:37–39. Based on this discovery, the inventors provide methods for "enhancing the condition of non-diseased skin," which comprise "topically administering a therapeutically effective amount of adenosine or an adenosine analog to a region of non-diseased skin of the mammal containing dermal cell." *Id.* at 1:48–60. The methods require that "[t]he adenosine is added so that it does not cause proliferation of the dermal cell." *Id.* at 59–60. "The therapeutically effective amount of adenosine used in [these] methods is

preferably 10^{-3} M to 10^{-7} M, more preferably 10^{-4} M to 10^{-6} M, and most preferably about 10^{-4} M." *Id.* at 2:13–16.

C. Challenged Claims

Petitioner challenges claims 1–7 and 9 of the '327 patent. Claim 1, the only independent claim, is reproduced below:

> 1. A method for enhancing the condition of unbroken skin of a mammal by reducing one or more of wrinkling, roughness, dryness, or laxity of the skin, without increasing dermal cell proliferation, the method comprising topically applying to the skin a composition comprising a concentration of adenosine in an amount effective to enhance the condition of the skin without increasing dermal cell proliferation, wherein the adenosine concentration applied to the dermal cells is 10^{-4} M to 10^{-7} M.

Ex. 1001, 10:17–27.

D. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1–7 and 9 of the '327 patent on the following grounds (Pet. 6):

Ground	References	Basis	Claims Challenged
1	DE '107[1]	§ 102(b)	1, 3–7, and 9
2	DE '107	§ 103(a)	1, 3–7, and 9
3	JP '153[2] and DE '107	§ 103(a)	1–7 and 9

[1] Schönrock et al., DE 195 45 107 A1, published June 5, 1997 ("DE '107"). DE '107 was originally published in German. Ex. 1003. All citations herein are to Exhibit 1004, the English translation of DE '107 provided by the Petitioner.

[2] Murayama, JP H9-157153 A, published June 17, 1997 ("JP '153"). JP '153 was originally published in Japanese. Ex, 1005. All citations herein are to Exhibit 1006, the English translation of JP '153 provided by the Petitioner.

Petitioner submits the Declarations of Dr. R. Randall Wickett (Ex. 1010) and Dr. S. Jamal Mustafa (Ex. 1011) in support of institution of *inter partes* review.

II. ANALYSIS

A. Person of Ordinary Skill in the Art

Factual indicators of the level of ordinary skill in the art include "the various prior art approaches employed, the types of problems encountered in the art, the rapidity with which innovations are made, the sophistication of the technology involved, and the educational background of those actively working in the field." *Jacobson Bros., Inc. v. U.S.*, 512 F.2d 1065, 1071 (Ct. Cl. 1975); *see also Orthopedic Equip. Co., Inc. v. U.S.*, 702 F.2d 1005, 1011 (Fed. Cir. 1983) (quoting with approval *Jacobson Bros*.).

Petitioner contends that the person of ordinary skill "would have a Bachelor[']s degree in Biochemistry or Chemistry with some academic exposure to, or industry courses or research in, topical delivery of drugs or cosmetic ingredients." Pet. 25. At this stage in the proceeding, Patent Owner does not challenge Petitioner's definition. Accordingly, for purposes of this Decision, we accept Petitioner's definition, which is supported by Dr. Wickett's declaration (Ex. 1010, ¶ 28) and is consistent with the level of skill reflected in the asserted prior art references. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (the prior art itself can reflect the appropriate level of ordinary skill in the art).

Moreover, we have reviewed the credentials for Drs. Wickett and Mustafa (Exs. 1010 and 1011) and, at this stage in the proceeding, we consider Drs. Wickett and Mustafa to be qualified to provide opinions on the

requisite level of skill and the knowledge of a person of ordinary skill in the art at the time of the invention.

B. Claim Construction

On April 16, 2018, Patent Owner filed a motion under 37 C.F.R. § 42.100(b) requesting that the Board apply a district court-type claim construction like that provided in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (en banc) in this proceeding. Paper 6. Patent Owner filed the motion within 30 days from filing the petition.[3] Patent Owner certified that the patent will expire within 18 months from the Notice of Filing Date Accorded to Petition. *Id.* at 1. In addition, Patent Owner represented that Petitioner does not oppose the motion. *Id.* Because Patent Owner satisfies all the requirements under 37 C.F.R. § 42.100(b), and because the Board interprets claims of an expired patent using the principles set forth in *Phillips*, we grant Patent Owner's request. Accordingly, in this proceeding, we will give claim terms their ordinary and customary meaning, as would be understood by a person of ordinary skill in the art, at the time of the invention, in light of the language of the claims, the specification, and the prosecution history of record. *Phillips*, 415 F.3d at 1313. We also consider the extrinsic evidence presented by Petitioner. *Id.* at 1317.

We construe claim terms only to the extent necessary to resolve the controversy. *See, e.g., Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999). For purposes of this decision, we need only

[3] Due to a technical issue with the original filing, Patent Owner refiled this motion on April 27, 2018. Paper 6, 3. Patent Owner represents that the original motion was filed using the Board's E2E system and emailed to the Petitioner on April 16, 2018. *Id.* Patent Owner further represents that Petitioner does not oppose refiling the motion. *Id.*

construe the limitation in claim 1 requiring "topically applying to the skin a composition comprising a concentration of adenosine" and the limitation requiring "wherein the adenosine concentration applied to the dermal cells is 10^{-4} M to 10^{-7} M." Ex. 1001, 10:18–26.

i. Construction of: "topically applying to the skin a composition comprising a concentration of adenosine"

Claim 1 of the '327 patent requires "topical" application of a composition containing adenosine to "unbroken skin." Petitioner contends that "topical" application of a composition containing adenosine to "unbroken skin" requires that "a composition be applied directly to the outer, epidermal layer of the skin that is intact and does not have any damage, such as wounds or cuts, burns, etc., such that the inner, dermal layer of the skin is not exposed." Pet. 28.

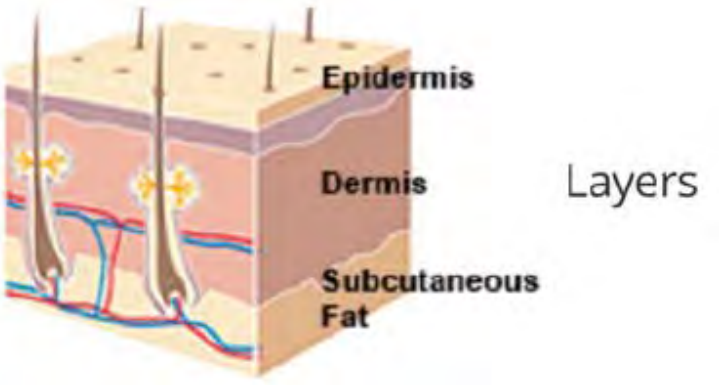
Patent Owner does not oppose Petitioner's proposed construction. Moreover, Petitioner's construction is in accord with the plain meaning of the terms "topical" and "unbroken." *See,* Pet. 28–29 (arguing that the person of ordinary skill in the art would have understood "topical" to mean "applied to the exterior surface of the target" and "unbroken," with regard to skin, to mean "free from any cuts, wounds, burns, or other damage that would expose the inner layers of the skin."). It is also consistent with the Specification and the prosecution history. *See, e.g.*, Ex. 1001, 5:10–29 (distinguishing topical administration from "oral, subdermal, intradermal, or intravenous" administration); Ex. 1009, 67 (arguing that the claimed method was distinguishable over a prior art reference because the reference involved application of adenosine to "open wounds such as burns"). Accordingly, for purposes of this decision, we adopt Petitioner's proposed construction of the

phrase "topically applying to the skin a composition comprising a concentration of adenosine."

ii. Construction of: "wherein the adenosine concentration applied to the dermal cells is 10^{-4} M to 10^{-7} M."

Claim 1 of the '327 patent requires that "the adenosine concentration applied to the dermal cells is 10^{-4} M to 10^{-7} M." Petitioner proposes that this language should be construed to require "a concentration of adenosine ***in the composition*** that is topically applied to an unbroken, epidermal layer of a region of the skin containing the dermal cells to be from 10^{-4} M to 10^{-7} M (*i.e.*, 0.00000265 to 0.00265 wt %)." Pet. 27. Patent Owner contends that Petitioner's proposed construction is contrary to the ordinary meaning of "dermal" and proposes that the claim language "be construed to mean what it says – that the recited concentration is the concentration that is applied to the dermal cells." Prelim. Resp. 11. We find that Patent Owner has the better position.

There is no dispute that the skin is comprised of multiple layers. Pet. 13; Ex. 1010 ¶ 31; Prelim. Resp. 13, n. 1. As the '327 patent explains, "[s]kin includes a surface layer, known as the epidermis, and a deeper connective tissue layer, known as the dermis." Ex. 1001, 1:19–20. The multiple layers of skin are illustrated in the below figure.



The above figure was provided by the Patent Owner and was reproduced from the website of the American Academy of Dermatology Association. Prelim. Resp. 13, n. 1. It depicts the three separate layers of the skin: the epidermis (the top layer), the dermis (the second layer), and subcutaneous fat (the bottom layer). *Id.*

The fundamental question presented by Petitioner in connection with its proposed construction is whether the recited concentration is applied to the dermal cells or to the epidermal cells.[4] The claim language at issue supplies a clear answer. As discussed above, claim 1 recites that the concentration of adenosine is "applied to the dermal cells."

This construction gives different meanings to the claim terms "the skin" and "the dermal cells," and is thus consistent with the cannon that "[d]ifferent claim terms are presumed to have different meanings." *Bd. Of Regents of the Univ. of Tex. Sys. v. BENQ Am. Corp.*, 533 F.3d 1362, 1371 (Fed. Cir. 2008). In contrast, we do not discern any meaningful difference between an "epidermal layer of the skin that is intact," which is the construction we have adopted for "applying to the skin," and an "epidermal layer of a region of the skin containing the dermal cells," which is the construction Petitioner proposes for adenosine "applied to the dermal cells." One would expect that if the Patent Owner had intended both "applications" recited in the claim 1 to be made to the same cells, Patent Owner would have

[4] Petitioner does not identify, and we do not discern in the current record, evidence to suggest that there is a meaningful difference between the "epidermal layer of a region of the skin containing the dermal cells" recited in Petitioner's proposed claim construction, and the epidermis. *See*, Ex. 1010, ¶ 31 ("Skin is comprised of many layers, including an outer, epidermal layer, which covers multiple inner layers (including the dermal layers)").

used the same term to describe both applications.

Construing the phrase "concentration applied to the dermal cells" to require what it says – i.e., application to the dermal cells – is consistent with the disclosure provided in the Specification. In order for a concentration of topically applied adenosine to be "applied to the dermal cells," it must penetrate the epidermis. The Specification expressly contemplates that adenosine will penetrate the skin. *See e.g.*, Ex. 1001, 5:13–14 ("For topical application, the penetration of the adenosine into skin tissue may be enhanced by a variety of methods known to those of ordinary skill in the art."). The Specification also provides examples in which a concentration of adenosine matching the high end of that recited in the claims (10^{-4} M) is applied directly to dermal cells (fibroblasts). *Id.* at 9:5–51. This suggests that the inventors contemplated dermal cells receiving the recited concentration of adenosine.

Petitioner argues that "the only disclosure in the '327 patent where adenosine is 'applied to dermal cells' is associated with *ex vivo* methods (direct application to dermal fibroblasts in cell cultures), and not *in vivo* methods (topical application to human skin) as required by claim 1." Pet. 32. Petitioner further argues that "topical application of adenosine is described in the '327 patent with respect to application of [a] composition containing adenosine to a region of the epidermal layer of the skin containing dermal cells." *Id.* Petitioner contends that these disclosures of *in vivo* topical application contrast with the Specification's disclosure of "*ex vivo* application of adenosine directly to dermal cells (fibroblasts) in a culture medium in a laboratory—*i.e.* ***not relating to topical application to the skin***." *Id.* at 33.

The disclosures identified by Petitioner provide little guidance with respect to the fundamental question posed in connection with Petitioner's proposed construction: is the recited concentration applied to the dermal cells or to the epidermal cells? We acknowledge that the Specification describes methods where adenosine is topically applied to the epidermis and where adenosine is applied *ex vivo* directly to dermal cells. However, as discussed *supra*, the Specification expressly contemplates that adenosine will penetrate the skin. *See e.g.*, Ex. 1001, 5:13–14. Accordingly, these disclosures do not speak to whether the concentration recited in the claims represents the concentration of adenosine at the time it is applied to the epidermis, or whether it instead represents the concentration of adenosine after it has penetrated to the dermis.

We acknowledge that the prosecution history provides some support for Petitioner's proposed construction. In particular, during prosecution, the Patent Owner compared prior art concentrations of adenosine that were recited as a percentage of the total weight of the composition to the concentration recited in the claims as being "applied to dermal cells." For example, Patent Owner stated that the low end of the range recited in DE '107 (0.001% wt) "corresponds to 3.88 x 10^{-5} adenosine" which is "between the 10^{-4}M and 10^{-5}M concentration recited in the claims." Ex. 1009, 84.[5]

[5] On August 28, 2018, after Patent Owner filed its Preliminary Response, the parties contacted the Board by email. Ex. 3001. In the correspondence provided to the Board, Petitioner asserted that Patent Owner failed to "bring to the Board's attention positions that were argued by Patent Owner in continuation applications claiming priority to the '327 and '513 patents, which are contrary to the positions Patent Owner now takes in the POPRs." *Id.* at 4. Petitioner asserted that during prosecution of U.S. Patent Application No. 10/680,370 ("the '370 application"), which includes a

While this statement, and related arguments, provide some support for Petitioner's proposed construction, we do not find them sufficient to overcome the plain and unambiguous language of the claims. *Phillips*, 415 F.3d at 1312 (noting that "[i]t is a 'bedrock principle' of patent law that 'the claims of a patent define the invention to which the patentee is entitled the right to exclude'" and that it would be "unjust to the public, as well as an evasion of the law, to construe [a claim] in a manner different from the plain import of its terms."). More particularly, we do not find in Patent Owner's prosecution arguments an attempt to redefine the term "dermal cells" or to disavow claim scope. *See Thorner v. Sony Computer Entertainment America LLC*, 669 F.3d 1362, 1365 (Fed. Cir. 2012). In this regard, we note that the Patent Owner expressly corrected the Examiner when the Examiner

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limitation like that at issue here, Patent Owner "argued that the concentration of ATP in a prior art ***composition*** (the '649 patent) was outside the claimed concentration range of adenosine analog '***applied to the dermal cells***.'" *Id.* Petitioner contends that this position "is contrary to Patent Owner's position in the POPRs that the claimed concentration is the concentration that reaches the dermal cells." *Id.* Petitioner sought leave to file a Reply to address this issue. *Id.* at 1. We denied Petitioner's request. *Id.* The Petition expressly anticipated that Patent Owner would make the argument that Petitioner now seeks to address. *See* Pet. 36-37 ("Thus, the applicant may take the position in this proceeding that the language 'the adenosine concentration applied to the dermal cells is 10^{-4} M to 10^{-7} M' refers to the concentration of adenosine that ultimately reaches the dermal cells, after topical application to the unbroken epidermal layer of the skin."). Accordingly, Petitioner should have addressed this issue in their Petition. Moreover, the arguments made by Patent Owner in connection with the '370 application are substantially similar to those it made – and disclosed to the Board – in connection with prosecution of the application discussed herein. *See*, Ex. 1009, 84; Prelim Resp. 17–18. As such, we consider the arguments based the '370 application to be cumulative to arguments already of record.

stated in the reasons for allowance that the claims were directed to "administering adenosine at a concentration of 10^{-4} M to 10^{-7} M, to the skin" stating "applicant notes that the claimed concentration of adenosine is applied to the dermal cells." Ex. 1009, 117 (reasons for allowance) and 123 (Patent Owner's comments on reasons for allowance).

Petitioner argues that when adenosine is topically applied (as required by claim 1), it is not possible to determine the amount of adenosine that would ultimately reach the dermal cells after penetrating the epidermal layer of the skin.[6] *See,* Ex. 1010, ¶ 34 (declaration of Dr. Wickett, opining that, in 1998, the skilled artisan would have understood that "it was not possible to calculate with any reasonable certainty an amount of adenosine that reaches the dermal cells when topically applied in view of the numerous variables that would need to be identified and factored into any such calculation."). Ex. 1010, ¶ 34. Thus, according to Petitioner, the "only way the claimed concentration would make sense (i.e., be capable of being determined) is [if] the claimed concentration of adenosine is the amount in the composition that is topically applied, and not the amount that reaches the dermal cells." *Id.* ¶ 35. In addition, Petitioner argues that construing the recited concentration to mean the amount applied to the dermal cells would render the claims invalid for failing to provide adequate written description. Pet. 37–38.

Patent Owner disputes Petitioner's contention that it would not have been possible to determine the amount of adenosine that would penetrate the epidermis. Prelim. Resp. 21 (citing Exhibit 2002, a published patent

[6] Dr. Mustafa opines, "at least some of any concentration of adenosine that is topically applied to the epidermis will be metabolized by epidermal cells and not reach the dermal layer." Ex. 1011, ¶ 14.

application assigned to L'Oréal, as evidence of a skin construct that could have been used to "assess impact on the dermal layer when a compound is applied topically to the epidermis"). Patent Owner also disputes Petitioner's contention that the Specification fails to support its proposed construction. Prelim. Resp. 20; *see also id.* at 15 (asserting that "the patent identifies the proper concentration at the dermal layer and verifies it using *ex vivo* testing of dermal cells, and it explains that application of that concentration at the dermal layer can be achieved by applying a compound topically in a way where the proper concentration of adenosine penetrates to the dermal layer").

We need not resolve these disputes because, even if we credit Petitioner's assertion that Patent Owner's proposed construction renders the claimed process inoperable and/or invalid for lack of written description support, the language of the claims is unambiguous. *Phillips*, 415 F.3d at 1327 (noting that "the maxim that claims should be construed to preserve their validity . . . [has been] limited . . . to cases in which 'the court concludes, after applying all the available tools of claim construction, that the claim is still ambiguous'"). Where the claim language is unambiguous, the Federal Circuit has rejected arguments, like those presented by Petitioner, that construing the claim as written would render the claim invalid and/or produce a nonsensical result. *See Chef America, Inc. v. Lamb–Weston, Inc.*, 358 F.3d 1371, 1374 (Fed. Cir. 2004) (listing cases and stating, "[t]his court . . . repeatedly and consistently has recognized that courts may not redraft claims, whether to make them operable or to sustain their validity"). In *Chef America*, the court declined to construe a claim that required "heating . . . dough ***to*** a temperature in the range of about 400° F. to

850° F . . . as if it read 'heating the ... dough ***at*** a temperature in the range of'" 400° F. to 850° F, even though heating the dough "to" the claimed temperature would burn the dough to a crisp. *Id.* at 1373 (emphasis added). The Federal Circuit explained "we have repeatedly declined to rewrite unambiguous patent claim language" so that it can "perform the function the patentees intended." *Id.* at 1375.

Here, as in *Chef America*, the disputed claim language is unambiguous. It requires an adenosine concentration "applied to the dermal cells." Although "a patentee can act as his own lexicographer to specifically define terms of a claim contrary to their ordinary meaning," *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357 (Fed. Cir. 1999), as discussed above, we discern nothing in the Specification or the prosecution history that suggests the Patent Owner defined "dermal cells" to mean anything other than "dermal cells." Accordingly, we construe the "concentration applied to the dermal cells" to mean what it says – that the recited concentration is the concentration that is applied to the dermal cells.

C. Ground 1: Anticipation by DE '197

Petitioner asserts that claims 1, 3–7, and 9 are anticipated by DE '107. Pet. 40–57. We have reviewed Petitioner's assertions and supporting evidence, and, for the reasons discussed below, we conclude that Petitioner has not demonstrated a reasonable likelihood of prevailing in showing that claims 1, 3–7, and 9 were anticipated by DE '107.

i. Asserted Prior Art

DE '107

DE '107 relates to the "[u]se of an effective content of adenosine in cosmetic or dermatological preparations" and, more particularly, the "[u]se

of adenosine for enhancing cell proliferation in human skin." Ex. 1004, Abstract. DE '107 discloses:

> The present invention . . . includes a cosmetic process for protection of the skin and hair against oxidative or photoxidative processes which is characterized in that a cosmetic agent containing an effective adenosine concentration is applied in sufficient quantity to the skin or hair.
>
> The adenosine content in said preparations is preferably 0.001% by weight to 10% by weight, and particularly 0.01% by weight to 6% by weight relative to the total weight of the preparations.

Id. at 14:10–20. DE '107 discloses 6 examples, each of which include 0.10 % wt. adenosine. *Id.* at 14:35–17:3. DE '107 claims "the use of adenosine for enhancing cell proliferation in human skin." *Id.* at 18:3–4. As discussed above DE '107 was considered during prosecution of the '327 patent.

ii. Analysis

Claim 1 requires that "the adenosine concentration applied to the dermal cells is 10^{-4} M to 10^{-7} M." Petitioner finds that this element is disclosed in DE '107 by applying a claim construction that interprets this limitation to require a concentration "applied to an unbroken, epidermal layer of a region of the skin containing the dermal cells." As discussed above, we have construed the claims to require that the recited concentration be applied to the dermal cells. Because the Petition does not identify evidence reflecting the concentration of adenosine applied to the dermal cells, we find that Petitioner has not demonstrated a reasonable likelihood of prevailing in showing that claims 1, 3–7, and 9 were anticipated by DE '107.

D. Ground 2: Obviousness in view of DE '197

Petitioner asserts that claims 1, 3–7, and 9 would have been obvious in view of DE '107. Pet. 57–60. We have reviewed Petitioner's assertions and supporting evidence, and, for the reasons discussed below, we conclude that Petitioner has not demonstrated a reasonable likelihood of prevailing in showing that claims 1, 3–7, and 9 were obvious in view of DE '107.

i. Disclosures of the Asserted Prior Art

DE '107

The disclosure of DE '107 is discussed *supra p.* 15.

ii. Analysis

Claim 1 requires that "the adenosine concentration applied to the dermal cells is 10^{-4} M to 10^{-7} M." Petitioner finds that this element is disclosed in DE '107 by applying a claim construction that interprets this limitation to require a concentration "applied to an unbroken, epidermal layer of a region of the skin containing the dermal cells." As discussed above, we have construed the claims to require that the recited concentration be applied to the dermal cells. Because the Petition does not identify evidence reflecting the concentration of adenosine applied to the dermal cells, we find that Petitioner has not demonstrated a reasonable likelihood of prevailing in showing that claims 1, 3–7, and 9 were obvious in view of DE '107.

E. Ground 3: Obviousness in view of DE '197 and JP '153

Petitioner asserts that claims 1–7 and 9 would have been obvious in view of the combination of DE '107 and JP '153. Pet. 62–77. We have reviewed Petitioner's assertions and supporting evidence, and, for the

reasons discussed below, we conclude that Petitioner has not demonstrated a reasonable likelihood of prevailing in showing that claims 1–7, and 9 would have been obvious in view of the combination of DE ’107 and JP ’153.

i. Disclosures of the Asserted Prior Art

DE ’107

The disclosure of DE ’107 is discussed *supra p.* 15.

JP ’153

JP’153 discloses the use of topical skin compositions in order to prevent signs of ageing, including wrinkles. Ex. 1006, ¶ 15. More specifically, JP ’153 discloses that “adenosine and derivatives thereof, and hamamelitannin, an extract of two or more plants” exert a synergistic effect when they are used concomitantly in “preparations for external use on the skin.” *Id.* ¶¶ 6–7. JP ’153 further teaches that compounds that include either adenosine or hamamelitannin, but not both, do not achieve the same effect. *Id.* ¶ 11 and Tables 1 and 2. JP ’153 discloses that compositions comprising 0.01–10% wt. adenosine are “suitable” and exemplifies compositions containing adenosine in amount of 0.02%. *Id.* ¶¶ 12, 21, 22.

ii. Analysis

Claim 1 requires that “the adenosine concentration applied to the dermal cells is 10^{-4} M to 10^{-7} M.” Petitioner finds that this element is disclosed in the combination of DE ’107 and JP ’153 by applying a claim construction that interprets this limitation to require a concentration “applied to an unbroken, epidermal layer of a region of the skin containing the dermal cells.” As discussed above, we have construed the claims to require that the recited concentration be applied to the dermal cells. Because the Petition does not identify evidence reflecting the concentration of adenosine applied

to the dermal cells, we find that Petitioner has not demonstrated a reasonable likelihood of prevailing in showing that claims 1, 3–7, and 9 were obvious in view of the combination of DE ’107 and JP ’153.

III. CONCLUSION

For the foregoing reasons, we deny the Petition and do not institute trial as to any of the challenged claims of the ’327 patent. Specifically, we decline to institute *inter partes* review on the ground that claims 1, 3–7, and 9 are anticipated by DE ’107, on the ground that claims 1, 3–7, and 9 would have been obvious in view of DE ’107, and on the ground that claims 1–7 and 9 would have been obvious in view of the combination of DE ’107 and JP ’153.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is denied as to all the challenged claims of the ’327 patent.

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Paper No. 10
Entered: September 7, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

L'ORÉAL USA, INC.
Petitioner,

v.

UNIVERSITY OF MASSACHUSETTS
Patent Owner.

Case IPR2018-00779
Patent 6,645,513 B1

Before CHRISTOPHER G. PAULRAJ, ROBERT A. POLLOCK, and DAVID COTTA, *Administrative Patent Judges*.

COTTA, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 314(a)

I. INTRODUCTION

L'Oréal USA, Inc. ("Petitioner" or "L'Oréal") filed a petition requesting an *inter partes* review of claims 1–7 and 9 of U.S. Patent No. 6,645,513 B2 (Ex. 1002, "the '513 patent"). Paper 2 ("Pet."). The University of Massachusetts ("Patent Owner" or "UMass") filed a Preliminary Response to the Petition. Paper 8 (Prelim. Resp.).

Institution of an *inter partes* review is authorized by statute when "the information presented in the petition . . . and any response . . . shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314; *see* 37 C.F.R. §§ 42.4, 42.108. Upon considering the Petition, the Preliminary Response, and the cited evidence, we conclude that Petitioner has not satisfied its burden under 35 U.S.C. § 314(a) to show that there is a reasonable likelihood that it would prevail with respect to at least one of the challenged claims.

A. Related Proceedings

Petitioner and Patent Owner identify the following district court proceeding as relating to the '513 patent: *University of Massachusetts Medical School and Carmel Laboratories, LLC v. L'Oréal S.A. and L'Oréal USA, Inc.*, No. 1:17-cv-00868 (D. Del.). Pet. 3–4; Paper 5, 2. Petitioner and Patent Owner identify the following *inter partes* review proceeding as related to the '513 patent: IPR2018-00778, which challenges the patentability of U.S. Patent No. 6,423,327 ("the '327 patent"). *Id*. The '327 patent is the parent of the '513 patent. *Id.*

B. The '513 Patent (Ex. 1002)

The '513 patent issued Nov. 11, 2003, identifying James G. Dobson, Jr. and Michael F. Ethier as co-inventors. Ex. 1002. The patent discloses "methods and compositions for enhancing the condition of skin." *Id.* at 1:45–46.

The '513 patent teaches that "[s]kin includes a surface layer, known as the epidermis, and a deeper connective tissue layer, known as the dermis." *Id.* at 1:25–26. "The dermis is composed of a variety of cell types, including fibroblasts." *Id.* at 1:29–30. "As skin ages, or is exposed to UV light and other environmental insults, changes in the underlying dermis can lead to the functional and morphological changes associated with damaged skin." *Id.* at 1:32–36. According to the '513 patent, "[d]ecreases in the abundance and function of products of the fibroblasts, which include collagen and proteoglycans, are believed to play major roles in wrinkled and damaged skin." *Id.* at 1:36–39.

The '513 patent discloses that the inventors "discovered that adenosine stimulates DNA synthesis, increases protein synthesis, and increases cell size in cultures of human skin fibroblasts." *Id.* at 1:42–44. Based on this discovery, the inventors provide methods for "enhancing the condition of non-diseased skin" which comprise "topically administering a therapeutically effective amount of adenosine or an adenosine analog to a region of non-diseased skin of the mammal containing dermal cell." *Id.* at 1:45–65. The methods require that "[t]he adenosine is added so that it does not cause proliferation of the dermal cell." *Id.* at 64–65. "The therapeutically effective amount of adenosine used in [these] methods is

preferably 10^{-3} M to 10^{-7} M, more preferably 10^{-3} M to 10^{-6} M, and most preferably about 10^{-4} M." *Id.* at 2:20–24.

C. Challenged Claims

Petitioner challenges claims 1–7 and 9 of the '513 patent. Claim 1, the only independent claim, is reproduced below:

> 1. A method for enhancing the condition of unbroken skin of a mammal by reducing one or more of wrinkling, roughness, dryness, or laxity of the skin, without increasing dermal cell proliferation, the method comprising topically applying to the skin a composition comprising a concentration of adenosine in an amount effective to enhance the condition of the skin without increasing dermal cell proliferation, wherein the adenosine concentration applied to the dermal cells is 10^{-3} M to 10^{-7} M.

Ex. 1001, 10:17–27.

D. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1–7 and 9 of the '513 patent on the following grounds (Pet. 6):

Ground	References	Basis	Claims Challenged
1	JP '153[1]	§ 102(b)	1–7, and 9
2	JP '153	§ 103(a)	4
3	JP '153 and DE '107[2]	§ 103(a)	1–7 and 9

[1] Murayama, JP H9-157153 A, published June 17, 1997 ("JP '153"). JP '153 was originally published in Japanese. Ex, 1005. All citations herein are to Exhibit 1006, the English translation of JP '153 provided by the Petitioner.

[2] Schönrock et al., DE 195 45 107 A1, published June 5, 1997 ("DE '107"). DE '107 was originally published in German. Ex. 1003. All citations herein are to Exhibit 1004, the English translation of DE '107 provided by the Petitioner.

Petitioner submits the Declarations of Dr. R. Randall Wickett (Ex. 1010) and Dr. S. Jamal Mustafa (Ex. 1011) in support of institution of *inter partes* review.

II. ANALYSIS

A. Person of Ordinary Skill in the Art

Factual indicators of the level of ordinary skill in the art include "the various prior art approaches employed, the types of problems encountered in the art, the rapidity with which innovations are made, the sophistication of the technology involved, and the educational background of those actively working in the field." *Jacobson Bros., Inc. v. U.S.*, 512 F.2d 1065, 1071 (Ct. Cl. 1975); *see also Orthopedic Equip. Co., Inc. v. U.S.*, 702 F.2d 1005, 1011 (Fed. Cir. 1983) (quoting with approval *Jacobson Bros*.).

Petitioner contends that the person of ordinary skill "would have a Bachelor['s] degree in Biochemistry or Chemistry with some academic exposure to, or industry courses or research in, topical delivery of drugs or cosmetic ingredients." Pet. 13. At this stage in the proceeding, Patent Owner does not challenge Petitioner's definition. Accordingly, for purposes of this Decision, we accept Petitioner's definition, which is supported by Dr. Wickett's declaration (Ex. 1010, ¶ 28) and is consistent with the level of skill reflected in the asserted prior art references. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (the prior art itself can reflect the appropriate level of ordinary skill in the art).

Moreover, we have reviewed the credentials for Drs. Wickett and Mustafa (Exs. 1010 and 1011) and, at this stage in the proceeding, we consider Drs. Wickett and Mustafa to be qualified to provide opinions on the

requisite level of skill and the knowledge of a person of ordinary skill in the art at the time of the invention.

B. Claim Construction

On April 19, 2018, Patent Owner filed a motion under 37 C.F.R. § 42.100(b) requesting that the Board apply a district court-type claim construction like that provided in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (en banc) in this proceeding. Paper 6. We granted Patent Owner's request in an order entered June 21, 2018. Accordingly, in this proceeding, we will give claim terms their ordinary and customary meaning, as would be understood by a person of ordinary skill in the art, at the time of the invention, in light of the language of the claims, the specification, and the prosecution history of record. *Phillips*, 415 F.3d at 1313. We also consider the extrinsic evidence presented by Petitioner. *Id.* at 1317.

We construe claim terms only to the extent necessary to resolve the controversy. *See, e.g., Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999). For purposes of this decision, we need only construe the limitation in claim 1 requiring "topically applying to the skin a composition comprising a concentration of adenosine" and the limitation requiring "wherein the adenosine concentration applied to the dermal cells is 10^{-3} M to 10^{-7} M." Ex. 1002, 10:17–26.

i. Construction of: "topically applying to the skin a composition comprising a concentration of adenosine"

Claim 1 of the '513 patent requires "topical" application of a composition containing adenosine to "unbroken skin." Petitioner contends that "topical" application of a composition containing adenosine to "unbroken skin" requires that "a composition be applied directly to the outer, epidermal layer of the skin that is intact and does not have any

damage, such as wounds or cuts, burns, etc., such that the inner, dermal layer of the skin is not exposed." Pet. 16.

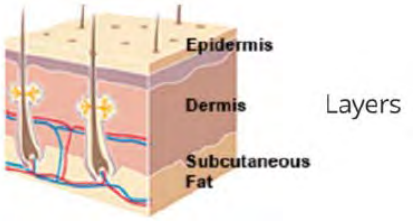
Patent Owner does not oppose Petitioner's proposed construction. Moreover, Petitioner's construction is in accord with the plain meaning of the terms "topical" and "unbroken." *See,* Pet. 16–17 (arguing that the person of ordinary skill in the art would have understood "topical" to mean "applied to the exterior surface of the target" and "unbroken," with regard to skin, to mean "free from any cuts, wounds, burns, or other damage that would expose the inner layers of the skin."). It is also consistent with the Specification and the prosecution history. *See, e.g.*, Ex. 1002, 5:16–36 (distinguishing topical administration from "oral, subdermal, intradermal, or intravenous" administration); Ex. 1009, 67 (arguing that the claimed method was distinguishable over a prior art reference because the reference involved application of adenosine to "open wounds such as burns"). Accordingly, for purposes of this decision, we adopt Petitioner's proposed construction of the phrase "topically applying to the skin a composition comprising a concentration of adenosine."

ii. Construction of: "wherein the adenosine concentration applied to the dermal cells is 10^{-3} M to 10^{-7} M."

Claim 1 of the '513 patent requires that "the adenosine concentration applied to the dermal cells is 10^{-3} M to 10^{-7} M." Petitioner proposes that this language should be construed to require "***the concentration of adenosine in the composition that is topically applied to the unbroken, outer epidermal layer of a region of the skin containing the dermal cells***" to be from 10^{-3} M to 10^{-7} M. Pet. 20. Patent Owner contends that Petitioner's proposed construction is contrary to the ordinary meaning of "dermal" and proposes that the claim language "be construed to mean what it says – that the recited

concentration is the concentration that is applied to the dermal cells." Prelim. Resp. 12. We find that Patent Owner has the better position.

There is no dispute that the skin is comprised of multiple layers. Pet. 8; Ex. 1010 ¶ 31; Prelim. Resp. 13, n. 2. As the '513 patent explains, "[s]kin includes a surface layer, known as the epidermis, and a deeper connective tissue layer, known as the dermis." Ex. 1002, 1:25–26. The multiple layers of skin are illustrated in the below figure.



The above figure was provided by the Patent Owner and was reproduced from the website of the American Academy of Dermatology Association. Prelim. Resp. 13, n. 2. It depicts the three separate layers of the skin: the epidermis (the top layer), the dermis (the second layer), and subcutaneous fat (the bottom layer). *Id.*

The fundamental question presented by Petitioner in connection with its proposed construction is whether the recited concentration is applied to the dermal cells or to the epidermal cells.[3] The claim language at issue supplies a clear answer. As discussed above, claim 1 recites that the concentration of adenosine is "applied to the dermal cells."

This construction gives different meanings to the claim terms "the

[3] Petitioner does not identify, and we do not discern in the current record, evidence to suggest that there is a meaningful difference between the "outer epidermal layer of a region of the skin containing the dermal cells" recited in Petitioner's proposed claim construction, and the epidermis. *See*, Ex. 1010, ¶ 31 ("Skin is comprised of many layers, including an outer, epidermal layer, which covers multiple inner layers (including the dermal layers)").

skin" and "the dermal cells," and is thus consistent with the cannon that "[d]ifferent claim terms are presumed to have different meanings." *Bd. Of Regents of the Univ. of Tex. Sys. v. BENQ Am. Corp.,* 533 F.3d 1362, 1371 (Fed. Cir. 2008). In contrast, we do not discern any meaningful difference between an "epidermal layer of the skin that is intact," which is the construction we have adopted for "applying to the skin," and an "epidermal layer of a region of the skin containing the dermal cells," which is the construction Petitioner proposes for adenosine "applied to the dermal cells." One would expect that if the Patent Owner had intended both "applications" recited in the claim 1 to be made to the same cells, Patent Owner would have used the same term to describe both applications.

Construing the phrase "concentration applied to the dermal cells" to require what it says – i.e., application to the dermal cells – is consistent with the disclosure provided in the Specification. In order for a concentration of topically applied adenosine to be "applied to the dermal cells," it must penetrate the epidermis. The Specification expressly contemplates that adenosine will penetrate the skin. *See e.g.,* Ex. 1002, 5:20–23 ("For topical application, the penetration of the adenosine into skin tissue may be enhanced by a variety of methods known to those of ordinary skill in the art."). The Specification also provides examples in which a concentration of adenosine within the range recited in the claims (10^{-4} M) is applied directly to dermal cells (fibroblasts). *Id.* at 9:7–51. This suggests that the inventors contemplated dermal cells receiving the recited concentration of adenosine.

Petitioner argues that "the only disclosure in the '513 patent where adenosine is 'applied to dermal cells' is associated with *ex vivo* methods (direct application to dermal fibroblasts in cell cultures), and not *in vivo*

methods (topical application to human skin) as required by claim 1." Pet. 20. Petitioner further argues that "topical application of adenosine is described in the '513 specification with respect to application of [a] composition containing adenosine to a ***region of the epidermal layer of the skin containing dermal cells***." *Id.* at 21. Petitioner contends that these disclosures of *in vivo* topical application contrast with the Specification's disclosure of "*ex vivo* application of adenosine directly to dermal cells (fibroblasts) in a culture medium in a laboratory—*i.e.* ***not relating to topical application to the skin***." *Id.* at 22.

The disclosures identified by Petitioner provide little guidance with respect to the fundamental question posed in connection with Petitioner's proposed construction: is the recited concentration applied to the dermal cells or to the epidermal cells? We acknowledge that the Specification describes methods where adenosine is topically applied to the epidermis and where adenosine is applied *ex vivo* directly to dermal cells. However, as discussed *supra*, the Specification expressly contemplates that adenosine will penetrate the skin. *See e.g.*, Ex. 1001, 5:13–14. Accordingly, these disclosures do not speak to whether the concentration recited in the claims represents the concentration of adenosine at the time it is applied to the epidermis, or whether it instead represents the concentration of adenosine after it has penetrated to the dermis.

We acknowledge that the prosecution history of the parent application provides some support for Petitioner's proposed construction. In particular, during prosecution, the Patent Owner compared prior art concentrations of adenosine that were recited as a percentage of the total weight of the composition to the concentration recited in the claims as being "applied to

dermal cells." For example, Patent Owner stated that the low end of the range recited in DE '107 (0.001% wt) "corresponds to 3.88 x 10^{-5} adenosine" which is "between the 10^{-4}M and 10^{-5}M concentration recited in the claims." Ex. 1009, 84.[4]

While this statement, and related arguments, provides some support for Petitioner's proposed construction, we do not find them sufficient to overcome the plain and unambiguous language of the claims. *Phillips*, 415

[4] On August 28, 2018, after Patent Owner filed its Preliminary Response, the parties contacted the Board by email. Ex. 3001. In the correspondence provided to the Board, Petitioner asserted that Patent Owner failed to "bring to the Board's attention positions that were argued by Patent Owner in continuation applications claiming priority to the '327 and '513 patents, which are contrary to the positions Patent Owner now takes in the POPRs." *Id.* at 4. Petitioner asserted that during prosecution of U.S. Patent Application No. 10/680,370 ("the '370 application"), which includes a limitation like that at issue here, Patent Owner "argued that the concentration of ATP in a prior art ***composition*** (the '649 patent) was outside the claimed concentration range of adenosine analog '***applied to the dermal cells***.'" *Id.* Petitioner contends that this position "is contrary to Patent Owner's position in the POPRs that the claimed concentration is the concentration that reaches the dermal cells." *Id.* Petitioner sought leave to file a Reply to address this issue. *Id.* at 1. We denied Petitioner's request. *Id.* The Petition expressly anticipated that Patent Owner would make the argument that Petitioner now seeks to address. See Pet. 26 ("Thus, the applicant may take the position in this proceeding that the language 'the adenosine concentration applied to the dermal cells is 10^{-3} M to 10^{-7} M' refers to the concentration of adenosine that ultimately reaches the dermal cells, after topical application to the unbroken epidermal layer of the skin."). Accordingly, Petitioner should have addressed this issue in their Petition. Moreover, the arguments made by Patent Owner in connection with the '370 application are substantially similar to those it made – and disclosed to the Board – in connection with prosecution of the application discussed herein. *See,* Ex. 1009, 84; Prelim Resp. 18–19. As such, we consider the arguments based the '370 application to be cumulative to arguments already of record.

F.3d at 1312 (noting that "[i]t is a 'bedrock principle' of patent law that 'the claims of a patent define the invention to which the patentee is entitled the right to exclude'" and that it would be "unjust to the public, as well as an evasion of the law, to construe [a claim] in a manner different from the plain import of its terms."). More particularly, we do not find in Patent Owner's prosecution arguments an attempt to redefine the term "dermal cells" or to disavow claim scope. *See*, *Thorner v. Sony Computer Entertainment America LLC*, 669 F.3d 1362, 1365 (Fed. Cir. 2012). In this regard, we note that the Patent Owner expressly corrected the Examiner when the Examiner stated in the reasons for allowance that the claims were directed to "administering adenosine at a concentration of 10^{-4} M to 10^{-7} M, to the skin," stating "applicant notes that the claimed concentration of adenosine is applied to the dermal cells." Ex. 1009, 117 (reasons for allowance) and 123 (Patent Owner's comments on reasons for allowance).

Petitioner argues that when adenosine is topically applied (as required by claim 1), it is not possible to determine the amount of adenosine that would ultimately reach the dermal cells after penetrating the epidermal layer of the skin.[5] *See*, Ex. 1010, ¶ 34 (declaration of Dr. Wickett, opining that, in 1998, the skilled artisan would have understood that "it was not possible to calculate with any reasonable certainty an amount of adenosine that reaches the dermal cells when topically applied in view of the numerous variables that would need to be identified and factored into any such calculation."). Ex. 1010, ¶ 34. Thus, according to Petitioner, the "only way the claimed

[5] Dr. Mustafa opines, "at least some of any concentration of adenosine that is topically applied to the epidermis will be metabolized by epidermal cells and not reach the dermal layer." Ex. 1011, ¶ 15.

concentration would make sense (i.e., be capable of being determined) is [if] the claimed concentration of adenosine is the amount in the composition that is topically applied, and not the amount that reaches the dermal cells." *Id.* ¶ 35. In addition, Petitioner argues that construing the recited concentration to mean the amount applied to the dermal cells would render the claims invalid for failing to provide adequate written description. Pet. 26–27.

Patent Owner disputes Petitioner's contention that it would not have been possible to determine the amount of adenosine that would penetrate the epidermis. Prelim. Resp. 23 (citing Exhibit 2002, a published patent application assigned to L'Oréal, as evidence of a skin construct that could have been used to "assess impact on the dermal layer when a compound is applied topically to the epidermis"). Patent Owner also disputes Petitioner's contention that the Specification fails to support its proposed construction. Prelim. Resp. 22; *see also id.* at 16 (asserting that "the patent identifies the proper concentration at the dermal layer and verifies it using *ex vivo* testing of dermal cells, and it explains that application of that concentration at the dermal layer can be achieved by applying a compound topically in a way where the proper concentration of adenosine penetrates to the dermal layer").

We need not resolve these disputes because, even if we credit Petitioner's assertion that Patent Owner's proposed construction renders the claimed process inoperable and/or invalid for lack of written description support, the language of the claims is unambiguous. *Phillips,* 415 F.3d at 1327 ("the maxim that claims should be construed to preserve their validity. . . [has been] limited . . . to cases in which 'the court concludes, after applying all the available tools of claim construction, that the claim is still

ambiguous'"). Where the claim language is unambiguous, the Federal Circuit has rejected arguments, like those presented by Petitioner, that construing the claim as written would render the claim invalid and/or produce a nonsensical result. *See, Chef America, Inc. v. Lamb–Weston, Inc.*, 358 F.3d 1371, 1374 (Fed. Cir. 2004) (listing cases and stating: "[t]his court . . . repeatedly and consistently has recognized that courts may not redraft claims, whether to make them operable or to sustain their validity"). In *Chef America*, the court declined to construe a claim that required "heating . . . dough ***to*** a temperature in the range of about 400° F. to 850° F . . . as if it read 'heating the ... dough ***at*** a temperature in the range of'" 400° F. to 850° F, even though heating the dough "to" the claimed temperature would burn the dough to a crisp. *Id.* at 1373 (emphasis added). The Federal Circuit explained "we have repeatedly declined to rewrite unambiguous patent claim language" so that it can "perform the function the patentees intended." *Id.* at 1375.

Here, as in *Chef America*, the disputed claim language is unambiguous. It requires an adenosine concentration "applied to the dermal cells." Although "a patentee can act as his own lexicographer to specifically define terms of a claim contrary to their ordinary meaning," *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357 (Fed.Cir.1999), as discussed above, we discern nothing in the Specification or the prosecution history that suggests the Patent Owner defined "dermal cells" to mean anything other than "dermal cells." Accordingly, we construe the "concentration applied to the dermal cells" to mean what it says – that the recited concentration is the concentration that is applied to the dermal cells.

C. Ground 1: Anticipation by JP '153

Petitioner asserts that claims 1–7 and 9 were anticipated by JP '153. Pet. 30–49. We have reviewed Petitioner's assertions and supporting evidence, and, for the reasons discussed below, we conclude that Petitioner has not demonstrated a reasonable likelihood of prevailing in showing that claims 1–7 and 9 were anticipated by JP '153.

i. Asserted Prior Art

JP '153

JP '153 discloses the use of topical skin compositions in order to prevent signs of ageing, including wrinkles. Ex. 1006, ¶ 15. More specifically, JP '153 discloses that "adenosine and derivatives thereof, and hamamelitannin, an extract of two or more plants" exert a synergistic effect when they are used concomitantly in "preparations for external use on the skin." Id. ¶¶ 6–7. JP '153 further teaches that compounds that include either adenosine or hamamelitannin, but not both, do not achieve the same effect. Id. ¶ 11 and Tables 1 and 2. JP'153 discloses that compositions comprising 0.01–10% wt. adenosine are "suitable" and exemplifies compositions containing adenosine in amount of 0.02%. Id. ¶¶ 12, 21, 22.

ii. Analysis

Claim 1 requires that "the adenosine concentration applied to the dermal cells is 10^{-3} M to 10^{-7} M." Petitioner finds that this element is disclosed in DE '107 by applying a claim construction that interprets this limitation to require a concentration "applied to an unbroken, epidermal layer of a region of the skin containing the dermal cells." As discussed above, we have construed the claims to require that the recited concentration be applied to the dermal cells. Because the Petition does not identify

evidence reflecting the concentration of adenosine applied to the dermal cells, we find that Petitioner has not demonstrated a reasonable likelihood of prevailing in showing that claims 1–7, and 9 were anticipated by JP ’153.

D. Ground 2: Obviousness in view of JP ’153

Petitioner asserts that claim 4 would have been obvious in view of JP ’153. Pet. 49–52. We have reviewed Petitioner’s assertions and supporting evidence, and, for the reasons discussed below, we conclude that Petitioner has not demonstrated a reasonable likelihood of prevailing in showing that claim 4 would have been obvious in view of JP ’153.

i. Disclosures of the Asserted Prior Art

JP ’153

The disclosure of JP ’153 is discussed *supra p.* 14–15.

ii. Analysis

Claim 4 depends from claim 1 and further requires “wherein the adenosine concentration is about 10^{-3} M.” Petitioner does not identify any evidence or advance any arguments in connection with Ground 2 that address the deficiencies discussed above with respect to Ground 1. Accordingly, we find that Petitioner has not demonstrated a reasonable likelihood of prevailing in showing that claim 4 would have been obvious in view of JP ’153.

E. Ground 3: Obviousness in view of DE ’197 and JP ’153

Petitioner asserts that claims 1–7 and 9 would have been obvious in view of the combination of DE ’107 and JP ’153. Pet. 52–69. We have reviewed Petitioner’s assertions and supporting evidence, and, for the reasons discussed below, we conclude that Petitioner has not demonstrated a

reasonable likelihood of prevailing in showing that claims 1–7, and 9 would have been obvious in view of the combination of DE ’107 and JP ’153.

iii. Disclosures of the Asserted Prior Art

JP ’153

The disclosure of JP ’153 is discussed *supra p.* 14–15.

DE ’107

DE ’107 relates to the “[u]se of an effective content of adenosine in cosmetic or dermatological preparations” and, more particularly, the “[u]se of adenosine for enhancing cell proliferation in human skin.” Ex. 1004, Abstract. DE ’107 discloses:

> The present invention . . . includes a cosmetic process for protection of the skin and hair against oxidative or photoxidative processes which is characterized in that a cosmetic agent containing an effective adenosine concentration is applied in sufficient quantity to the skin or hair.
>
> The adenosine content in said preparations is preferably 0.001% by weight to 10% by weight, and particularly 0.01% by weight to 6% by weight relative to the total weight of the preparations.

Id. at 14:10–20. DE ’107 discloses 6 examples, each of which include 0.10 % wt. adenosine. Id. at 14:35–17:3. DE ’107 claims “the use of adenosine for enhancing cell proliferation in human skin.” Id. at 18:3–4.

iv. Analysis

Claim 1 requires that “the adenosine concentration applied to the dermal cells is 10^{-3} M to 10^{-7} M.” Petitioner finds that this element is disclosed in the combination of JP ’153 and DE ’107 by applying a claim construction that interprets this limitation to require a concentration “applied

to an unbroken, epidermal layer of a region of the skin containing the dermal cells." As discussed above, we have construed the claims to require that the recited concentration be applied to the dermal cells. Because the Petition does not identify evidence reflecting the concentration of adenosine applied to the dermal cells, we find that Petitioner has not demonstrated a reasonable likelihood of prevailing in showing that claims 1, 3–7, and 9 would have been obvious in view of the combination of DE '107 and JP '153.

III. CONCLUSION

For the foregoing reasons, we deny the Petition and do not institute trial as to any of the challenged claims of the '513 patent. Specifically, we decline to institute *inter partes* review on the ground that claims 1–7 and 9 are anticipated by JP '153, on the ground that claim 4 would have been obvious in view of JP '153, and on the ground that claims 1–7 and 9 would have been obvious in view of the combination of JP '153 and DE '107.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is denied as to all the challenged claims of the '513 patent.

IPR2018-00779
Patent 6,645,513 B2

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Paper No. 12
Filed: November 16, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

L'ORÉAL USA, INC.,
Petitioner,

v.

UNIVERSITY OF MASSACHUSETTS,
Patent Owner.

Case IPR2018-00778
Patent 6,423,327 B1

Before CHRISTOPHER G. PAULRAJ, ROBERT A. POLLOCK, and DAVID COTTA, *Administrative Patent Judges*.

COTTA, *Administrative Patent Judge*.

DECISION
Denying Petitioner's Request for Rehearing
37 C.F.R. § 42.71(d)

I. INTRODUCTION

L'Oréal USA, Inc. ("Petitioner" or "L'Oréal") filed a petition requesting an *inter partes* review of claims 1–7 and 9 of U.S. Patent No. 6,423,327 B1 (Ex. 1001, "the '327 patent"). Paper 2 ("Pet."). The University of Massachusetts ("Patent Owner" or "UMass") filed a Preliminary Response to the Petition. Paper 7 ("Prelim. Resp."). On

September 7, 2018, after consideration of the Petition and Preliminary Response, we entered a Decision denying institution of *inter partes* review Paper 9 ("Dec."). On October 11, 2018, Petitioner filed a Corrected Request for Rehearing (Paper 11, "Req. Reh'g") seeking reconsideration of the Decision.[1]

For the reasons stated below, Petitioner's Request for Rehearing is denied.

II. ANALYSIS

Standard of Review

When reconsidering a decision on institution, we review the decision for an abuse of discretion. 37 C.F.R. § 42.71(c). An abuse of discretion may be found if a decision is based on an erroneous interpretation of law, if a factual finding is not supported by substantial evidence, or if the decision represents an unreasonable judgment in weighing relevant factors. *Star Fruits S.N.C. v. U.S.*, 393 F.3d 1277, 1281 (Fed. Cir. 2005); *Arnold P'ship v. Dudas*, 362 F.3d 1338, 1340 (Fed. Cir. 2004); *In re Gartside*, 203 F.3d 1305, 1315–16 (Fed. Cir. 2000). The party requesting rehearing has the burden of showing the decision should be modified, which includes specifically identifying all matters the party believes we misapprehended or overlooked. 37 C.F.R. § 42.71(d).

[1] Petitioner filed a Request for Rehearing on October 9, 2018. Paper 10. Because the request was incorrectly captioned, with the permission of the Board (Ex. 3002), Petitioner refiled a request for rehearing correcting this clerical error. Paper 11. All citations herein are to the Corrected Request for Rehearing.

Background

Petitioner challenged claims 1–7 and 9 of the '327 patent on three related grounds: that claims 1, 3–7, and 9 are anticipated by DE '107[2]; that claims 1, 3–7, and 9 are obvious over DE '107; and that claims 1–7 and 9 would have been obvious over the combination of JP '153[3] and DE '107. Pet. 11–12. We declined to institute *inter partes* review. Dec. 15–19.

Petitioner's Request for Rehearing focuses on our construction of the limitation in claim 1 requiring that "the adenosine concentration applied to the dermal cells is 10^{-4} M to 10^{-7} M." In the Petition, Petitioner argued that this limitation should be construed to mean "a concentration of adenosine ***in the composition*** that is topically applied to an unbroken, epidermal layer of a region of the skin containing the dermal cells to be from 10^{-4} M to 10^{-7} M (*i.e.*, 0.00000265 to 0.00265 wt %)." Pet. 27. In the Decision denying institution, we rejected Petitioner's proposed construction and construed this limitation to mean "mean what it says – that the recited concentration is the concentration that is applied to the dermal cells." Dec. 15.

Legal Principles

For the reasons discussed in connection with our institution decision, we applied a district court-type claim construction like that provided in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (en banc). Dec. 6.

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[2] Schönrock et al., DE 195 45 107 A1, published June 5, 1997 ("DE '107"). DE '107 was originally published in German. Ex. 1003. All citations herein are to Exhibit 1004, the English translation of DE '107 provided by the Petitioner.

[3] Murayama, JP H9-157153 A, published June 17, 1997 ("JP '153"). JP '153 was originally published in Japanese. Ex, 1005. All citations herein are to Exhibit 1006, the English translation of JP '153 provided by the Petitioner.

Under this standard, we gave claim terms their ordinary and customary meaning, as would be understood by a person of ordinary skill in the art, at the time of the invention, in light of the language of the claims, the specification, and the prosecution history of record. *Phillips*, 415 F.3d at 1313. We also considered the extrinsic evidence presented by Petitioner. *Id.* at 1317. Petitioner does not challenge our decision to apply the *Phillips* claim construction standard. Req. Reh'g 2.

Analysis

Claim 1 of the '327 patent, the only independent claim, requires "topically applying to the skin a composition comprising a concentration of adenosine." In the Decision, we construed this limitation to require that "a composition be applied directly to the outer, epidermal layer of the skin that is intact . . . such that the inner, dermal layer of the skin is not exposed." Dec. 7–8. Petitioner agrees that this is the correct construction. Req. Reh'g 4.

Claim 1 also requires that "the adenosine concentration applied to the dermal cells is 10^{-4} M to 10^{-7} M." In the Decision, we construed this limitation to require that the recited concentration is "the concentration that is applied to the dermal cells." Dec. 15. Petitioner argues that we "incorrectly applied *Phillips* by interpreting only two words of the claim, *i.e.* 'dermal cells,' in isolation, overlooking the remaining language of the claims and therefore failing to accord sufficient weight to the specification and file history or Petitioner's evidence." Req. Reh'g 2. We are not persuaded.

Any construction of the phrase "concentration applied to the dermal cells" must ascribe some meaning to the term "dermal cells." As discussed

in the Decision, there is no dispute that the skin is comprised of multiple layers, including the epidermis, the dermis, and subcutaneous fat. Dec. 8–9. Our construction gives the term "dermal cells" its ordinary meaning by construing it to refer to "dermal cells"—i.e., the dermis or dermal layer. We do not find in the record, and Petitioner does not suggest, another way to interpret the limitation "concentration applied to the dermal cells" consistent with the ordinary meaning of the words "dermal cells."

Petitioner proposes that we construe the limitation "concentration applied to the dermal cells" to mean "a concentration . . . applied to an unbroken, epidermal layer of a region of the skin containing the dermal cells." Pet. 27. However, as noted in the Decision, there is no meaningful difference between the "epidermal layer of a region of the skin containing the dermal cells" recited in Petitioner's proposed claim construction, and the epidermis. Dec. 9 n.4. Petitioner's proposed construction is, thus, contrary to the language of the claim, because it changes the meaning of "dermal cells" to "epidermal cells."

Petitioner argues, in effect, that the ordinary meaning of the term "dermal cells" changes when it is considered "within the context of the immediately-preceding words '***applied to***,' and the ***single recited application step***." Req. Reh'g 3. According to Petitioner, there is only one step in claim 1 in which adenosine is "applied" and that step requires application to the skin (which we interpreted to mean the epidermal layer of the skin). Petitioner contends the claim term "applied" in the limitation "applied to the dermal cells" must be understood to refer back to this step of applying adenosine to the epidermal layer of the skin because, otherwise,

"the language '***the adenosine concentration applied***' would lack antecedent basis." *Id.* at 4. We are not persuaded.

As discussed in the Decision, the Specification discloses not only that adenosine may be topically applied to the epidermal layer of the skin, but also that adenosine so applied will penetrate the epidermis to reach the dermal layer. Dec. 10 (citing Ex. 1001, 5:13–14 ("For topical application, the penetration of the adenosine into skin tissue may be enhanced by a variety of methods known to those of ordinary skill in the art.")). Topical application of adenosine will, therefore, result in adenosine being brought into contact with both the epidermis and the dermis. As also discussed in the Decision, the specification provides examples in which a concentration of adenosine matching the high end recited in the claims (10^{-4} M) is applied directly to dermal cells (fibroblasts), suggesting that the inventors considered it desirable for the dermal cells to receive the claimed concentration of adenosine. *Id.* In this context, the meaning of claim 1 is clear: adenosine is first topically applied to the epidermal layer of the skin and, only after it penetrates this outer skin layer, is a specific concentration (10^{-4} M to 10^{-7} M) of the adenosine "applied" to the dermal cells.

Petitioner argues that our construction is incorrect because it "concludes that 'applied to the dermal cells' means 'reached' or 'received by' the dermal cells, or 'penetrates through' the skin to reach the dermal cells." Req. Reh'g 12. Petitioner asserts that "[s]uch an interpretation improperly alters the meaning of 'topically applying' and 'applied.'" *Id.*

This argument, however, fails to account for the context provided by the Specification which, as discussed above, teaches that adenosine will penetrate the skin. Particularly when considered in this context, we do not

read the term "applied" so narrowly as to exclude an application which reaches its target destination (here the "dermal cells") by passing through a layer that overlies the target destination (here the epidermis). This is consistent with the ordinary meaning of "apply" — i.e., "to bring into physical contact with or close proximity to." Ex. 3003 (definition 9 from dictionary.com (last accessed Oct. 26, 2018), *see also*, definition 8). Here, adenosine is brought into physical contact with the dermal cells. Nothing in the language of the claims, as interpreted in light of the intrinsic and extrinsic evidence, requires that adenosine be applied *directly* to the dermal cells.

Petitioner argues that we erred in failing to find a prosecution disclaimer. Req. Reh'g 5–10. More particularly, Petitioner argues that our acknowledgement that the Patent Owner "compared prior art concentrations of adenosine that were recited as a percentage of the ***total weight of the composition to the concentration recited in the claims as being 'applied to the dermal cells'***" requires that we find a prosecution disclaimer. *Id.* at 6 (internal citation omitted). We are not persuaded.

A prosecution history disclaimer must be clear and unambiguous. "[W]hile the prosecution history can inform whether the inventor limited the claim scope in the course of prosecution, it often produces ambiguities created by ongoing negotiations between the inventor and the PTO. . . . Therefore, the doctrine of prosecution disclaimer only applies to unambiguous disavowals." *Grober v. Mako Prods., Inc*., 686 F.3d 1335, 1341 (Fed. Cir. 2012) (citing *Abbott Labs. v. Sandoz, Inc*., 566 F.3d 1282, 1289 (Fed. Cir. 2009)). A "heavy presumption" exists in favor of the ordinary meaning of claim language. *Bell Atl. Network Servs., Inc. v. Covad*

Commc'ns Grp., Inc., 262 F.3d 1258, 1268 (Fed. Cir. 2001) (internal quotation marks and citation omitted). To overcome this presumption, the patentee must "clearly set forth" and "clearly redefine" a claim term away from its ordinary meaning. *Id.* (internal quotation marks and citations omitted). The disavowal must be "unmistakable" and "unambiguous." *Dealertrack, Inc. v. Huber*, 674 F.3d 1315, 1322 (Fed. Cir. 2013). This standard is "exacting." *Thorner v. Sony Computer Entm't Am. LLC*, 669 F.3d 1362, 1366 (Fed. Cir. 2012).

Here, during prosecution, Patent Owner stated that the low end of the range recited in DE '107 (0.001% wt) "corresponds to 3.8×10^{-5} adenosine" which is "between the 10^{-4} M and 10^{-5} M concentrations recited in the claims."[4] Ex. 1009, 84. Patent Owner did not use this statement to distinguish the claimed adenosine concentration from a concentration disclosed in the prior art. Rather, Patent Owner used it to support the argument that the "extremely broad range of adenosine concentrations listed in . . . [DE '107] is not supported by reality." *Id*. More specifically, Patent Owner argued that, although DE '107 disclosed a concentration of adenosine within the recited range, in contrast to the challenged claims, DE '107 taught (incorrectly accordingly to the Patent Owner) that this level of adenosine increases cell proliferation. *Id.*

As recognized in our Decision (Dec. 11), although Patent Owner's comparison of the claimed concentration to a prior art concentration provides some support for Petitioner's proposed construction, it does not

[4] In our Decision, we cited this statement as an example of Patent Owner comparing the concentration of adenosine recited as a percentage of the total weight of the composition to the concentration recited in the claims as being "applied to the dermal cells." Dec. 11.

"clearly redefine" the phrase "applied to the dermal cells" or alter the scope of the claims such that the recited concentration of adenosine need not reach the dermal cells. Nor does it disclaim subject matter found in the prior art or, otherwise, "unmistakably" disavow application of the recited concentration to the dermal cells.

This is particularly true when the statement is considered in the context of the prosecution history as a whole. *Ecolab, Inc., v. FMC Corp.*, 569 F.3d 1335, 1342 (Fed. Cir. 2009) ("Even if an isolated statement appears to disclaim subject matter, the prosecution history as a whole may demonstrate that the patentee committed no clear and unmistakable disclaimer."). Specifically, in arguing that the amount of adenosine recited in DE '107 does not increase cell proliferation, Patent Owner submitted results from tests in which adenosine was applied directly to dermal cells (fibroblasts) at concentrations of 10^{-4} M and 10^{-5} M. Ex. 1009, 84, 89–90. This suggests that the inventors contemplated dermal cells receiving the recited concentration of adenosine. Patent Owner also relied on these test results as the basis for the statement that "the presently claimed invention is based on the demonstration that the recited concentrations of adenosine do not increase cell proliferation." Ex. 1009, 84. Again, this suggests that "the recited concentrations of adenosine" — i.e., the concentrations recited in the claim — are those applied to the dermal cells.

In addition, as noted in the Decision, Patent Owner expressly corrected the Examiner when the Examiner stated in the reasons for allowance that the claims were directed to "administering adenosine at a concentration of 10^{-4} M to 10^{-7} M, to the skin," stating "applicant notes that the claimed concentration of adenosine is applied to the dermal cells." Ex.

1009, 117 (reasons for allowance) and 123 (Patent Owner's comments on reasons for allowance). This suggests that the Patent Owner did not intend for the concentration recited in the claims to be the concentration applied to the skin.

In sum, while the prosecution history does include a passage that is arguably consistent with Petitioner's proposed construction, it does not include an "unmistakable" and "unambiguous" disavowal, and does not "clearly set forth" and "clearly redefine" the phrase "applied to the dermal cells."

Petitioner argues that our claim construction is erroneous because it "lacks both enablement and written description support." Req. Reh'g 13. We are not persuaded for the reasons discussed at length in the Decision. Dec. 13–15.

Petitioner argues that we misapplied *Chef America, Inc. v. Lamb-Weston, Inc*., 358 F.3d 1371 (Fed. Cir. 2004), "by not affording proper weight to the context of the claim, specification, and file history." Req. Reh'g 14. More particularly, Petitioner asserts that, in contrast to our Decision, which Petitioner asserts "merely dismiss[es] construction of the challenged claim term as 'unambiguous,' the court in *Chef America* properly conducted a thorough analysis of the claim language, specification, and file history to determine that the specification supported, and patentee there intended for, the meaning of the term . . . [at issue] in view of the prosecution." *Id.* at 14–15. We are not persuaded because, as explained in the Decision, our construction is also supported by the claim language, the specification, and the prosecution history. Dec. 8–15.

Accordingly, Petitioner has not persuaded us that we have misapprehended or overlooked any matters with respect to our decision to deny institution. 37 C.F.R. § 42.71(d).

III. CONCLUSION

For the foregoing reasons, we conclude that Petitioner has not shown that the Board abused its discretion in denying institution of the challenged claims. *See* 37 C.F.R. § 42.71(d).

ORDER

Accordingly, it is

ORDERED that Petitioner's Request for Rehearing is *denied.*

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Paper No. 13
Filed: November 16, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

L'ORÉAL USA, INC.,
Petitioner,

v.

UNIVERSITY OF MASSACHUSETTS,
Patent Owner.

Case IPR2018-00779
Patent 6,645,513 B2

Before CHRISTOPHER G. PAULRAJ, ROBERT A. POLLOCK, and DAVID COTTA, *Administrative Patent Judges*.

COTTA, *Administrative Patent Judge*.

DECISION
Denying Petitioner's Request for Rehearing
37 C.F.R. § 42.71(d)

I. INTRODUCTION

L'Oréal USA, Inc. ("Petitioner" or "L'Oréal") filed a petition requesting an *inter partes* review of claims 1–7 and 9 of U.S. Patent No. 6,645,513 B2 (Ex. 1002, "the '513 patent"). Paper 2 ("Pet."). The University of Massachusetts ("Patent Owner" or "UMass") filed a Preliminary Response to the Petition. Paper 8 ("Prelim. Resp."). On

September 7, 2018, after consideration of the Petition and Preliminary Response, we entered a Decision denying institution of *inter partes* review Paper 10 ("Dec."). On October 11, 2018, Petitioner filed a Corrected Request for Rehearing (Paper 12, "Req. Reh'g") seeking reconsideration of the Decision.[1]

For the reasons stated below, Petitioner's Request for Rehearing is denied.

II. ANALYSIS

Standard of Review

When reconsidering a decision on institution, we review the decision for an abuse of discretion. 37 C.F.R. § 42.71(c). An abuse of discretion may be found if a decision is based on an erroneous interpretation of law, if a factual finding is not supported by substantial evidence, or if the decision represents an unreasonable judgment in weighing relevant factors. *Star Fruits S.N.C. v. U.S.*, 393 F.3d 1277, 1281 (Fed. Cir. 2005); *Arnold P'ship v. Dudas*, 362 F.3d 1338, 1340 (Fed. Cir. 2004); *In re Gartside*, 203 F.3d 1305, 1315–16 (Fed. Cir. 2000). The party requesting rehearing has the burden of showing the decision should be modified, which includes specifically identifying all matters the party believes we misapprehended or overlooked. 37 C.F.R. § 42.71(d).

[1] Petitioner filed a Request for Rehearing on October 9, 2018. Paper 11. Because the request was incorrectly captioned, with the permission of the Board (Ex. 3002), Petitioner refiled a request for rehearing correcting this clerical error. Paper 12. All citations herein are to the Corrected Request for Rehearing.

Background

Petitioner challenged claims 1–7 and 9 of the '513 patent on three related grounds: that claims 1–7, and 9 are anticipated by JP '153[2]; that claim 4 is obvious over JP '153; and that claims 1–7 and 9 would have been obvious over the combination of JP '153 and DE '107[3]. Pet. 6–7. We declined to institute *inter partes* review. Dec.

Petitioner's Request for Rehearing focuses on our construction of the limitation in claim 1 requiring that "the adenosine concentration applied to the dermal cells is 10^{-3} M to 10^{-7} M." In the Petition, Petitioner argued that this limitation should be construed to mean "a concentration of adenosine ***in the composition*** that is topically applied to an unbroken, epidermal layer of a region of the skin containing the dermal cells to be from 10^{-3} M to 10^{-7} M (*i.e.*, 0.0265 to 0.00000265 wt %)." Pet. 15. In the Decision denying institution, we rejected Petitioner's proposed construction and construed this limitation to mean "mean what it says – that the recited concentration is the concentration that is applied to the dermal cells." Dec. 14.

Legal Principles

For the reasons discussed in connection with our institution decision, we applied a district court-type claim construction like that provided in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (en banc). Dec. 6.

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[2] Murayama, JP H9-157153 A, published June 17, 1997 ("JP '153"). JP '153 was originally published in Japanese. Ex, 1005. All citations herein are to Exhibit 1006, the English translation of JP '153 provided by the Petitioner.

[3] Schönrock et al., DE 195 45 107 A1, published June 5, 1997 ("DE '107"). DE '107 was originally published in German. Ex. 1003. All citations herein are to Exhibit 1004, the English translation of DE '107 provided by the Petitioner.

Under this standard, we gave claim terms their ordinary and customary meaning, as would be understood by a person of ordinary skill in the art, at the time of the invention, in light of the language of the claims, the specification, and the prosecution history of record. *Phillips*, 415 F.3d at 1313. We also considered the extrinsic evidence presented by Petitioner. *Id.* at 1317. Petitioner does not challenge our decision to apply the *Phillips* claim construction standard. Req. Reh'g 2.

Analysis

Claim 1 of the '513 patent, the only independent claim, requires "topically applying to the skin a composition comprising a concentration of adenosine." In the Decision, we construed this limitation to require that "a composition be applied directly to the outer, epidermal layer of the skin that is intact . . . such that the inner, dermal layer of the skin is not exposed." Dec. 6–7. Petitioner agrees that this is the correct construction. Req. Reh'g 4.

Claim 1 also requires that "the adenosine concentration applied to the dermal cells is 10^{-3} M to 10^{-7} M." In the Decision, we construed this limitation to require that the recited concentration is "the concentration that is applied to the dermal cells." Dec. 14.

Petitioner argues that we "incorrectly applied *Phillips* by interpreting only two words of the claim, *i.e.* 'dermal cells,' in isolation, overlooking the remaining language of the claims and therefore failing to accord sufficient weight to the specification and file history or Petitioner's evidence." Req. Reh'g 2. We are not persuaded.

Any construction of the phrase "concentration applied to the dermal cells" must ascribe some meaning to the term "dermal cells." As discussed

in the Decision, there is no dispute that the skin is comprised of multiple layers, including the epidermis, the dermis, and subcutaneous fat. Dec. 8. Our construction gives the term "dermal cells" is ordinary meaning by construing it to refer to "dermal cells" — i.e., the dermis or dermal layer. We do not find in the record, and Petitioner does not suggest, another way to interpret the limitation "concentration applied to the dermal cells" consistent with the ordinary meaning of the words "dermal cells."

Petitioner proposes that we construe the limitation "concentration applied to the dermal cells" to mean "a concentration . . . applied to an unbroken, epidermal layer of a region of the skin containing the dermal cells." Pet. 15. However, as noted in the Decision, there is no meaningful difference between the "epidermal layer of a region of the skin containing the dermal cells" recited in Petitioner's proposed claim construction, and the epidermis. Dec. 8 n.3. Petitioner's proposed construction is, thus, contrary to the language of the claim, because it changes the meaning of "dermal cells" to "epidermal cells."

Petitioner argues, in effect, that the ordinary meaning of the term "dermal cells" changes when it is considered "within the context of the immediately-preceding words '***applied to***,' and the ***single recited application step***." Req. Reh'g 3. According to Petitioner, there is only one step in claim 1 in which adenosine is "applied" and that step requires application to the skin (which we interpreted to mean the epidermal layer of the skin). Petitioner contends the claim term "applied" in the limitation "applied to the dermal cells" must be understood to refer back to this step of applying adenosine to the epidermal layer of the skin because, otherwise,

"the language '***the adenosine concentration applied***' would lack antecedent basis." *Id.* at 4. We are not persuaded.

As discussed in the Decision, the Specification discloses not only that adenosine may be topically applied to the epidermal layer of the skin, but also that adenosine so applied will penetrate the epidermis to reach the dermal layer. Dec. 9 (citing Ex. 1002, 5:20–23 ("For topical application, the penetration of the adenosine into skin tissue may be enhanced by a variety of methods known to those of ordinary skill in the art.")). Topical application of adenosine will, therefore, result in adenosine being brought into contact with both the epidermis and the dermis. As also discussed in the Decision, the specification provides examples in which a concentration of adenosine within the range recited in the claims (10^{-4} M) is applied directly to dermal cells (fibroblasts), suggesting that the inventors considered it desirable for the dermal cells to receive the claimed concentration of adenosine. *Id.* In this context, the meaning of claim 1 is clear: adenosine is first topically applied to the epidermal layer of the skin and, only after it penetrates this outer skin layer, is a specific concentration (10^{-4} M to 10^{-7} M) of the adenosine "applied" to the dermal cells.

Petitioner argues that our construction is incorrect because it "concludes that 'applied to the dermal cells' means 'reached' or 'received by' the dermal cells, or 'penetrates through' the skin to reach the dermal cells." Req. Reh'g 12. Petitioner asserts that "[s]uch an interpretation improperly alters the meaning of 'topically applying' and 'applied.'" *Id.*

This argument, however, fails to account for the context provided by the Specification which, as discussed above, teaches that adenosine will penetrate the skin. Particularly when considered in this context, we do not

read the term "applied" so narrowly as to exclude an application which reaches its target destination (here the "dermal cells") by passing through a layer that overlies the target destination (here the epidermis). This is consistent with the ordinary meaning of "apply" — i.e., "to bring into physical contact with or close proximity to." Ex. 3003 (definition 9 from dictionary.com (last accessed Oct. 26, 2018), *see also*, definition 8). Here, adenosine is brought into physical contact with the dermal cells. Nothing in the language of the claims, as interpreted in light of the intrinsic and extrinsic evidence, requires that adenosine be applied *directly* to the dermal cells.

Petitioner argues that we erred in failing to find a prosecution disclaimer. Req. Reh'g 5–10. More particularly, Petitioner argues that our acknowledgement that the Patent Owner "compared prior art concentrations of adenosine that were recited as a percentage of the ***total weight of the composition to the concentration recited in the claims as being 'applied to the dermal cells'***" requires that we find a prosecution disclaimer. *Id.* at 6 (internal citation omitted). We are not persuaded.

A prosecution history disclaimer must be clear and unambiguous. "[W]hile the prosecution history can inform whether the inventor limited the claim scope in the course of prosecution, it often produces ambiguities created by ongoing negotiations between the inventor and the PTO. Therefore, the doctrine of prosecution disclaimer only applies to unambiguous disavowals." *Grober v. Mako Prods., Inc*., 686 F.3d 1335, 1341 (Fed. Cir. 2012) (citing *Abbott Labs. v. Sandoz, Inc*., 566 F.3d 1282, 1289 (Fed. Cir. 2009)). A "heavy presumption" exists in favor of the ordinary meaning of claim language. *Bell Atl. Network Servs., Inc. v. Covad*

Commc'ns Grp., Inc., 262 F.3d 1258, 1268 (Fed. Cir. 2001). To overcome this presumption, the patentee must "clearly set forth" and "clearly redefine" a claim term away from its ordinary meaning. *Id*. The disavowal must be "unmistakable" and "unambiguous." *Dealertrack, Inc. v. Huber*, 674 F.3d 1315, 1322 (Fed. Cir. 2013). This standard is "exacting." *Thorner v. Sony Computer Entm't Am. LLC*, 669 F.3d 1362, 1366 (Fed. Cir. 2012).

Here, during prosecution of the parent of the '513 patent, Patent Owner stated that the low end of the range recited in DE '107 (0.001% wt) "corresponds to 3.8 x 10^{-5} adenosine" which is "between the 10^{-4} M and 10^{-5} M concentration recited in the claims."[4] Ex. 1009, 84. Patent Owner did not use this statement to distinguish the claimed adenosine concentration from a concentration disclosed in the prior art. Rather, Patent Owner used it to support the argument that the "extremely broad range of adenosine concentrations listed in . . . [DE '107] is not supported by reality." *Id*. More specifically, Patent Owner argued that, although DE '107 disclosed a concentration of adenosine within the recited range, in contrast to the challenged claims, DE '107 taught (incorrectly accordingly to the Patent Owner) that this level of adenosine increases cell proliferation. *Id.*

As recognized in our Decision (Dec. 11), although Patent Owner's comparison of the claimed concentration to a prior art concentration provides some support for Petitioner's proposed construction, it does not "clearly redefine" the phrase "applied to the dermal cells" or alter the scope of the claims such that the recited concentration of adenosine need not reach

[4] In our Decision, we cited this statement as an example of Patent Owner comparing the concentration of adenosine recited as a percentage of the total weight of the composition to the concentration recited in the claims as being "applied to the dermal cells." Dec. 11.

the dermal cells. Nor does it disclaim subject matter found in the prior art or, otherwise, "unmistakably" disavow application of the recited concentration to the dermal cells.

This is particularly true when the statement is considered in the context of the prosecution history as a whole. *Ecolab, Inc., v. FMC Corp.*, 569 F.3d 1335, 1342 (Fed. Cir. 2009) ("Even if an isolated statement appears to disclaim subject matter, the prosecution history as a whole may demonstrate that the patentee committed no clear and unmistakable disclaimer."). Specifically, in arguing that the amount of adenosine recited in DE '107 does not increase cell proliferation, Patent Owner submitted results from tests in which adenosine was applied directly to dermal cells (fibroblasts) at concentrations of 10^{-4} M and 10^{-5} M. Ex. 1009, 84, 89–90. This suggests that the inventors contemplated dermal cells receiving the recited concentration of adenosine. Patent Owner also relied on these test results as the basis for the statement that "the presently claimed invention is based on the demonstration that the recited concentrations of adenosine do not increase cell proliferation." *Id.* at 84. Again, this suggests that "the recited concentrations of adenosine" — i.e., the concentrations recited in the claim — are those applied to the dermal cells.

In addition, as noted in the Decision, Patent Owner expressly corrected the Examiner when the Examiner stated in the reasons for allowance of the parent patent application that the claims were directed to "administering adenosine at a concentration of 10^{-4} M to 10^{-7} M, to the skin," stating "applicant notes that the claimed concentration of adenosine is applied to the dermal cells." Ex. 1009, 117 (reasons for allowance) and 123 (Patent Owner's comments on reasons for allowance). This suggests that the

Patent Owner did not intend for the concentration recited in the claims to be the concentration applied to the skin.

In sum, while the prosecution history does include a passage that is arguably consistent with Petitioner's proposed construction, it does not include an "unmistakable" and "unambiguous" disavowal, and does not "clearly set forth" and "clearly redefine" the phrase "applied to the dermal cells."

Petitioner argues that our claim construction is erroneous because it "lacks both enablement and written description support." Req. Reh'g 13. We are not persuaded for the reasons discussed at length in the Decision. Dec. 12–14.

Petitioner argues that we misapplied *Chef America, Inc. v. Lamb-Weston, Inc.*, 358 F.3d 1371 (Fed. Cir. 2004), "by not affording proper weight to the context of the claim, specification, and file history." Req. Reh'g 14. More particularly, Petitioner asserts that, in contrast to our Decision, which Petitioner asserts "merely dismiss[es] construction of the challenged claim term as 'unambiguous,' the court in *Chef America* properly conducted a thorough analysis of the claim language, specification, and file history to determine that the specification supported, and patentee there intended for, the meaning of the term [at issue] in view of the prosecution." *Id.* at 14–15. We are not persuaded because, as explained in the Decision, our construction is also supported by the claim language, the specification, and the prosecution history. Dec. 7–14.

Accordingly, Petitioner has not persuaded us that we have misapprehended or overlooked any matters with respect to our decision to deny institution. 37 C.F.R. § 42.71(d).

III. CONCLUSION

For the foregoing reasons, we conclude that Petitioner has not shown that the Board abused its discretion in denying institution of the challenged claims. *See* 37 C.F.R. § 42.71(d).

ORDER

Accordingly, it is

ORDERED that Petitioner's Request for Rehearing is *denied.*

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TAB 09

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

L'OREAL USA, INC.
Petitioner

v.

UNIVERSITY OF MASSACHUSETTS
Patent Owner

IPR2018-00778
Patent No. 6,423,327

PATENT OWNER PRELIMINARY RESPONSE

Petitioner nevertheless asserts that "the only disclosure in the '327 patent where adenosine is 'applied to dermal cells' is associated with *ex vivo* methods (direct application to dermal fibroblasts in cell cultures), and not *in vivo* methods (topical application to human skin) as required by claim 1." (Paper 2 at 32.)

Petitioner's argument about what the specification discloses is incorrect.

In the '327 Patent, direct application to dermal cells *ex vivo* was done to illustrate the effect of particular concentrations at the dermal layer, again confirming that the recited range is at the dermal layer. (Ex. 1001 at 9:5-50.) Accordingly, the specification explains that adenosine containing compositions are "preferably applied [to the dermal cells] by topical routes to exert local therapeutic effects," and that they "may be applied directly and mechanically rubbed into the skin," or "incorporated into a transdermal patch that is applied to the skin." (Ex. 1001 at 5:12-17 (emphasis supplied).) The specification goes on to explain, "the penetration resulting from these methods is enhanced with a chemical transdermal delivery agent such as dimethyl sulfoxide (DMSO) or the nonionic surfactant, n-decylmethyl sulfoxide (NDMS), as described in Choi et al., Pharmaceutical Res., 7(11): 1099, 1990." (Ex. 1001 at 5:19-25.)

In short, the patent identifies the proper concentration at the dermal layer and verifies it using *ex vivo* testing of dermal cells, and it explains that application of that concentration at the dermal layer can be achieved by applying a compound

TAB 10

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNIVERSITY OF MASSACHUSETTS and CARMEL LABORATORIES, LLC, Plaintiffs, v. L'ORÉAL USA, INC., Defendant.	)	C.A. No. 17-868-CFC-SRF

DECLARATION OF PROFESSOR GERALD B. KASTING, PH.D.

I, Professor Gerald B. Kasting, Ph.D., declare as follows:

I. INTRODUCTION

1. I have been asked by counsel for L'Oréal USA, Inc. to consider what the language "wherein the adenosine concentration applied to the dermal cells is", which appears in certain claims of U.S. Patent Nos. 6,423,327 and 6,645,513 (collectively, "the patents-in-suit"), would mean to a person of ordinary skill in the art in view of the claims, the specification, and the prosecution history.

2. I have also been asked to provide an explanation of scientific and technical concepts concerning the subject matter of the patents-in-suit and my discussion of the meaning of this claim language.

II. QUALIFICATIONS

3. My academic background, professional experience, and list of publications are set forth in my *curriculum vitae*, attached hereto as Exhibit A. Below I briefly describe my qualifications.

4. I received a Ph.D. degree in physical chemistry in 1980 from Massachusetts Institute of Technology in Cambridge, MA, under the supervision of Dr. Carl W. Garland. I was a research chemist at Procter & Gamble Company ("P&G"), from 1980 to 1993. In subsequent years, between 1993 and 1999, I continued as a Senior Scientist at P&G, directing research programs in the Health and Skin Care areas with a particular emphasis on topical delivery of drugs and

cosmetic agents, as well as mathematical modeling of such delivery. From 1999 to 2006, I served as Associate Professor of Pharmaceutics and Cosmetic Science at the University of Cincinnati College of Pharmacy, and, from 2006 to the present, I have served as Professor in the same department, whilst also serving as Director of Graduate Studies from 2008 to 2011 and as Chair, Division of Pharmaceutical Sciences from 2011 to 2013.

5. As evidenced by my *curriculum vitae*, I have been working in the field of transdermal and topical delivery of substances since 1983. The focus of my research has been the analysis of structure-property relationships for delivery of agents into and through the skin and the development of predictive mathematical models for this phenomenon. Specifically, we have focused on the development of computational models for absorption of substances into and through the skin with the objective of developing better tools for prediction of topical delivery of drugs and cosmetic agents, transdermal drug delivery, and dermal exposure to noxious agents.

6. During nine years of my industry career, from 1990-1998, I worked in a skin care technology group on the delivery of cosmetic benefit agents from topical formulations. My work was primarily focused on the measurement and improvement of such delivery to develop facial moisturizers with anti-ageing benefits. During this period, I worked with various forms of vitamins A, B, C, D,

and E as well as other agents including phytic acid, lysophosphatidic acid and N-acetyl cysteine. For some agents we also developed prototype formulations that were taken to clinical trials.

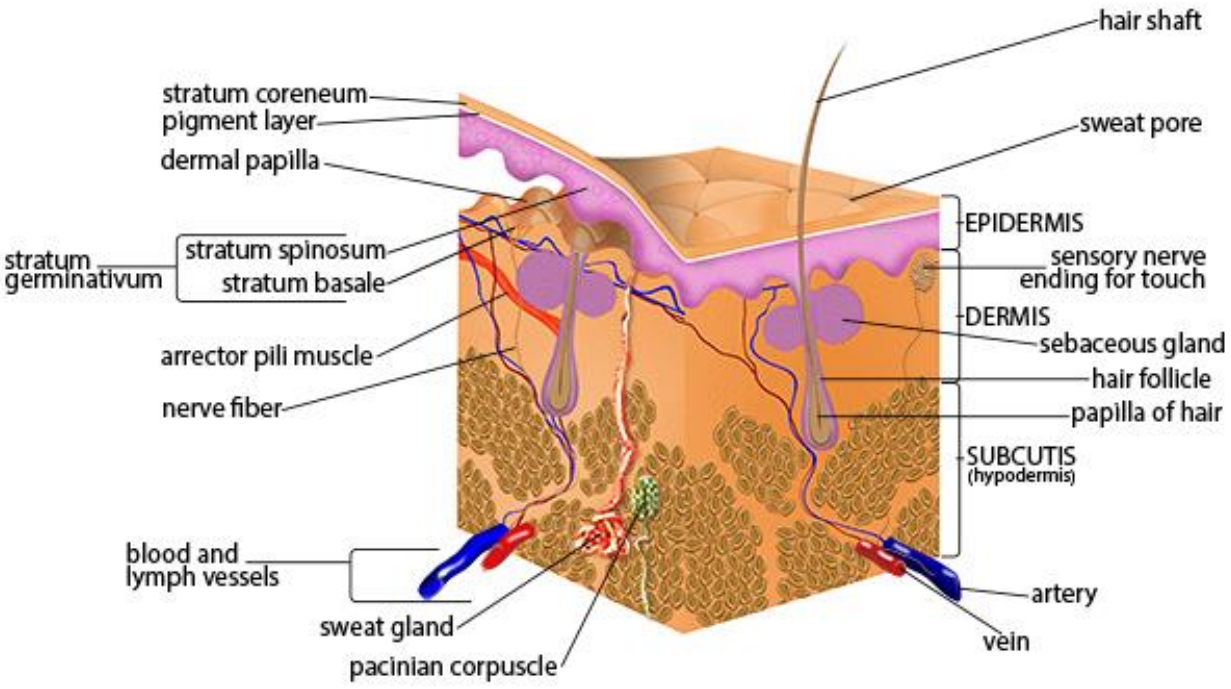
7. I am well versed in the biology and physical dynamics of both transdermal and topical delivery of agents, including drugs and cosmetic agents. I have served as a reviewer for a number of leading peer reviewed journals, including *J Controlled Rel*, *Pharm Res*, *Int J Pharm*, *J Invest Dermatol*, *Toxicol Sci*, *Toxicol in Vitro*, *Food Chem Toxicol*, *Ind Eng Chem*, *Biophys J*, *J Appl Physiol*, *Eur J Pharm Sci*, *Int J Cosmet Sci*, *Cutan Ocular Toxicol*, *J Pharm Sci*, *Pharm Devel Technol*, and *J Cosmet Chem*, and as an editorial board member for the latter three journals. I have published my work as well as various review articles in the field of drug delivery in numerous peer reviewed journals.

8. Over the course of my career, I have published more than 120 articles, and hold eight patents associated with my work. I am a two-time recipient of the Shaw Mudge Award from the Society of Cosmetic Chemists. In 2013, I received the Excellence in Doctoral Mentoring Award from the University of Cincinnati for my work with graduate students and, in 2019, I received the Excellence Award for Faculty-to-Faculty Research Mentoring from the Winkle College of Pharmacy.

9. I am being compensated at my standard rate of $300 per hour for time spent working as an expert consultant on this matter. In the previous four years, I have testified in the following cases: *Leo Pharma v. Perrigo*, C.A. Nos. 16-430, 18-401 (D. Del.).

III. TECHNOLOGICAL BACKGROUND

10. **Skin.** The skin is the largest organ in the body and serves a variety of functions, including acting as a barrier for water loss from the body and to the entry of chemicals or microorganisms from the environment. A schematic diagram of the skin is shown below:



Source: https://training.seer.cancer.gov/melanoma/anatomy/

As can be seen from the diagram above, the skin is divided into multiple layers, including the epidermis and dermis. The epidermis is a cellular tissue that provides the primary barrier for preventing both water loss from the body and entry of topically applied substances into the systemic circulation; it also acts a barrier for ultraviolet light, allergens, and microbes that contact or impinge upon the skin. The dermis is a fibrous tissue that provides mechanical strength and integrity to the skin. There is a fat layer beneath the dermis sometimes called the hypodermis, but it is not technically part of the skin. It is a reservoir for nutrient storage, and the base location of hair follicles and sweat glands.

11. The epidermis is a rapidly growing and differentiating tissue that itself comprises different regions having distinct characteristics. Typically, healthy epidermis contains about 15 layers of living cells and 10-20 layers of cornified cells (dried, flattened cells that have lost their nuclei) comprising the stratum corneum (the outer most layer). Approximately one layer of cells is lost per day, so the entire epidermis replaces itself about once a month.

12. The dermis is beneath the epidermis. The dermis is made up of cells, a fibrous extracellular matrix, and a ground substance. The dermal cells include fibroblasts, mast cells, mononuclear phagocytes, and lymphocytes. The extracellular matrix is made up of collagen and elastin. The ground substance is made up of primarily glycosaminoglycans, such as hyaluronic acid and dermatan

sulfate. The dermis has two sublayers, the papillary dermis (upper layer) and the reticular dermis (lower layer). The cells within the dermis, including fibroblasts, make up only a small portion of the dermis as a whole.

13. **Cosmetic and topical formulations**. As a result of various factors, including environmental conditions, such as sun exposure, and natural processes, such as normal aging, the human skin can exhibit fine lines, wrinkles, dryness, age spots, sagging, enlarged pores, sallowness, and so on. Cosmetic skin care products are, as their name suggests, used to improve the condition and appearance the skin.

14. It is often desirable to administer cosmetic and dermatological products topically, as this is both convenient for consumers and patients and allows for topical or local action at the skin with minimal systemic activity. When administered topically, the cosmetic product or composition is applied directly to the surface of the skin. Topical administration can also be referred to as dermal administration in the cosmetic and pharmaceutical context, as shown by the following exemplary citations:

- C.L. Baer & B.R. Williams, *Clinical Pharmacology and Nursing* (1996), at page 70 (Appx A0297): ("Dermal route" means "topical medication administration by application to the skin").

- OECD Guidelines for the Testing of Chemicals, Section 4. Test No. 411: Subchronic Dermal Toxicity: 90-day Study (1981), at page 1 (Appx A0301) ("Dose in a dermal test is the amount of test substance applied to the skin (applied daily in subchronic tests).").
- R. Woodrow, *Essentials of Pharmacology for Health Occupations* (1997), at page 52 (Appx A0320) ("Topical drug forms include drugs for dermal application and drugs for mucosal application. Those for *dermal* application include: *Cream or ointment*.").

Whether described as topical administration or dermal administration, the principle is the same: the product is applied directly to the surface of the skin.

15. Topical cosmetic and dermatological products generally contain one or more benefit agents (for cosmetic products) or active ingredients (for drug products) along with other inactive ingredients that collectively make up the product formulation. The benefit agents are used to treat or improve a particular condition, depending on the purpose of the product. The inactive ingredients can serve a number of different purposes. For example, they may be used simply as fillers; they can also be used to improve the "feel" of the formulation to the hands, face, or other area to which it is applied.

16. For dermatological and cosmetic compositions/products, it is common to describe the composition in terms of its unit composition. In other

words, the ingredients of the composition are identified along with their respective weights and/or weight percentages per unit.[1] An example is shown below from a patent publication that was discussed during prosecution of the patents-in-suit:

Example 2

O/W After-Sun Lotion

	Wt.-%
Stearic acid	2.00
Glyceryl stearate	1.00
Isopropyl palmitate	6.00
Caprylic / capric triglyceride	5.00
Buxus chinensis	2.00
Carbomer	0.20
NaOH (45%)	0.20
Glycerin	5.00
Ethanol	5.00
Adenosine	0.10
Preservative / fragrance	q.s.
Water, add until	100.00

DE 19545107 at 10 (Appx A0092) (reproduced from prosecution history of U.S. Patent No. 6,423,327). Similarly, when topical skin products (or other products for topical administration) are marketed to the public, the benefit agent(s) or active ingredient(s) are generally identified by their weight percentages in the

[1] Weight percentages of an ingredient can also be represented as a concentration, *e.g.*, 0.1% adenosine is the equivalent of roughly 3.8×10^{-3} M adenosine.

composition. The following examples, which are far from exhaustive, are taken from the 50th Edition of the *Physicians' Desk Reference* (1996) (Appx A0329-39):

- **EMLA® Cream.** EMLA Cream "is an emulsion" indicated as "a topical anesthetic for use on normal intact skin." *Id.* at 545-546 (AppxA0331-32) [Description, Indication and Usage]. The product information identifies the active ingredients (lidocaine and prilocaine) by reference to their respective percentages of the composition (2.5% and 2.5%). *Id.* at 545 (Appx A0331) [Description]. EMLA Cream "provides dermal analgesia by the release of lidocaine and prilocaine from the cream into the epidermal and dermal layers of the skin". *Id.* [Clinical Pharmacology].
- **Eucerin Plus Creme.** Eucerin Plus Creme is a moisturizing alpha-hydroxy cream that is used "to help relieve severely dry, flaky skin", which is applied topically. *Id.* at 641 (Appx A0334) [Indications]. The alpha-hydroxy acid and moisturizing compounds are identified by reference to their percentages of the composition that is topically applied (2.5% sodium lactate, 10% urea). *Id.* [Actions and Uses]. A person of ordinary skill in the art would understand that the alpha-hydroxy acid compound penetrates the outer layer of the skin following application.
- **Drithocreme®.** "Drithocreme® is a pale yellow topical cream containing 0.1%, 0.25%, 0.5% or 1.0% (HP) anthralin USP", the active ingredient, in a

formulation composed of various other components, that is used to treat psoriasis (a skin disease). *Id.* at 905 (Appx A0335) [Description]. The concentration of the active ingredient is again described by reference to the percentage of the composition of which it is a part. *Id.* Anthralin works by penetrating into the skin and it was hypothesized that Drithocreme's active ingredient inhibited DNA synthesis and provided a "slowing down of epidermal mitosis". *Id.* [Clinical Pharmacology].

- **Novacet® Lotion.** Novacet Lotion is applied topically and is used for the control of acne vulgaris, acne rosacea, and seborrheic dermatitis. *Id.* at 1054 (Appx A0339) [Indications, Dosage and Administration]. Based on its accepted method of action, a person of ordinary skill in the art would understand that the active ingredients penetrate through the outer layer of the skin. The active ingredients are identified by reference to their concentrations by weight percentages in the composition ("sodium sulfacetamide 10% and sulfur 5%"). *Id*. [Description].

As described above, many of these products act beneath the surface of the skin and are, accordingly, delivered to the different layers of the skin. In my experience, it would be strange for a component of a skin care product to be described with reference to the concentration of that component that reaches a certain part of the skin, even if that was the desired site of action.

17. Depending on the product, a topical cosmetic composition may act on different parts of the skin, such as the epidermis or the dermis. If a scientist desires to deliver a component of the composition to the dermis, the component must first permeate through the epidermis following topical application. The permeation rate and extent are affected by numerous factors, including the properties of the compounds being administered, the components of the composition, metabolism within the different sublayers of the epidermis, and the process by which the administered compounds are cleared by the body. As a result, the amount of a compound that is applied to the skin is greater than the amount that permeates to a particular layer within the skin, often by large amounts. Moreover, depending on where the composition is being applied—*e.g.*, on the forehead or under the eyes—more or less of a composition would be used due to the size of the area and, possibly, the permeability of the particular skin.

18. **Adenosine**. Adenosine is a naturally occurring nucleoside in the human body. *See, e.g.*, *Physicians' Desk Reference* (1996) at 1021 (Appx A0337) ("Adenosine is an endogenous nucleoside occurring in all cells of the body."). Adenosine has been used in medical products for a number of years. *See, e.g.*, *id.* In addition, topical application of adenosine has been reported to be effective for improving the condition of human skin, as is shown by, for example, DE 19545107 and Hartzshtark et al., "The use of indentometry to study the effect

of agents known to increase skin c-AMP content", *Experientia* 41 (1985) ("Hartzshtark") (AppxA0291-92), both of which were discussed during prosecution of the patents-in-suit.

19. The translation of DE 19545107 provided during the prosecution of U.S. Patent No. 6,423,327 describes the "the use of adenosine in cosmetic and dermatological preparations" for "the care and prevention of aged skin". *See* DE 19545107 at 2-3 (Appx A0084-85). The compositions described, which include creams and lotions, would be suitable for topical application to the skin. *See id*. at Examples (Appx A0091-94). The concentration of adenosine in these compositions is described as "preferably 0.001% to 10% by weight", and the numbered examples use 0.1% adenosine by weight. *See id.* at 3, 9-12 (Appx A00085, A0091-94). In each case, the concentration of adenosine is described with reference to the weight percentage in the composition. *Id.* I understand that there have been discussions regarding dermal cell proliferation amongst the parties, and that the translation of DE 19545107 refers to "increasing cell proliferation" or "enhancement of cell proliferation in human skin". *Id.* at Cover, 2 (Appx A0083-84). I note, though, that DE 19545107 does not say that adenosine increases dermal cell proliferation, and a person of ordinary skill in the art would not understand it in that way. In fact, when DE 19545107 discusses cell proliferation, it is in the context of epidermal cells, not dermal cells. *See id*. at 2(e) (Appx

A0084) (discussing "[a]bnormal regulation of cell division (proliferation) . . . in the epidermis") (emphasis added).

20. Hartzshtark reports that 0.1% adenosine compositions improved skin "firmness" when measured by low pressure indentometry following topical application. Hartzshtark at 378-379 (Appx A0291-92). The table in Hartzshtark describes the concentration of adenosine with reference to the weight percentage in the composition applied to the skin. *Id*. at 379 (Appx A0292). I note that Hartzshtark does not mention cell proliferation at all, including dermal cell proliferation.

IV. PRINCIPLES OF CLAIM CONSTRUCTION

21. I understand that patent claim terms are to be given their ordinary and customary meaning as understood by a person of ordinary skill in the art at the time of the invention. I further understand that claim terms should be interpreted in the context of the claim itself and in view of the patent as a whole, including the specification, as well as the prosecution history.

22. In my opinion, a person of ordinary skill in the art with respect to the patents-in-suit would have a degree in biochemistry, chemistry, or a related field (such as biology, pharmaceutical chemistry, pharmacy, medicine, clinical pharmacology, or another pharmaceutical science-related field), with some exposure to, or industry courses or research in, the topical delivery of drugs or

cosmetic ingredients. My opinions expressed below regarding the meaning of "wherein the adenosine concentration applied to the dermal cells is" would not change if the level of skill were determined to be somewhat different (*e.g.*, either somewhat higher or lower).

23. For the purposes of my analysis, I have considered how the disputed term of the patents-in-suit would be understood by a person of ordinary skill in the art as of October 1998. However, my opinions would not change if I considered a somewhat earlier or later time period.

V. "WHEREIN THE ADENOSINE CONCENTRATION APPLIED TO THE DERMAL CELLS IS"

A. Summary of Opinions

24. In forming my opinions, I have reviewed the patents-in-suit and the prosecution documents provided to me by L'Oréal USA's counsel. I further understand that L'Oréal USA has proposed that the claim language "wherein the adenosine concentration applied to the dermal cells is" be construed as "wherein the adenosine concentration applied to the skin containing the dermal cells is", while the plaintiffs have proposed that it be construed as "plain and ordinary meaning" or "wherein the adenosine concentration that reaches the dermal cell layer is".

25. It is my opinion that as of October 1998, a person of ordinary skill in the art reading the patents-in-suit would have understood the claim

language "wherein the adenosine concentration applied to the dermal cells is" from claim 1 of each of the patents-in-suit, in the context of those patents, to mean "wherein the adenosine concentration applied to the skin containing the dermal cells is".

26. It is further my opinion that the construction proposed by the plaintiffs ("wherein the adenosine concentration that reaches the dermal cell layer is") does not reflect the meaning of the claim phrase as it is used in the patents-in-suit. A person of ordinary skill in the art would understand that the plaintiffs' proposed construction does not fit with the descriptions provided in the patents-in-suit or the context of cosmetic/dermatological products to which the patents-in-suit are addressed.

B. A Person of Ordinary Skill in the Art's Understanding of "wherein the adenosine concentration applied to the dermal cells is"

27. The claims of the patents-in-suit involve topically applying adenosine. Claim 1 from the '327 patent is reproduced below:

> 1. A method for enhancing the condition of unbroken skin of a mammal by reducing one or more of wrinkling, roughness, dryness, or laxity of the skin, without increasing dermal cell proliferation, the method comprising topically applying to the skin a composition comprising a concentration of adenosine in an amount effective to enhance the condition of the skin without increasing dermal cell proliferation, wherein the adenosine concentration applied to the dermal cells is 10^{-4} M to 10^{-7} M.

'327 Patent, claim 1.[2] Because the claims require topical application "to the skin" of "a composition comprising a concentration of adenosine in an amount effective to enhance the condition of the skin", a person of ordinary skill in the art would know that the adenosine could not be applied directly to the dermal cells. That is because, as noted above, dermal cells reside in the dermis, which is beneath the epidermis and not exposed in unbroken skin. *See* paragraphs 10-12 above.

28. A person of ordinary skill in the art would thus understand that the most natural reading of the language in light of the specification, and given the context of cosmetic/dermatological products, is that the two phrases concerning the adenosine concentration refer to a single adenosine concentration which is applied topically to the skin, namely "10^{-4} M to 10^{-7} M" or "10^{-3} M to 10^{-7} M".[3] Such an understanding is consistent with how the benefit agent or active ingredient in

[2] The claims of the patents-in-suit refer to adenosine using molar concentration expressed in scientific notation. The range "10^{-3} M to 10^{-7} M" expressed using decimals would be 0.001 M to 0.0000001 M. So 10^{-3} M is a higher concentration than 10^{-7} M. Likewise, a concentration such as 3.8 x 10^{-3} M (0.0038 M) is larger (almost four times larger) than 10^{-3} M (0.001 M).

[3] As noted above (paragraph 17), depending on the area of treatment, more or less of the composition may be applied. Moreover, when referring to the composition, the specification refers to the concentration of adenosine in that composition, *see* '327 patent, 1:43-2:8, 2:30-34; *id.* at 2:13-17, 2:38-40, and how much that may be applied to a given area, *see* '327 patent, 5:35-37. So, for example, a 100 ng dose of adenosine at a concentration of 10^{-7} M would need a volume of 3.74 mL. Whereas a 10 mg dose of adenosine at a concentration of 10^{-3} M would need a volume of 37.4 mL.

topical products is generally described. *See* paragraph 16 above. Such an understanding is also consistent with the specification's references to topical application of adenosine in those concentrations when discussing "the invention." '327 patent, 1:43-2:8, 2:30-34; *id.* at 2:13-17, 2:38-40; *see also* paragraph 14 above.[4]

29. The specification also contains a discussion of experimental work, *see id*., 6:14-9:50, which a person of ordinary skill in the art would understand to disclose that certain alleged benefits could be obtained when *ex vivo* fibroblasts were cultured with adenosine at concentrations of 10^{-4} or 10^{-6} M. But this does not suggest that the concentration ranges appearing in the claims are what actually reach the dermal cells. I first note that the specification describes a broader concentration, which coincides with the claimed ranges, that is applied to the skin, '327 patent, 1:43-2:8, 2:13-17, 2:38-40, which is consistent with the fact that not all topically applied adenosine will reach the dermis. I note further that this experimental work does not involve topical application of adenosine to the skin, but rather *ex vivo*/*in vitro* experiments.[5] As a result, a person of ordinary skill

[4] The specification does refer to "providing fibroblasts from the mammal ex vivo, culturing the fibroblasts in the presence of adenosine, and reintroducing the fibroblasts into the mammal." '327 patent, 2:9-13. A person of ordinary skill in the art would understand that this does not involve topical application to the skin, but some way of reintroducing the cultured fibroblasts to the body.

[5] This work is described in the "Experimental Information" section of the specification. '327 patent, 6:15-9:50. Although the experimental parameters

in the art would understand that the inventors are asserting that, when adenosine is topically applied in those ranges, the alleged benefits described in the experimental section of the patent could be achieved.

30. In addition, a person of ordinary skill in the art would not understand the claim language "wherein the adenosine concentration applied to the dermal cells is" "10^{-4} M to 10^{-7} M" or "10^{-3} M to 10^{-7} M" to refer to a specific, identified concentration of adenosine that "reaches the dermal cell layer", as proposed in the plaintiffs' claim construction noted above. This is true because, for example, the specification does not describe the concentration of adenosine that reaches the dermal cells following topical application. Further, as noted above, the degree to which a compound penetrates into and through the different layers of the skin is dependent on a number of factors, including, among other things, the characteristics of the compound and formulation, metabolism, and clearance. There is no description of how to account for this in the specification.[6] Further, the

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differed somewhat depending on whether cell size, DNA synthesis, or protein synthesis was being studied, each of the experiments involved *in vitro* cell cultures. '327 patent, 6:15-31, 7:18-29, 7:50-58, 8:49-57, 8:59-65. That is, human cells that had been obtained from existing cell lines were grown in a laboratory under artificial conditions, exposed to adenosine, and then the different parameters were measured. *Id.* The concentrations of adenosine used in these experiments involving skin cells were 10^{-4} M (DNA synthesis), 10^{-6} M to 10^{-4} M (protein synthesis), and 10^{-4} M (cell size). '327 patent, 7:50-53, 8:52-54, 9:5-8.

[6] In addition, in discussing topical applications, the specification states that the "penetration of the adenosine into the skin tissue may be enhanced by a variety of methods known to those of ordinary skill in the art", such as "mechanically

specification does not contain any description of how to determine the adenosine concentration at the dermal layer. Such calculations are unnecessary when the concentration referred to is, as in the patents-in-suit and as is typically the case in cosmetic/dermatological products, the concentration of the composition.

31. I note further, as discussed above, that there is a distinction between dermal cells, such as fibroblasts and mast cells, and the dermis or dermal layer, which has a large non-cellular component. *See* paragraph 12 above. I do not see any basis in the claims or the specification of the patents-in-suit to equate "dermal cell layer" with dermal cells.

* * *

32. I have also reviewed what I understand to be the relevant prosecution documents provided by L'Oréal USA's counsel, and it is my opinion that they are consistent with the ordinary meaning of the phrase "wherein the adenosine concentration applied to the dermal cells is" as captured in L'Oréal USA's proposed construction.

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rub[bing]" the composition "into the skin" or using a "chemical transdermal delivery agent". '327 patent, 5:10-24. A person of ordinary skill in the art would understand this paragraph to be simply discussing factors associated with topical applications, and not to suggest that a specific concentration of adenosine reaches a particular area within the skin.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct. Executed on February 5, 2020.

Gerald B. Kasting

Gerald B. Kasting

Exhibit A

CURRICULUM VITAE

Gerald B. Kasting
Professor of Pharmaceutics and Cosmetic Science
James L. Winkle College of Pharmacy
The University of Cincinnati
231 Albert Sabin Way
Cincinnati, Ohio 45267-0514

HOME ADDRESS

1151 Beverly Hill Drive
Cincinnati, Ohio 45208

Home Telephone: (513) 321-1119
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Cellular Telephone: (513) 484-6474

EDUCATION

Ph.D. Massachusetts Inst. of Technology, 1976-80, Physical Chemistry
Major Professor: Carl W. Garland
Thesis Title: "High Pressure Heat Capacity of Cyanobiphenyl Liquid Crystals Near the Nematic-Smectic A Transition"

B.A. Vanderbilt University, 1971-75, Chemistry, magna cum laude, high honors in chemistry

HONORS AND AWARDS

Excellence Award for Faculty-to-Faculty Research Mentoring, Winkle Col of Pharmacy, 2019
Excellence in Doctoral Mentoring Award, University of Cincinnati, 2013
Co-Chair, Gordon Research Conference on Barrier Function of Mammalian Skin, 2005
Society of Cosmetic Chemists, Shaw Mudge Award (best paper at national meeting), 2001
Society of Cosmetic Chemists, Shaw Mudge Award (best paper at national meeting), 1996

National Science Foundation Graduate Fellow
Phi Beta Kappa
Breckenridge Scholar
American Institute of Chemists Outstanding Senior Chemistry Major

High school Co-valedictorian
Courier-Journal Outstanding Student
National Merit Scholarship Award Winner
National Honor Society

PROFESSIONAL EXPERIENCE

2014-2017 PI, P&G/UCRI Skin Science and Technology Center of Excellence
2011-2013 Chair, Division of Pharmaceutical Sciences, Winkle College of Pharmacy
2008-2011 Director of Graduate Studies, Winkle College of Pharmacy, Univ. of Cincinnati

2006-present Professor, University of Cincinnati College of Pharmacy
Mathematical Modeling of Percutaneous Absorption

Development of improved methods for predicting the systemic absorption rates and local skin concentrations resulting from topical exposure to therapeutic agents or to hazardous chemicals.

1999-2006 Associate Professor, University of Cincinnati College of Pharmacy

1980-1993 Research chemist, The Procter & Gamble Company, Cincinnati, Ohio
1993-1999 Senior Scientist, The Procter & Gamble Company, Cincinnati, Ohio

1998-1999 Skin Beauty Care Technology Division
Skin Benefits for Rinse-off Products
Application of skin repair technologies to personal cleansing products including soap bars and shower gels. Deposition of ingredients on skin.

1994-1998 Skin Beauty Care Technology/Cosmetic & Fragrance Technology Division
Visual Improvement of Aging Skin
Formulation and delivery of actives for novel skin repair technologies. Design and execution of human facial appearance studies. Mathematical modeling of skin penetration process.

1990-1994 Hair & Skin Care Technology Division
Photoprotection Section
Formulation and delivery of actives for novel skin repair and photoprotection technologies.

1987-1990 Health & Personal Care Technology Division
Biopharmaceutics Section
Characterization of drug actives, topical and transdermal dose form development, skin iontophoresis studies and modeling. Intranasal dosing technology, droplet sizing and dose distribution for metered dose nasal sprays.

1984-1987 Health & Personal Care Technology Division
Novel Analgesics Section
Preformulation studies, antinoceptive testing, QSAR analysis, metabolism assays, pharmacokinetic/ADE studies, parenteral dose form development.

1983-1984 Health & Personal Care Technology Division
Topical Anti-inflammatories Section
In vitro skin penetration studies, penetration aid technology, iontophoresis studies, skin penetration modeling.

1980-1983 Corporate Research Division
Lubricant Additive Development
Design and evaluation of new antiwear additives for automotive engine oils based on proprietary fatty acid chemistry.

1975 (summer) Chemist, Lawrence Livermore Laboratories, Livermore, California
Chelate solvent extraction of actinides and lanthanides.

1974 (summer) Student, Oak Ridge National Laboratories, Oak Ridge, Tennessee
Contrast enhancement of radiographs using optical spatial filtering techniques.

1971-1973 (summer) Technician, ATEC Associates, Inc., Louisville, Kentucky
Soil and concrete testing.

PROFESSIONAL AFFILIATIONS

Scientific and Professional Societies

American Association of Pharmaceutical Sciences 1986-2004
2002 Chair -- Dermatopharmaceutics Focus Group
1996 Chair -- Dermatopharmaceutics Focus Group
Phi Beta Kappa

Gordon Research Conference on Barrier Function of Mammalian Skin, 1989-2017
2003 Co Vice-Chair
2005 Co Chair

Scientific Journals

Pharmaceutics
Journal of Pharmaceutical Science, editorial board, 1992 – 2001; 2004-present
Pharmaceutical Development and Technology, editorial board
AAPS Journal, referee
European Journal of Pharmaceutics and Biopharmaceutics, referee
International Journal of Pharmaceutics, referee
Journal of Controlled Release, referee
Molecular Pharmaceutics, referee
Pharmaceutical Research, referee
Cosmetic Science
Journal of Cosmetic Science, referee
International Journal of Cosmetic Science, referee
Biophysics
Biophysical Journal, referee
Biopolymers and Peptide Science, referee
Chemistry
Colloids and Surfaces B, referee
Journal of the Royal Society Interface, referee
Dermatology/Medicine
Cough, referee
Journal of Investigative Dermatology, referee
Engineering
American Institute of Chemical Engineers Journal, referee
Industrial and Engineering Chemistry Research, referee
Environmental Health
Environmental Health Perspectives, referee
Environmental Science and Technology, referee
…..Indoor Air, referee
Journal of Exposure Science and Enivironmental Epidemiology, referee
Journal of Occupational and Environmental Hygiene, referee
Physiology
Journal of Applied Physiology, referee
Skin Pharmacology and Physiology, referee

Toxicology
Cutaneous and Ocular Toxicology, referee
Food and Chemical Toxicology, referee
Regulatory Toxicology and Pharmacology, referee

Toxicology and Applied Pharmacology Toxicological Sciences, referee
Toxicology in Vitro, referee

Review Boards

Reparative Medicine Study Section ZRG1 SSS-M 01 (NIH), 2002-03
Tissue Engineering BRP Study Section MOSS G 52 (NIH), 2003-04, 2009
Study Section AA-1 (NIH), 2004
Study Section MOSS-D 12 (NIH), 2005
Study Section MTE (NIH), 2008
Study Section ZRG1 BST-E (NIH), 2008
Study Section MOSS-G 03M, 2009

PERSONAL

Date of Birth: January 2, 1953

Married

Children: Elinor, 35; Jonathan, 29.

Interests: Triathlon (running, biking, swimming), waterskiing, youth soccer, guitar. Four-time division winner, Little Miami Triathlon; 1999 ascent – Mt. Kilimanjaro; 2005 descent & ascent – Grand Canyon. Many of these are now *former* interests, but I still like to bike!

RESEARCH SUPPORT

Pending Research Support

Research contract Kasting PI 07/01/19– 06/30/21
Gentle Cleansing and Mildness Technology Development $200,000
This project involves the characterization of the rheological and emulsification properties of natural and sulfate-free surfactant compositions with the objective of improving both factors.
Procter & Gamble/UCRI
Role: PI
Effort: 0.27 mos. academic year, 0.27 mos. recess equivalent

U01 research contract Li (PI) 9/01/2019 – 8/31/2021
Development of Bioequivalence Approach for Topical Ungual Product $500,000
FDA
The objectives of this project are to (a) utilize appropriate methods to measure the critical attributes of ungual topical dosage forms that affect drug penetration into the nail plate and nail bed and (b) develop an *in vitro* permeation test and pharmacokinetics model that can identify the failure modes for bioequivalence.
Role: co-Investigator
Effort: 0.44 mos. academic year; 0.20 mos. recess

Current Research Support

Research contract Kasting PI 07/1/17– 12/31/19
Gentle Cleansing and Mildness Technology Development $200,000

This project involves the development of preclinical assays for determination of surfactant mildness in rinse-off products and their correlation with clinical testing results
Procter & Gamble/UCRI
Role: PI
Effort: 0.27 mos. academic year, 0.27 mos. recess equivalent

Research grant Heikenfeld (PI) 7/1/16 – 6/30/19
Chronologically Correlated Sweat Biosensing $548,299
NSF
This project represents another step in the development of on-skin biomarker sensing in sweat. Our role is to develop an advanced computational model for sweat production and biomarker levels therein.
Role: co-I
Effort: 0.11 mos. academic year; 0.11 mos. recess

Completed Research Support

Research contract Kasting PI 12/18/17– 06/30/18
Solubility-based Thermodynamic Model for Topical Delivery of $75,000
Benefit Agents from ShortList Formulations
This project involves the estimation of skin penetration properties of benefit agents incorporated in novel skin care formulations.
Procter & Gamble/UCRI
Role: PI
Effort: 0.13 mos. academic year, 0.13 mos. recess equivalent

CBET-1335822 Kasting PI 09/01/13 – 08/31/17
Collaborative Research: GOALI: Multiscale Theory and $405,852
Computer Simulation of Skin Absorption Phenomena UC portion: $196,890
NSF-CBET (GOALI)
This was a collaborative project among G.B. Kasting (University of Cincinnati), J.M. Nitsche (SUNY-Buffalo) and L.C. Nitsche (U. of Illinois at Chicago) with the Procter & Gamble company as the industrial partner (R. H. DeVane). Its objective is to develop a multiscale computational model that more accurately predicts transient dermal absorption based on highly realistic representations of (i) the multiphase ultra- and microstructures of stratum corneum, viable epidermis and dermis layers of skin, and (ii) solute binding to tissue constituents and transporter proteins. The model will be incorporated into an accessible computational platform directly useful to the product development, toxicology and regulatory communities.
Role: PI
Effort: 0.37 mos. academic year; 0.32 mos. recess

LRI-B13 Kasting (PI) 09/01/13 – 08/31/17
Development of a Mechanistic In Silico Multi-scale Framework 500,000 euros
to Assess Dermal Absorption of Chemicals UC portion: 300,933 euros
Cefic
This was a collaborative project in skin absorption modeling involving one other academic unit (University of Warwick) and three industrial companies (Procter & Gamble, Unilever, BASF).
Role: PI
Effort: 0.74 mos. academic year; 0.32 mos. recess

1U01FD004942-03 Li (PI) 9/01/2015 – 8/31/2017

Tiered Testing Strategy for Assessing Thermal Effects $250,000
on Transdermal Products
FDA
The objectives of this project were to (a) investigate the in vitro release test conditions for identifying heat effects on transdermal delivery and (b) develop an in vitro test process to be used in the reviews of transdermal products to ensure that generic products do not introduce any additional safety risks.
Role: co-I
Effort: 0.9 mos. academic year; 0.4 mos. recess

URC Strategic Collaborative research grant (5 co-PIs) 7/1/15 - 12/31/16
Non-invasive biosensing through skin: Integrated reverse iontophoresis $125,000
extraction and electrochemical impedance spectroscopy detection
Univ. of Cincinnati Research Council
This project tested the feasibility of extracting cortisol from interstitial fluid using reverse iontophoresis/electro-osmosis technology
Role: co-PI
Effort: 0.08 mos. academic year

Research contract Kasting (PI) 07/01/14 – 06/30/17
Zinc Pyrithione Dissolution and Release from Coacervates $165,000
Procter & Gamble/UCRI
This was a research project with the Beauty Care sector of P&G in which we will help to elucidate the mechanism by which the antidandruff agent zinc pyrithione dissolves from coacervate deposits on the surface of the scalp.
Role: PI
Effort: 0.2 mos. academic year; 0.2 mos. recess equivalent

Research contract Kasting (PI) 07/1/15– 06/30/17
Understanding the mechanism of skin hydration and its impact $48,861
on barrier function by simulation
Procter & Gamble/UCRI
This project involved the development of an advanced computational model for simulating hydration effects in baby skin, particularly in the diapered area. The target was to develop the ablility to predict exogenous solute uptake as well as transepidermal water loss.
Role: PI
Effort: 0.28 mos. academic year, 0.28 mos. recess equivalent

Research contract Kasting/Heineman (co-PIs) 07/1/15– 06/30/17
Surfactant skin/scalp mildness & hair stripping methods/ $150,000
mechanisms/new materials
This project involved the development of preclinical assays for determination of surfactant mildness in rinse-off products and their correlation with clinical testing results
Procter & Gamble/UCRI
Role: co-PI
Effort: 0.22 mos. academic year, 0.22 mos. recess equivalent

Research contract Zhang (PI) 07/1/15– 12/31/16
Beauty Care pro-active delivery to body/skin – $219,752
Mechanistic understanding of penetration and metabolism on skin/scalp health benefit
Procter & Gamble/UCRI
The goal of this project was to develop a mechanistic understanding of the skin mildness benefits imparted by the nonionic surfactant, glycerol monoleate

Role: co-I
Effort: 0.04 mos. academic year, 0.04 mos. recess equivalent

Y2-004 Kasting/Heikenfeld (co-PIs) 3/1/15– 2/30/16
Stimulation of Sudo-Motor Axon Reflex Sweating $55,000
NSF CADMIM Center
The goal of this project was to investigate a novel way of chemically stimulating sweat secretion in areas adjacent to the site of chemical delivery
Role: co-I
Effort: (not supported on this grant)

U01 research contract Li/ (PI) 9/01/2014– 8/31/2015
Model for Predicting Dermal Absorption and Local Drug Concentration $200,000
on Transdermal Products
FDA
This project developed a physiologically based dermal absorption model that allows the prediction of drug concentration at the drug site of action in the skin. The successful development of such a model will improve the evaluation of generic dermatological drug products and assist the preparation of drug product guidance. Hence, more affordable topical drugs will be able to reach the public quickly as generic drugs.
Role: co-I
Effort: 0.9 mos. academic year; 0.4 mos. recess

1U01FD004942-02 Li (PI) 9/01/2014 – 8/31/2015
Tiered Testing Strategy for Assessing Thermal Effects $250,000
on Transdermal Products
FDA
The objectives of this project were to (a) investigate the in vitro release test conditions for identifying heat effects on transdermal delivery and (b) develop an in vitro test process to be used in the reviews of transdermal products to ensure that generic products do not introduce any additional safety risks.
Role: co-I
Effort: 0.9 mos. academic year; 0.4 mos. recess

Research contract Kasting (PI) 9/01/2014 – 1/01/2015
Co-uptake and Desorption of Glycerin and Water $15,800
from Human Stratum Corneum
The Procter & Gamble Company
The objective of this project was to obtain a working knowledge of co-uptake and transport of glycerin and water in the skin's outer layer, in order to better predict the performance of cosmetic products applied to skin.
Role: PI

Research contract Kasting (PI) 07/01/14 – 06/30/15
P&G-UCRI Skin Science and Technology Center of Excellence $235,000
Procter & Gamble COP portion: $95,000
This is a center grant from P&G that in Year 1 will support research in A&S Chemistry and the College of Pharmacy.
Role: PI
Effort: (not applicable)

ES-002 Heikenfeld/Kasting (co- PIs) 03/1/14– 02/30/15

The Microfluidics of On Skin Technologies $50,000
NSF CADMIM Center
The objectives of this project were to develop on-skin sensing technology for biomarkers in human sweat.
Role: co-PI
Effort: (not supported by this grant)

1U01FD004942-01 Li (PI) 9/15/2013 – 8/31/2014
Tiered Testing Strategy for Assessing Thermal Effects on Transdermal Products $494,430
FDA
The objectives of this project were to (a) investigate the in vitro release test conditions for identifying heat effects on transdermal delivery and (b) develop an in vitro test process to be used in the reviews of transdermal products to ensure that generic products do not introduce any additional safety risks.
Role: Co-investigator
Effort: 1.1 mos. academic year; 0.5 mos. recess

Research contract Kasting (PI) 07/01/10 – 06/31/14
ZnPT Dissolution and Transport On and Through Skin $130,000
Procter & Gamble
This is a research project with the Beauty Care sector of P&G in which we helped to elucidate the mechanism by which the antidandruff agent zinc pyrithione exerts its antimicrobial action on hair and skin.
Role: PI

2 R01 OH007529-A1 Kasting (PI) 09/01/07 – 07/31/13
Mechanistically-Based In Silico Estimation of Dermal Absorption in the Workplace $1,954,729
NIOSH/CDC
This was a collaborative project with J. M. Nitsche (SUNY Buffalo Dept. of Chem. Engineering) and J. C. Kissel (U. Washington Occupational and Environmental Engineering) to develop improved mathematical models for the skin absorption of hazardous chemicals following occupational or environmental exposures.
Role: PI

2R01GM063559-06A2 Li (PI) 08/03/09-05/31/13
Iontophoresis to Improve Nail Disease Treatment : $942,000
NIH/NIAMS
Our role was to provide measurements of nail conductivity for selected salts along with a theoretical framework (Aim 2 of project).
Role: Co-investigator(12%effort)

Research contract Kasting (PI) 05/01/11 – 04/30/13
Skin Concentrations of Topical Drugs: Structure-Activity Relationship for Selected Compounds $52,800
Merck & Company
This project was designed to determine the effect of structure on skin absorption of selected Merck compounds formulated in simple o/w emulsion bases.
Role: PI

Research contract Kasting (PI) 04/01/08 – 03/31/11
Prediction of Epidermal Bioavailability of Contact Allergens 330,000 Euro

COLIPA
This was a continuation of the joint research project with the contact allergy research group at Procter & Gamble to develop better risk assessments for consumer products with regard to elicitation of allergic responses.
Role: PI

5R01CA114095 Abdel-Malek (PI) 09/27/06 – 07/31/10
Discovery of Alpha-MSH Analogs for Skin Cancer Prevention
NIH/NCI
This was a joint research project with other UC Medical Center personnel on development of peptide-mimetic analogs of α-melanotropic stimulating hormone as topical anticancer agents.
Role: co-investigator

Research contract Kasting (PI) 04/01/05 – 03/31/08
Development of a Toxicodynamic Model to Better Predict Epidermal Bioavailability of Contact Allergens 240,000 Euro
COLIPA
This was a joint research project with the contact allergy research group at Procter & Gamble to develop better risk assessments for consumer products with regard to elicitation of allergic responses.
Role: PI

Research contract Kasting (PI) 7/01/05 – 6/30/07
Development of a Screening Tool for Follicular Delivery $40,000
P&G
This was an exploratory project aimed at developing laboratory methods for evaluating targeted delivery to the hair follicle and sebaceous gland.

1 R01 OH007529 Kasting (PI) 09/01/02 – 08/31/06
Improved Methods for Dermal Exposure Estimation $1,333,670
NIOSH/CDC
This was a collaborative project with J. M. Nitsche (SUNY Buffalo Dept. of Chem. Engineering) to develop improved mathematical models for the skin absorption of hazardous chemicals following occupational or environmental exposures.

Research contract Kasting (PI) 3/01/05 – 2/28/06
α-Hydroxy Acid Skin Delivery and Retention $14,050
Kao Brands
This project was designed to support the risk assessment associated with Kao Brands' line of α- hydroxy acid-containing skin and hair care products.

Research contract Hoath (PI) 6/01/05 – 11/30/05
Development of a Standardized in Vitro Human Skin Equivalent for Assessment of Product Safety and Efficacy $78,000
This project tested the utility of a new growth system for cultured skin substitutes (developed in GBK's laboratories) as an in vitro test system for skin care consumer products.

RO1 DK61689-01 Roy-Chaudhury (PI) 08/05/02 – 07/31/06
Local Intiproliferative Therapy for Venous Neointimal Hyperplasia
NIH
The objective of this project was to develop drug-loaded polymer systems that reduce

the intravenous tissue growth leading to plugging of stents used in hemodialysis treatment of diabetic subjects. GBK has responsibility for modeling of drug release from the polymer systems.
Role: Collaborator

Industrial research contract Kasting (PI) 07/01/01 – 06/30/03
Impact of Novel Surfactant Systems on Topical Delivery 30,000
The Procter & Gamble Company
This project was an experimental investigation of the topical delivery properties of surfactant/water systems with an unusual cubic phase architecture.
Role: PI

Industrial research contract Kasting (PI) 11/01/01 – 05/30/03
Glycerol Skin Absorption Studies $10,450
The Andrew Jergens Company
This project was an experimental investigation of the skin deposition and absorption of the moisturizing agent, glycerol, from prototype skin cream formulations.
Role: PI

SHC #8670 Boyce (PI) 1/01/02 – 12/31/02
Shriner's Burns Institute
This project was directed toward characterization, use,and scale-up of cultured skin substitutes for burn allograft therapy.
Role: Consultant

GOALI BES-9818160 Nitsche (PI) 04/01/99 – 03/31/02
Comprehensive Model of Molecular Transport and Delivery Through the Skin $193,556
NSF
This project involved the initial development of a detailed mathematical model for drug transport in the skin, using 2-D and 3-D finite difference models to represent drug transport through a detailed skin microstructure.
Role: Industrial partner (obtained while at Procter & Gamble)

International Program for Animal Alternatives. Kasting (PI) 06/01/99–05/31/01
The Procter & Gamble Company $58,709
Predictive Computational Model of Skin Permeability to Reduce the Need for Animal Models: Experimental Studies
The major goal of this project was to measure microscopic transport properties pertinent to a detailed mathematical model of drug transport in skin.
Role: PI

University Research Council Faculty Support Grant. Kasting (PI) 09/01/99 – 12/31/99
Hydration Effect on Skin Permeability: Method Development $5,000
The University of Cincinnati
This project investigated a new technique for measuring the effect of water on stratum corneum permeability, with the objective of developing more a more precise understanding of this phenomenon for incorporation into broader mathematical models for skin permeability.
Role: PI

Industrial research contract Kasting (PI) 09/01/00 – 5/31/01
Skin Penetration of Botanical Ingredients $22,988
The Andrew Jergens Company
This project involved the determination of local tissue and systemic levels subsequent to

topical application of certain botanical ingredients. There were mathematical modeling and experimental confirmation aspects to the project. The primary objective was to support the dermal risk assessment for these materials.

Industrial research contract Kasting (PI) 09/01/00 – 10/31/00
In Vitro Skin Penetration II $10,445
The Procter & Gamble Company
This project involved continued evaluation of the topical delivery properties of two proprietary PG skin care ingredients.

Industrial research contract Kasting (PI) 03/01/00 – 6/31/00
In Vitro Skin Penetration $10,595
The Procter & Gamble Company
This project involved the evaluation of the topical delivery properties of two proprietary PG skin care ingredients.

RESEARCH PUBLICATIONS

1. Rush AK, Nash JF, Smith ED and Kasting GB. Formulation and artificial sebum effects on the in vitro percutaneous absorption of zinc pyrithione. *Skin Pharmacol Physiol,* in press (2019).

2. Nitsche LC, Kasting GB and Nitsche JM. Microscopic models of drug/chemical diffusion through the skin barrier: effects of diffusional anisotropy of the intercellular lipid. *J Pharm Sci* **108**:1692-1712 (2019).

3. Morris SAV, Thompson R, Glenn R, Ananthapadmanabhan KP and Kasting GB. Mechanisms of anionic surfactant penetration into human skin: Investigating monomer, micelle, and submicellar aggregate penetration theories. *Int J Cosmet Sci* **41**:55-66 (2019).

4. Morris SAV, McCardy NR, Thompson R, Allen T, Altmeier A, Wehmeyer K, Hinkle R, Jones M, Spruell R, Stoffolano P, Miller MA, Styczynski P, Glenn R and Kasting GB. Comparing surfactant penetration into human skin and resulting skin dryness using in vivo and in vitro methods. *J Cosmet Sci* **70**(1):33-45 (2019).

5. La Count TD, Jajack A, Heikenfeld J and Kasting GB. Modeling glucose transport from systemic circulation to sweat. *J Pharm Sci* **108**:364-371 (2019).

6. Kasting GB, Miller MA, LaCount TD and Jaworska J. A composite model for the transport of hydrophilic and lipophilic compounds across the skin. *J Pharm Sci* **108**:337-349 (2019).

7. Amidon GE, Anderson BD, Balthasar JP, Bergstrom C, Huang S-M, Kasting GB, Kesisoglou F, Khinast J, Mager D, Roberts CJ, Yu L. Fifty-eight years and counting: high-impact publishing in computational pharmaceutical sciences and mechanism-based modeling. *J Pharm Sci* **108**:2-7 (2019)

8. Zhang Q, Murawsky M, LaCount T, Kasting G and Li S. Transepidermal water loss and skin conductance as barrier integrity tests. *Toxicol in Vitro* **51**:129-135 (2018).

9. Yu F and Kasting GB. A geometrical model for transport of hydrophilic compounds in human stratum corneum. *Math Biosci* **300**:55-63 (2018).

10. Nitsche JM and Kasting GB. How predictable are human stratum corneum lipid/water partition coefficients? assessment and useful correlations for dermal absorption. *J Pharm Sci* **107**:727-738 (2018).

11. Simmers P, Sonner Z, Li K, Kasting G and Heikenfeld J. Greatly prolonged and localized sweat stimulation by iontophoretic delivery of the slowly-metabolized cholinergic agent carbachol. *J Dermatol Sci* **85**:71-76 (2017).

12. Sonner Z, Wilder E, Gaillard T, Kasting GB and Heikenfeld J. Integration of sudomotor axon reflex sweat stimulation for continuous sweat analyte analysis with individuals at rest. *Lab on a Chip* **17**:2550-2560 (2017).

13. Miller MA, Yu F, Kim K and Kasting GB. Uptake and desorption of hydrophilic compounds from human stratum corneum. *J Control Rel* **261**:307-317 (2017).

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Topical formulations: design and development, Two-day seminar sponsored by Technomics Publishing Company, Cincinnati, OH and Basel, Switzerland, October, 1998; Toronto, Canada, May, 1999.

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TAB 11

the bile of dogs is very rapidly cleared from the body of rats[9]. Experiment 2, a repeat of experiment 1, was conducted to check whether possibly induced liver enzymes affect biliary excretion of tritium activity, since in the rat an increase in heptic microsomal P-448-mediated enzyme activities has been reported already at doses of 2 ng of TCDD/kg[8]. Obviously, the small dose of ^{3}H-TCDD was not sufficient for a stimulation of TCDD-metabolism in the dog. From our results it is reasonable to assume that P-448-dependent liver enzymes are involved in the biotransformation of the dioxin. Because of the very distinct effect of TCDD, the most potent out of the group of P-448 inducers, no other classical inducer was investigated. It should be considered that a faster elimination might cause the acute toxicity of TCDD to decrease. In view of data from Beatty et al.[10], who found a higher LD_{50} in male weanling rats pretreated with TCDD (but also with phenobarbital) this seems likely, because the time during which the organism is in contact with this substance certainly plays an important role. Furthermore, available data suggest that TCDD is essentially eliminated from the body only in metabolized form. Whether inducibility of TCDD-metabolism is a phenomenon unique in the dog is a question that deserves further study.

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The use of indentometry to study the effect of agents known to increase skin c-AMP content

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Summary. Local, externally applied pharmacological agents which are assumed to raise the c-AMP level, decrease the low pressure indentation value of the forehead skin of certain human volunteers.
Key words. c-AMP, skin; indentometry; pharmacological manipulation of mechanical parameter.

Recently low pressure indentometry has been used to measure 'dermal hydration'[1,2] in vivo. This method is used for measuring an aspect of the efficiency of cosmetic treatments and also as a routine diagnostic instrument in medicocosmetic consultation[3]. The measuring system, procedure and instrumentation have been described elsewhere[3]. In essence they are based on low pressure procedures. A light metal measuring rod is counterbalanced so that the net pressure of the system is less than 1 g/cm^2. A circular plate at the end of the rod, having a surface area of 0.2 cm^2, serves as the contact area with the skin. The total weight of the system (including the counterbalance) is 6 g. The measuring rod can be loaded with specially constructed weights, thereby increasing the pressure from the starting pressure to any desired value. The routine final pressure used in our laboratory for in vivo measurements on humans is 10 g/cm^2. The rod is connected to a linear variable differential transformer (LVDT), the output of which is graphically recorded. The routine paper velocity used by us is 6 cm/min. The sensitivity of the measurements is $\pm$ 0.001 cm.

For many reasons[2], the routine measurements are performed on the forehead skin. The patient lies on his/her back with eyes closed and head resting on a wooden plate to prevent recording of breathing and heartbeats. The measuring rod is adjusted so that the plate is in contact with the forehead skin, and the electronic system is zeroed (starting pressure = 1 g/cm^2). The recorder is started and the base line is recorded for about 10–15 sec. The standard weight is now suddenly applied, and the resultant indentation recorded for 6 sec. The weight is then removed and the rebound phase ('elastic recovery') of the skin is recorded for a further 6 sec.

The indentation so measured by low pressure indentometry on the forehead skin is 0.04–0.09 cm. Without treatment, the mean change in the indentation of an individual point during the day is less than $\pm$ 0.003 cm.

It was shown that indentation is usually higher in the so-called 'cosmetically dry skin' cases, and always lower in the 'cosmetically not dry skin' cases, and further, that age increases indentation[3]. We also showed that indentation under our standardized conditions is increased by intradermal hyaluronidase and decreased by water, thus indicating that indentometry reflects the state of ground substance[4].

We wish to discuss here pharmacological agents affecting indentometry. Each substance was tested on four volunteers who had 'high indentation values' (0.06–0.08 cm). Triplicate measurements were carried out at four points on each volunteer (forehead skin). Then the substance was applied to the skin (1 ml during 10 min) and the indentation was recorded at different times; at each time a triplicate measurement at the same point. Statistical evaluation by paired t-test was carried out on the individual changes of each patient.

The table shows that agents known to increase c-AMP in skin by activating adenylate cyclase, such as adenosine[5], the β-agonist isoproterenol bitartarate[6] or the β_2-agonist terbutaline sulfate, or the phosphodiesterase inhibitor papaverine[7], all cause a decrease in indentation at approximately those concentrations at which they are known or supposed to cause an increase in the c-AMP content of the skin[5–7]. This decrease in indentation represents a firmer, younger skin. The final proof that c-AMP is involved can be seen in the table, from the strong effect of 0.1% N^6,O^2-dibutyryl c-AMP (sodium salt).

The action of the above agents is specific, since 0.3% solution of noradrenaline hydrochloride, histamine hydrochloride, serotonine hydrochloride, guanosine, or N^2,O^2-dibutyryl c-GMP failed to influence indentation significantly. Each active agent

Effect of agents connected with the adenylate cyclase system on low pressure indentation

Agent	Concentration of active part (%)	Decrease in indentation $\times 10^{-3}$ cm 1 h	2 h	3 h	5 h	6 h	7 h	10 h
N^6, O^2,-dibutyryl c-AMP (sodium salt)	0.1	NS	2.6 ± 1.0	3.5 ± 0.8	4.5 ± 0.8	6.8 ± 1.3	8.0 ± 1.2	5.0 ± 0.8
Isoproterenol (bitartarate)	0.1	5.0 ± 0.8	7.3 ± 1.0	7.3 ± 1.7	7.3 ± 1.2	–	5.2 ± 0.8	NS
Papaverine (hydrochloride)	5.0	4.5 ± 1.0	6.3 ± 1.0	5.8 ± 1.3	4.3 ± 1.0	NS	NS	
Adenosine	0.1	4.0 ± 0.5	4.2 ± 0.8	4.2 ± 0.8	4.0 ± 1.0	NS		
Terbutaline (sulfate)	0.3	2.7 ± 1.0	6.5 ± 1.2	4.7 ± 1.5	4.5 ± 1.7	–	4.0 ± 1.3	NS

NS = not significant at $p \leq 0.05$. Agents were freshly dissolved in distilled water. A premeasured 1 ml was self-applied in successive small doses over a 10-min period to the forehead skin of the volunteers. Each figure represents the mean ± SD from the mean of 16 experimental points in four volunteers.

was also tested at one-third of the concentrations shown in the table, and at this level all were ineffective.

We also measured the elastic recovery of the skin before and after the application of all the agents mentioned in this communication (for the method see Dikstein and Hartzshtark[1]. None of these agents had any influence on elastic recovery within the time scale of these experiments.

One can only speculate on the possible role of c-AMP. In our view, it stimulates the fibroblasts to synthetize hyaluronic acid[8]. We have shown, indeed, that hyaluronidase increases indentation[9]. On the other hand, β_2 receptors have been identified in the epidermis[10].

The idea that active emollients and moisturizers could work via a pharmacological route has already been suggested by Tronnier[11] and Idson[12]. Van Dorp[13] postulated that dry skin conditions could be treated by prostaglandins and essential fatty acids externally applied to the skin. Penneys et al.[14] showed that white petrolatum interferes with the metabolism of arachidonic acid in the skin.

In this communication, however, a physical parameter (compressibility – 'firmness') of the human skin in vivo has been shown to be dependent on a biochemical intermediate *and* its pharmacological manipulation.

It is hoped that our findings will contribute to the development of cosmetic or pharmaceutical preparations aimed at hindering the effects of aging on the human skin.

Added in proof: U.S. patent 3,978,213 (31.8.1976) deals with the cosmetic use of c-AMP and agents inhibiting c-AMP degradation.

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Growth inhibitory, insecticidal and antifeedant effects of some antileukemic and cytotoxic quassinoids on two species of agricultural pests[1]

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Summary. Several quassinoids, obtained by isolation and derivatization from *Simaba multiflora* and *Soulamea soulameoides*, were evaluated for growth inhibitory and insecticidal effects against the tobacco budworm *(Heliothis virescens)* and for antifeedant effects against *H. virescens* and the fall armyworm *(Spodoptera frugiperda)*. The relative activity of the quassinoids as insect growth inhibitors generally paralleled their known relative potency as antileukemic and cytotoxic agents.

Key words. Quassinoids; *Heliothis virescens*; *Spodoptera frugiperda*; growth inhibitory effects; antifeedant effects; antileukemic activity; cytotoxic activity.

It is becoming increasingly evident that certain natural products elicit activity in a number of biological systems (e.g., antileukemic, insect antifeedant, antispomatic, insect antiecdysis, cytotoxic and brine shrimp toxic activities)[2–5]. For example, Nakanishi has pointed out that natural products with electrophilic moieties tend to be cytotoxic and insect antifeedant[6].

Such multiplicity in biological activities attributed to individual natural products has prompted us to investigate some plant products, previously isolated as anticancer agents, for their effects on pest insects. The present report describes the growth inhibitory, insecticidal and antifeedant effects of 8 quassinoids (simaroubolides) on the larvae of the economically important

TAB 12

CLINICAL PHARMACOLOGY AND NURSING

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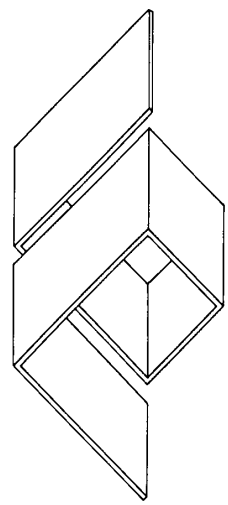

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The drug selections and dosages in this textbook are based on research and current recommendations by medical and nursing authorities. These selections and dosages comply with currently accepted standards, although they cannot be considered conclusive. For each patient, any drug or dosage recommendation must be considered in conjunction with clinical data and the latest package-insert information. This is particularly essential with new drugs. The authors and the publisher disclaim responsibility for any untoward effects caused by these suggested selections and dosages or from the reader's misinterpretation of this information.

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UNIT 2

THE NURSING PROCESS AND DRUG ADMINISTRATION

Most nurses will agree that medication administration is the most challenging, and sometimes most frightening, new experience for a nursing student. It is challenging because safe therapeutic medication administration requires technical competence, sound judgment, and meticulous attention to detail. It can be frightening because it is a complex activity that can harm the patient if not implemented properly.

Nurses are legally responsible for maintaining patient safety, ethically responsible for making moral nursing decisions, and professionally responsible for facilitating the therapeutic effects of medications. To meet these responsibilities, the nurse must apply a broad knowledge base to all aspects of care and must be aware of the related legal and ethical implications of nursing care.

OVERVIEW OF CHAPTERS

Unit Two provides the basic information necessary for the nurse to become knowledgeable and competent in safe, therapeutic drug administration. It not only presents general nursing responsibilities, such as dosage calculations and administration techniques, but also describes specific nursing care for pediatric, geriatric, pregnant, and breast-feeding patients. Although learning to administer medications is a complex task, the information contained in Unit Two should help the nurse successfully meet the challenge.

Chapter 6
The Nursing Process and Drug Therapy

Chapter 6 describes the nursing process as a framework for delivering nursing care. It discusses each step of the nursing process—assessment, diagnosis, planning, implementation, and evaluation—in relation to drug administration. It details the use of drug history and other information in assessing the patient and formulating nursing diagnoses. Then it describes planning, including the development of outcome criteria and interventions, such as patient teaching and promotion of patient compliance. The chapter concludes with a discussion of implementation and evaluation and the importance of documenting nursing activities related to drug therapy.

Chapter 7
Responsibilities in Drug Administration

Chapter 7 describes the essential components of a medication order and the seven types of medication orders typically used in hospitals. To help the nurse prevent medication errors, the chapter explores the five rights of medication administration and procedural safeguards. Then the chapter explores four types of drug delivery systems. It concludes with a discussion of the nurse's legal responsibilities and ethical obligations related to drug administration.

Chapter 8
Dosage Measurements and Calculations

After discussing factors that influence drug dosages, Chapter 8 surveys various systems of drug weights and measures, highlighting the metric, apothecaries', and household systems. Then the chapter introduces the fraction and ratio methods for conversions between systems of measurement. It illustrates the use of these methods and the "desired-available" method for computation of drug dosages. It concludes with special considerations for dosage calculations for pediatric and geriatric patients.

Chapter 9
Routes and Techniques of Administration

Chapter 9 begins by discussing drug forms and packaging. Then it details techniques for administering drugs by various routes, including the oral, sublingual, buccal, rectal, parenteral, intrathecal, epidural, intra-articular, dermal, ophthalmic, otic, nasal and sinus, respiratory, urethral, and vaginal routes. Throughout, the chapter emphasizes the rationales underlying nursing decisions about medication administration routes and techniques.

Glossary

Ampule: small, sterile, sealed glass or plastic container that holds a single drug dose.

Buccal route: oral medication administration in tablet form on the inside of the cheek.

Capsule: gelatin shell that dissolves in the stomach and contains drug in a powder, sustained-release bead, or liquid form.

Compliance: degree to which a patient follows the advice of a health care professional.

Cream: thick emollient (substance that softens tissue) that contains a paste-drug mixture of oil and water; designed for topical use.

Dermal route: topical medication administration by application to the skin.

Drops: medicated liquid administration in minute spheres.

Drug delivery system: institutional mechanism for obtaining medications from a general stock pharmacy for administration to patients in a clinical unit; also refers to dosage forms.

Elixir: flavored, sweetened hydroalcoholic (water and alcohol) liquid that contains a medicinal agent.

Enteric-coated tablet: tablet with a thin coating that prevents release and absorption of its contents until it reaches the small intestine.

Epidural route: medication administration through a catheter inserted into the space around the dura mater of the spinal column.

Ethical responsibility: duty that a nurse has to use fundamental moral values when making nursing decisions.

Evaluation: part of the nursing process in which the nurse judges the effectiveness of care based on preestablished criteria.

Goal: statement of the objective or aim of directed nursing care efforts.

Inhalant: medicinal vapor administered through the nose, trachea, or respiratory system.

Injection: introduction of a liquid into the body using a syringe; a solution of a medication suitable for injection.

Intra-articular route: medication administration by instillation or injection into a joint.

Intradermal route: medication administration by injection of small amounts of solution, usually antigens, between the epidermal and dermal (skin) layers.

Intramuscular route: medication administration by injection of a solution into a muscle.

Intraosseous route: medication administration by infusion into the medullary cavity of a long bone.

Intrathecal route: medication administration by direct injection through the theca (enclosing sheath) of the spinal cord into the subarachnoid space.

Intravenous route: medication administration by injection or infusion into a vein.

Intrauterine growth retardation: slowed growth of cells and part or all of the fetus, which may result from drug administration during gestation.

Legal responsibility: duty that a nurse has to abide by nursing practice acts and court decisions.

Lotion: medicated liquid applied topically to protect the skin or treat a dermatologic disorder.

Lozenge or **troche:** tablet containing a drug, flavoring, sweetener, and mucilage that is made to dissolve in the mouth.

Malpractice: wrongful conduct, improper discharge of duties, or failure of a professional to meet standards of care that causes harm to another. Negligence is a form of malpractice.

Milliequivalent: number of grams of a solute in one milliliter of a normal solution.

Negligence: failure to do something that could reasonably be expected to be done by an individual in a given situation or the performance of an act that a reasonable and prudent person would not do.

Nurse practice act: state (or Canadian provincial) legislation that describes educational requirements for professional licensure and professional scope of nursing practice.

Nursing care plan: written plan that includes prioritized goals, nursing interventions, and outcome criteria for a specific patient.

Nursing diagnosis: part of the nursing process in which the nurse uses a standard nomenclature to describe actual and potential patient care problems, their etiologies, and their signs and symptoms.

Nursing process: framework for nursing care that includes assessment, diagnosis, planning, implementation, and evaluation.

Ointment: semisolid, oil-based preparation that contains a medication for topical application.

Outcome criteria: statement of desired results that contains a content area, an action verb, a time frame, and criterion modifiers.

Over-the-counter (OTC) drug: drug available without a prescription.

Parenteral route: medication administration by injection, such as intradermal, intramuscular, intravenous, and subcutaneous injection.

Patch: thin membrane or gel base applied to the skin that releases a measured dose of medication over an extended period.

Percentage solution: solution in which the solute (solid) represents a percentage of the solution's total weight. For example, *0.9% saline solution* means that every 100 milliliters of solution contains 0.9 grams of sodium chloride (or every liter of solution contains 9 grams of sodium chloride).

Placebo: inactive substance, such as normal saline solution, or a less-than-effective dose of a substance, such as a vitamin, prescribed as if it were an effective medication dose.

Powder: small particles of medication obtained by grinding a solid drug.

Prescription: order for medication, therapy, or a therapeutic device given by a properly authorized person to a person properly authorized to dispense or perform the order.

Professional responsibility: duty that a nurse has to the standards of practice established by the profession as its code of ethics.

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Glossary *(continued)*

Rectal route: medication administration by insertion or infusion into the rectum.

Subcutaneous route: medication administration by injection of a substance under the skin into the layer of loose connective tissue.

Sublingual route: medication administration by placement of a tablet on the floor of the mouth under the tongue.

Suppository: medicated semisolid substance, usually cone-shaped, that melts or dissolves after insertion into a body cavity.

Suspension: preparation in which small particles of a solid drug are dispersed—but not dissolved—in a liquid for administration. Stirring or shaking the mixture maintains dispersal.

Syrup: concentrated solution that contains a medication, flavoring, sugar, and water.

Tablet: solid preparation in which medication is combined with inert ingredients and compressed into a shape.

Teratogenesis: development of physical defects in an embryo or fetus.

Tincture: liquid preparation that contains a medication and alcohol (alcoholic solution) or a medication, water, and alcohol (hydroalcoholic solution).

Vaginal route: medication administration by insertion or injection into the vagina.

Vial: small, glass, multidose medication container sealed with a rubber diaphragm.

Wax matrix tablet: wax, honeycomb structure that contains medication slowly released as the comb dissolves.

Chapter 10
The Pediatric Patient

Chapter 10 examines the special considerations for medication administration to pediatric patients. First the chapter describes age-related changes that affect a drug's pharmacokinetics, pharmacodynamics, and pharmacotherapeutics in pediatric patients. It illustrates these variations with specific examples and discusses the effects of drugs on normal growth and development. Next the chapter presents special pediatric dosage calculations and administration techniques. Lastly, it discusses family education and drug therapy.

Chapter 11
The Geriatric Patient

Chapter 11 presents special considerations for geriatric patients. It discusses the effects of aging and their influence on pharmacokinetics and pharmacodynamics in geriatric patients. Next it explores common drug related problems in elderly patients by body system. Then it discusses the nurse's role in reviewing medication regimens for geriatric patients and reviews ways to help cognitively impaired patients self-administer medication.

Chapter 12
The Pregnant or Breast-feeding Patient

Chapter 12 explores the pharmacokinetic changes that occur when a drug is given to a pregnant woman. It explains placental transport and the relationship between teratogenicity and drug administration at different gestational ages of the fetus. It also discusses medications used to treat pregnancy-related symptoms, such as heartburn, nausea and vomiting, constipation, and headache. It briefly touches on drugs used during labor and delivery.

For the breast-feeding patient, the chapter describes breast-milk formation and factors that influence drug transport to this milk—and to the breast-feeding infant. It concludes with guidelines to help the nurse counsel the pregnant or breast-feeding patient who needs drug therapy.

TAB 13

OECD GUIDELINES FOR TESTING OF CHEMICALS

SECTION 4 :

HEALTH EFFECTS

1. INTRODUCTORY INFORMATION

° Prerequisites

- Solid or liquid test substance
- Chemical identification of test substance
- Purity (impurities) of test substance
- Solubility characteristics
- pH (where appropriate)
- Stability, including stability in vehicle when so applied
- Melting point/boiling point

° Standard documents

There are no relevant international standards.

2. METHOD

A. INTRODUCTION, PURPOSE, SCOPE, RELEVANCE, APPLICATION AND LIMITS OF TEST

In the assessment and evaluation of the toxic characteristics of a chemical the determination of subchronic dermal toxicity may be carried out after initial information on toxicity has been obtained by acute testing. It provides information on possible health hazards likely to arise from repeated exposure by the dermal route over a limited period of time.

° Definitions

Subchronic dermal toxicity is the adverse effects occurring as a result of the repeated daily dermal application of a chemical to experimental animals for part (not exceeding 10 per cent) of a life span.

Dose in a dermal test is the amount of test substance applied to the skin (applied daily in subchronic tests). Dose is expressed as weight (g, mg) or as weight of the test substance per unit weight of test animal (e.g. mg/kg).

No-effect level/No-toxic-effect level/No-adverse-effect level is the maximum dose used in a test which produces no adverse effects. A no-effect level is expressed in terms of the weight of a substance given daily per unit weight of test animal (mg/kg).

Users of this Test Guideline should consult the Preface, in particular paragraphs 3, 4, 7 and 8.

Cumulative toxicity is the adverse effects of repeated doses occurring as a result of prolonged action on, or increased concentration of the administered substance or its metabolites in, susceptible tissue.

° Principle of the test method

The test substance is applied daily to the skin in graduated doses to several groups of experimental animals, one dose per group, for a period of 90 days. During the period of application the animals are observed daily to detect signs of toxicity. Animals which die during the test are necropsied, and at the conclusion of the test the surviving animals are sacrificed and necropsied.

B. DESCRIPTION OF THE TEST PROCEDURE

° Preparations

Healthy young adult animals are acclimatised to the laboratory conditions for at least 5 days prior to the test. Before the test, animals are randomised and assigned to the treatment and control groups. Shortly before testing fur is clipped from the dorsal area of the trunk of the test animals. Shaving may be employed, but it should be carried out approximately 24 hours before the test. Repeat clipping or shaving is usually needed at approximately weekly intervals. When clipping or shaving the fur care must be taken to avoid abrading the skin, which could alter its permeability. Not less than 10 per cent of the body surface area should be clear for the application of the test substance. The weight of the animal should be taken into account when deciding on the area to be cleared and on the dimensions of the covering. When testing solids, which may be pulverised if appropriate, the test substance should be moistened sufficiently with water or, where necessary, a suitable vehicle to ensure good contact with the skin. When a vehicle is used, the influence of the vehicle on penetration of skin by the test substance should be taken into account. Liquid test substances are generally used undiluted.

° Experimental animals

Selection of species

The adult rat, rabbit or guinea pig may be used. Other species may be used, but their use would require justification.

The following weight ranges at the start of the test are suggested in order to provide animals of a size which facilitates the conduct of the test:

rats, 200 to 300 g; rabbits, 2.0 to 3.0 kg; guinea pigs, 350 to 450 g.

Where a subchronic dermal study is conducted as a preliminary to a long term study, the same species and strain should be used in both studies.

Number and sex

At least 20 animals (10 female and 10 male) with healthy skin should be used at each dose level. The females should be nulliparous and non-pregnant. If interim sacrifices are planned the number should be increased by the number of animals scheduled to be sacrificed before the completion of the study. A satellite group of 20 animals (10 animals per sex) may be treated with the high dose level for 90 days and observed for reversibility, persistence, or delayed occurence, of toxic effects for a post-treatment period of appropriate length, normally not less than 28 days.

Housing and feeding conditions

Animals should be caged individually. The temperature in the experimental animal room should be 22°C (± 3°) for rodents or 20°C (± 3°) for rabbits and the relative humidity 30-70 per cent. When the lighting is artificial, the sequence should be 12 hours light, 12 hours dark. For feeding, conventional laboratory diets may be used with an unlimited supply of drinking water.

° Test conditions

Dose levels

At least three dose levels with a control and (where appropriate) a vehicle control should be used. Except for treatment with test substances, animals in the control group should be handled in an identical manner

to the test group subjects. The highest dose level should result in toxic effects but not produce an incidence of fatalities which would prevent a meaningful evaluation. The lowest dose level should not produce any evidence of toxicity. Where there is a usable estimation of human exposure the lowest level should exceed this. Ideally, the intermediate dose level(s) should produce minimal observable toxic effects. If more than one intermediate dose is used the dose levels should be spaced to produce a gradation of toxic effects. In the low and intermediate groups and in the controls the incidence of fatalities should be low, in order to permit a meaningful evaluation of the results.

If application of the test substance produces severe skin irritation the concentration should be reduced, although this may result in a reduction in, or absence of, other toxic effects at the high dose level. However, if the skin has been badly damaged early in the study, it may be necessary to terminate the study and undertake a new study at lower concentrations.

Limit test

If a test at one dose level of at least 1000 mg/kg body weight (but expected human exposure may indicate the need for a high dose level), using the procedures described for this study, produces no observable toxic effects and if toxicity would not be expected based upon data from structurally related compounds, then a full study using three dose levels may not be considered necessary.

Observations

A careful clinical examination should be made at least once each day. Additional observations should be made daily with appropriate actions taken to minimise loss of animals to the study, e.g. necropsy or refrigeration of those animals found dead and isolation or sacrifice of weak or moribund animals.

° Procedure

The animals are treated with the test substance, ideally for at least 6 hours per day on a 7-day per week basis, for a period of 90 days. However, based primarily on practical considerations, application on a 5-day per week basis is considered to be acceptable. Animals in a satellite group scheduled for follow-up observations should be kept for at least a further 28 days without treatment to detect recovery from, or persistence of, toxic effects.

The test substance should be applied uniformly over an area which is approximately 10 per cent of the total body surface area. With highly toxic substances the surface area covered may be less, but as much of the area should be covered with as thin and uniform a film as possible.

Between applications the test substance is held in contact with the skin with a porous gauze dressing and non-irritating tape. The test site should be further covered in a suitable manner to retain the gauze dressing and test substance and ensure that the animals cannot ingest the test substance. Restrainers may be used to prevent ingestion of the test substance, but complete immobilisation is not a recommended method.

Signs of toxicity should be recorded as they are observed, including the time of onset, the degree and duration. Cage-side observations should include, but not be limited to, changes in skin and fur, eyes and mucous membranes, as well as respiratory, circulatory, autonomic and central nervous system, somatomotor activity and behaviour pattern. Measurements should be made of food consumption weekly and the animals weighed weekly. Regular observation of the animals is necessary to ensure that animals are not lost from the study due to causes such as cannibalism, autolysis of tissues or misplacement. At the end of the study period all survivors in the non-satellite treatment groups are sacrificed. Moribund animals should be removed and sacrificed when noticed.

° Clinical examinations

The following examinations should be made:

(a) Ophthalmological examination, using an ophthalmoscope or equivalent suitable equipment, should be made prior to exposure to the test substance and at the termination of the study, preferably in all animals but at least in the high dose and control groups. If changes in the eyes are detected all animals should be examined.

(b) Haematology, including haematocrit, haemoglobin concentration, erythrocyte count, total and differential leucocyte count, and a measure of clotting potential, such as clotting time, prothrombin time, thromboplastin time, or platelet count, should be investigated at the end of the test period.

(c) Clinical biochemistry determinations on blood should be carried out at the end of the test period. Test areas which are considered appropriate to all studies are electrolyte balance, carbohydrate metabolism, liver and kidney function. The selection of specific tests will be influenced by observations on the mode of action of the substance. Suggested determinations are calcium, phosphorus, chloride, sodium, potassium, fasting glucose (with the period of fasting appropriate to the species), serum glutamic-pyruvic transaminase*, serum glutamic oxalaocetic transaminase**, ornithine decarboxylase, gamma glutamyl transpeptidase, urea nitrogen, albumen, blood creatinine, total bilirubin and total serum protein measurements. Other determinations which may be necessary for an adequate toxicological evaluation include analyses of lipids, hormones, acid/base balance, methaemoglobin, cholinesterase activity. Additional clinical biochemistry may be employed, where necessary, to extend the investigation of observed effects.

(d) Urinalysis is not required on a routine basis, but only when there is an indication based on expected or observed toxicity.

If historical baseline data are inadequate, consideration should be given to determination of haematological and clinical biochemistry parameters before dosing commences.

° Pathology

Gross necropsy

All animals should be subjected to a full gross necropsy which includes examination of the external surface of the body, all orifices, and the cranial, thoracic and abdominal cavities and their contents. The liver, kidneys, adrenals and testes must be weighed wet as soon as possible after dissection to avoid drying. The following organs and tissues should be preserved in a suitable medium for possible future histopathological examination: all gross lesions, brain - including sections of medulla/pons, cerebellar cortex and cerebral cortex, pituitary, thyroid/parathyroid, thymus, (trachea), lungs, heart, aorta, salivary glands, liver, spleen, kidneys, adrenals, pancreas, gonads, accessory genital organs, gall

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* Now known as serum alanine aminotransferase.

** Now known as serum aspartate aminotransferase.

bladder (if present), oesophagus, stomach, duodenum, jejunum, ileum, caecum, colon, rectum, urinary bladder, representative lymph node, (female mammary gland), (thigh musculature), peripheral nerve, (eyes), (sternum with bone marrow), (femur - including articular surface), (spinal cord at three levels - cervical, midthoracic and lumbar), and (exorbital lachrymal glands). (The tissues mentioned in brackets need only be examined if indicated by signs of toxicity or target organ involvement.)

Histopathology

(a) Full histopathology should be carried out on normal and treated skin and on organs and tissues of all animals in the control and high dose groups.

(b) All gross lesions should be examined.

(c) Target organs in other dose groups should be examined.

(d) Where rats are used lungs of animals in the low and intermediate dose groups should be subjected to histopathological examination for evidence of infection, since this provides a convenient assessment of the state of health of the animals. Further histopathological examination may not be required routinely on the animals in these groups but must always be carried out in organs which showed evidence of lesions in the high dose group.

(e) When a satellite group is used histopathology should be performed on tissues and organs identified as showing effects in other treated groups.

3. DATA AND REPORTING

° Treatment of results

Data may be summarised in tabular form, showing for each test group the number of animals at the start of the test, the number of animals showing lesions, the types of lesions and the percentage of animals displaying each type of lesion.

All observed results, quantitative and incidental, should be evaluated by an appropriate statistical method. Any generally accepted statistical method may be used; the statistical methods should be selected during the design of the study.

° Evaluation of results

The findings of a subchronic dermal toxicity study should be evaluated in conjunction with the findings of preceding studies and considered in terms of the observed toxic effects and the necropsy and histopathological findings. The evaluation will include the relationship between the dose of the test substance and the presence or absence, the incidence and severity, of abnormalities, including behavioural and clinical abnormalities, gross lesions, identified target organs, body weight changes, effects on mortality and any other general or specific toxic effects. A properly conducted subchronic test should provide a satisfactory estimation of a no-effect level.

° Test report

The test report must include the following information:

- species/strain used;
- toxic response data by sex and dose;
- time of death during the study or whether animals survived to termination;
- toxic or other effects;
- the time of observation of each abnormal sign and its subsequent course;
- food and body weight data;
- haematological tests employed and results with relevant baseline data;
- clinical biochemistry tests employed and results with relevant baseline data;
- necropsy findings;
- a detailed description of all histopathological findings; and
- statistical treatment of results where appropriate.

° Interpretation of the results

A subchronic dermal study will provide information on the effects of repeated dermal exposure to a substance. Extrapolation from the results of the study to man is valid to a limited degree, but it can provide useful information on the degree of percutaneous absorption of a substance, no-effect levels and permissible human exposure.

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TAB 14

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CHAPTER 4

Medication Preparations and Supplies

OBJECTIVES

Upon completion of this chapter, the student should be able to:

1. Differentiate between various oral drug forms: sublingual tablet versus buccal tablet, solution versus suspension, syrup versus elixir, enteric-coated tablet versus scored tablet, and timed-release capsule versus lozenge.
2. Explain what is meant by parenteral.
3. List four classifications of drugs that are commonly given by the rectal route.
4. Define the following types of injections and explain how they differ in administration and absorption rate: IV, IM, SC, and ID.
5. Compare the IV injections referred to as IV push, IV infusion, and IV piggyback.
6. List and define at least eight drug forms used for topical (both dermal and mucosal) administration.
7. Explain the advantages of administering drugs via a dermal patch.
8. Identify various supplies used in the preparation of medications.

The forms in which drugs are prepared are as numerous as the routes of administration. *Drug form* refers to the type of preparation in which the drug is supplied. Pharmaceutical companies prepare each drug in the form or forms most suitable for its intended route and means of absorption. *Drug form* and *drug preparation* are synonymous. The *PDR* lists the forms available for each drug under the heading "How Supplied." See Table 4.1 for abbreviations of some of the drug forms and routes of administration.

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TABLE 4.1. ABBREVIATIONS FOR DRUG ADMINISTRATION

Drug Forms		Routes	
cap	capsule	D	dermal
elix	elixir	ID	intradermal
		IM	intramuscular
gtt	drop	IV	intravenous
supp	suppository	IVPB	intravenous piggyback
susp	suspension	PO, p.o., per os	oral
tab	tablet	R	rectal
ung	ointment	SC, subcu, subq	subcutaneous
		T	topical

A Space-Age Drug Form

Great advances have occurred recently in developing a new drug form that may revolutionize the way a number of drugs are administered. The new drug form is the dermal patch, or *transdermal delivery system*. Dermal patches were taken on the space shuttles during the 1990s for the prevention of nausea. The key to the transdermal system is that the drug molecules are present in a variety of sizes and shapes that allow for absorption through the skin at various rates. Thus, a patch can provide a constant, even flow of a drug over a long period of time—hours or days. The drug, being released at a consistent rate, remains at an effective level in the blood, as opposed to rising and falling, as happens with pills. Advantages of this method of administration include:

- Easy application, with no discomfort or undesirable taste
- Effectiveness for long periods of time, hours for some drugs and days for others
- Consistent blood level of drug, since drug is released at varying rates, rather than all at one time

Dermal patches vary in size, shape, and color (Fig. 4.1). They are most commonly seen today on patients for the prevention of angina. Current marketing of dermal patches also includes others for the prevention of motion sickness (may be applied before traveling), for management of chronic pain (e.g., Duragesic; see Chapter 19), as a smoking deterrent (e.g., Habitrol and Nicoderm), and for estrogen replacement (e.g., Estraderm). Research is ongoing in the development of dermal patches for birth control, high blood pressure, ulcers, allergies, and heart conditions. Probably not all drug molecules will be adaptable to this drug form, but it certainly has opened new doors in the area of drug administration.

Standard Drug Forms

You probably have received medications in many of the standard forms at some time during your life. Each form is defined and listed below according to the routes

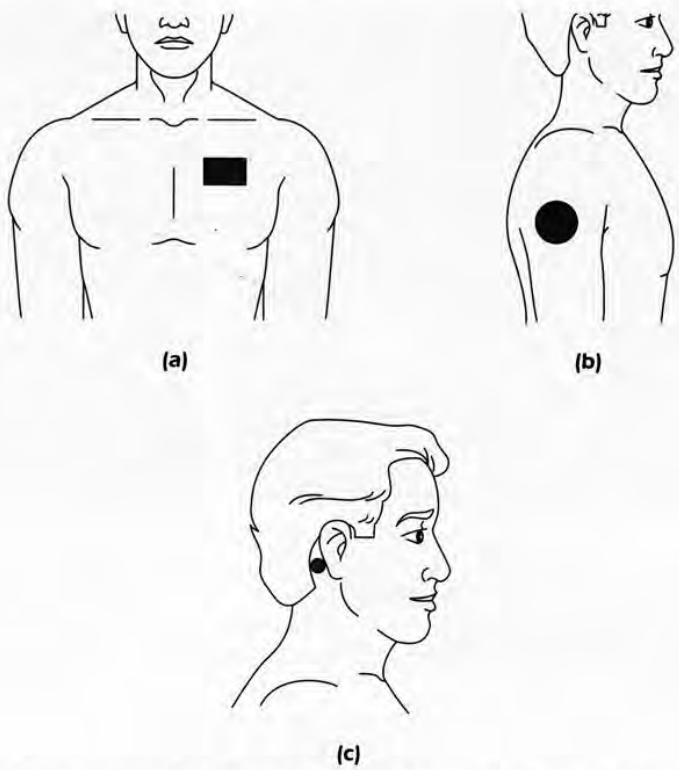

Figure 4.1 *Transdermal drug delivery. Dermal patches vary in size, shape, and color. (a, b) For prevention of angina pectoris, and for management of chronic pain; and (c) for prevention of motion sickness.*

of administration (see Fig. 4.2). As you read in Chapter 3, drugs may be administered through the gastrointestinal (GI) tract or parenterally. GI routes include oral, nasogastric tube, and rectal. Parenteral refers to any route not involving the GI tract, including injection, topical (skin or mucosal), and inhalation routes.

ORAL DRUG FORMS

Oral drug forms include:

Tablet. Disk of compressed drug; may be a variety of shapes and colors; may be coated to enhance easy swallowing; may be *scored* (evenly divided in halves or quarters by score lines) to enhance equal distribution of drug if it has been broken.

Enteric-coated tablet. Tablet with a special coating that resists disintegration by gastric juices. The coating dissolves further down the GI tract, in the enteric, or intestinal, region. Some drugs, such as aspirin, that are irritating to the stomach are available in enteric-coated tablets. To be effective, the coating must never be destroyed by chewing or crushing when it is administered.

Capsule. Drug contained within a gelatin-type container.

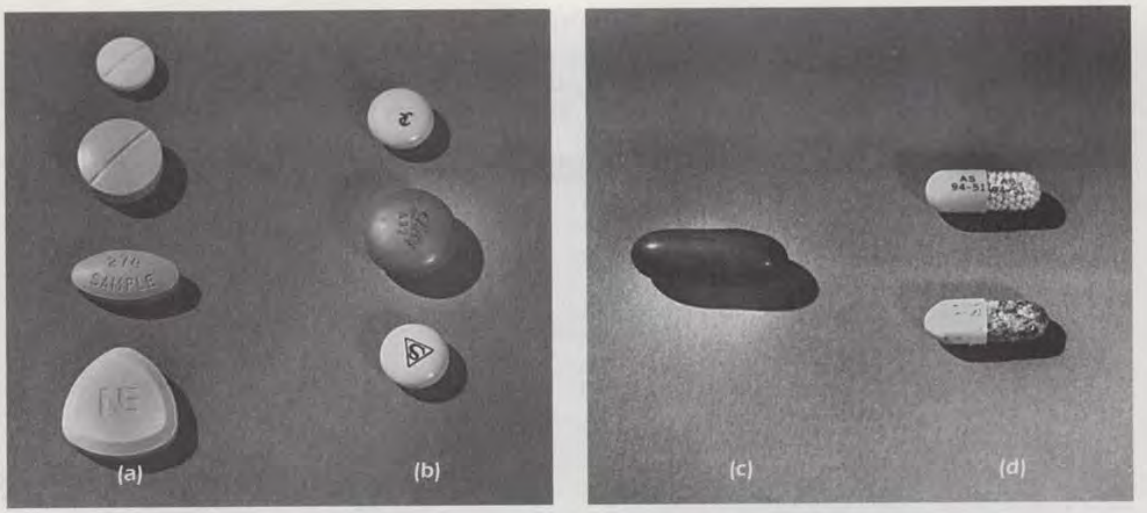

Figure 4.2 Oral drug forms. Tablets and capsules vary in size, shape, and color. (a) Tablets, scored and unscored; (b) enteric-coated tablets; (c) gelatin capsule; (d) timed-release capsules.

- Easier to swallow than noncoated tablets.
- Double chamber may be pulled apart to add drug powder to soft foods or beverages for patients who have difficulty swallowing (unless specifically contraindicated for absorption).

Timed-release (sustained-release) capsule. Capsule containing drug particles that have various coatings (often of different colors) that differ in the amount of time required before the coatings dissolve. This form of drug preparation is designed to deliver a dose of drug over an extended period of time. An advantage of taking a drug in the timed-release form is the decreased frequency of administration. For example, the tranquilizer Valium may be administered in tablet form, 5 mg tid, or in the timed-release form (Valrelease, 15 mg) only once qd. (See Table 5.1 for common abbreviations.) Because of the significance of the various coatings that encapsulate the drug particles, it is important that the small colored pellets *not* be crushed or mixed with foods. Damage to the coatings of drug pellets allows the drug to be released all at one time as it is administered. Such immediate release of drug is a potential overdose. Timed-release capsules should be swallowed whole, with no physical damage to the contents of the capsule.

Lozenge (troche). Tablet containing palatable flavoring, indicated for a local (often soothing) effect on the throat or mouth.

- Patient is advised not to swallow a lozenge; it should be allowed to slowly dissolve in the mouth.
- Patient is also advised *not* to drink liquids for approximately 15 min after administration, to prevent washing of the lozenge contents from the throat or mouth.

Suspension. Liquid form of medication that must be shaken well before administration because the drug particles settle at the bottom of the bottle. The drug is not evenly dissolved in the liquid.

- A cephalosporin (Keflex) suspension is a commonly used antibiotic suspension for children. This form is more easily ingested by children than are capsules of Keflex.

Emulsion. Liquid drug preparation that contains oils and fats in water.

Elixir, fluid extract. Liquid drug forms with alcohol base.

- Should be tightly capped to prevent alcohol evaporation.
- Should not be available to alcoholics.

Syrup. Sweetened, flavored liquid drug form. Cherry syrup drug preparations are common for children.

Solution. Liquid drug form in which the drug is totally evenly dissolved. Appearance is clear, rather than cloudy or settled (as with a suspension).

Many drug forms for the oral route are commonly available over the counter and include thousands of trade name products. The oral route is the easiest and probably the cheapest for administration. It is, however, *not* the route of choice for treatment of emergencies, acute pain, NPO* patients, or patients unable to swallow. Other routes, especially the parenteral routes, produce a more rapid absorption rate and drug effect.

RECTAL DRUG FORMS

Rectal drug forms include:

Suppository. Drug suspended in a substance, such as cocoa butter, that melts at body temperature.

Enema solution. Drug suspended in solution to be administered as an enema.

The rectal route of administration is often the choice if the patient is ordered to have nothing by mouth (NPO) or cannot swallow. The most common classifications of drugs given rectally include sedatives, antiemetics, and antipyretics. A local analgesic effect may also be achieved by this route. In the past, rectal administration of drug solutions was given for general anesthesia, but is not common today.

INJECTABLE DRUG FORMS

Injectable drug forms include:

Solution. Drug suspended in a sterile vehicle.

- Quite often the solutions have a sterile water base and are thus referred to as *aqueous* (aq) (waterlike) solutions.

*See Table 5.1 for common abbreviations.

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- Some solutions have an oil base, which tends to cause a more prolonged absorption time. The oily nature of these solutions makes them thick; thus they are referred to as viscous (thick) solutions.

Powder. Dry particles of drugs. The powder itself cannot be injected. It must be mixed with a sterile diluting solution (sterile water or saline solution) to render an injectable solution. This is termed *reconstitution* of a drug. Drugs are supplied undiluted in powder form because of the short period of time they remain stable after dilution.

The various injection routes differ according to the type of tissues into which the drug is deposited and the rate of absorption. Each is briefly defined below:

Intravenous. Injected directly into a vein. Immediate absorption and availability to major organs renders this route a dangerous one. IV drugs are usually administered by physicians, paramedics, or registered nurses. Types of intravenous injections include:

- IV push, a small volume of drug injected through a syringe and needle into the bloodstream.
- IV infusion or IV drip, a large volume of fluids, often with drugs added, which infuses continually into a vein.
- IV piggyback (IVPB), a drug diluted in moderate volume (50–100 ml) of fluid for intermittent infusion at specified intervals, usually q6–8h; the diluted solution is infused (piggyback) into a port on the main IV tubing or into a rubber adapter on the IV catheter (Fig. 4.3).

Intramuscular. Injected into a muscle, by positioning the needle and syringe at a 90-degree angle from the skin (Fig. 4.4). Absorption is fairly rapid due to the vascularity of muscle.

Subcutaneous. Injected into the fatty layer of tissue below the skin by positioning the needle and syringe at a 45-degree angle from the skin (Fig. 4.5). This may be the route of choice for drugs that should not be absorbed as rapidly as through the IV or IM routes.

Intradermal. Injected just beneath the skin, by positioning the needle and syringe at a 15-degree angle from the skin (Fig. 4.6). This route is used primarily for allergy skin testing. Because of the lack of vascularity in the dermis, absorption is slow. The greatest reaction is in the local tissues rather than systemic. When a small amount (0.1-0.2 cc) of drug is injected intradermally, the amount of redness that develops around the injection site can be used to determine whether a person is sensitive to the drug. Tuberculin (TB) skin tests (PPD) are also administered intradermally and the site is inspected 48–72 hours later for hardness (induration) and swelling. Redness (erythema) alone, *without swelling*, does not indicate a positive test result with PPD. The *raised area (induration)* is measured with a special ruler and the number of millimeters (mm) is documented. Check with your local Public Health Department regarding appropriate protocol with a positive PPD test result.

The less common parenteral routes, which are limited to a physician's administration, are:

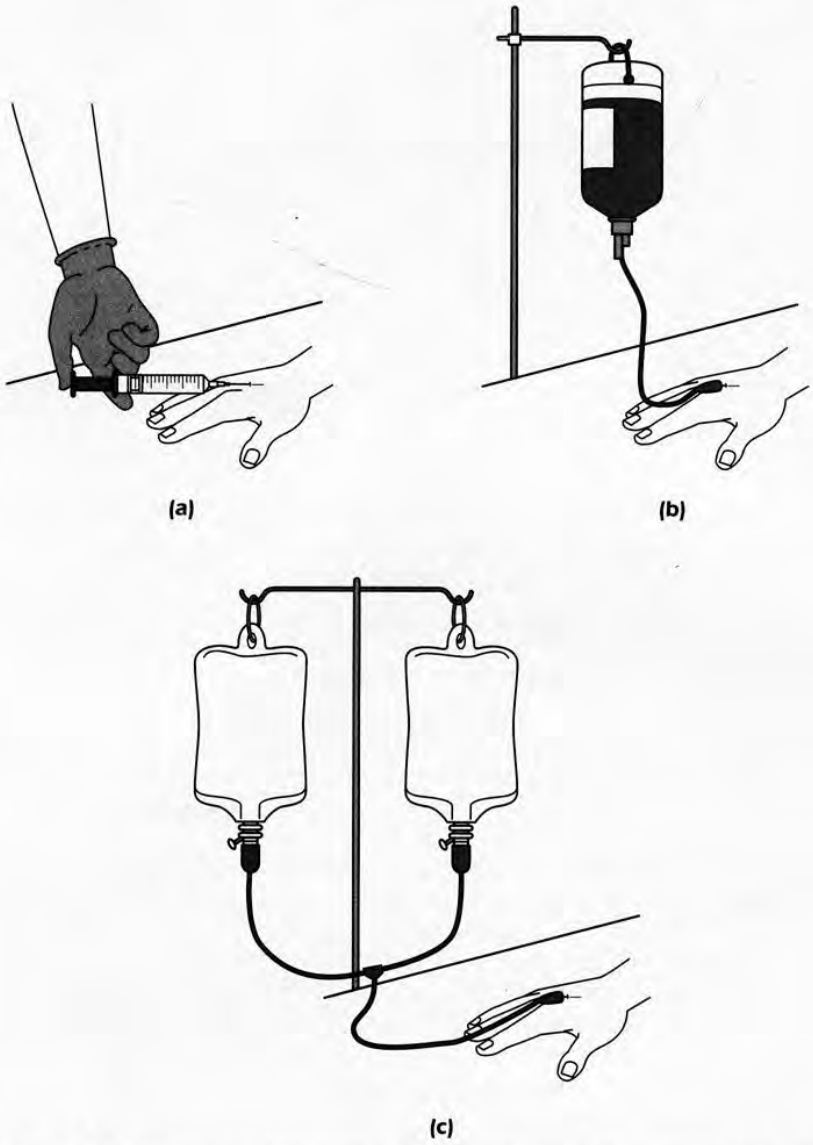

Figure 4.3 Intravenous administration. Different forms of IV injection include (a) IV push; (b) IV infusion (continuous); and (c) IV piggyback (intermittent).

Intracardiac. Injected directly into the heart. This route is used to administer adrenaline as a last resort to resuscitate a patient whose heart has stopped.

Intraspinal. Injected into the subarachnoid space, which contains cerebrospinal fluid (CSF) that surrounds the spinal cord. Drugs injected by this route are frequently anesthetics, which render a lack of sensation to those regions of the body distal to the intraspinal injection.

Intracapsular (intra-articular). Injected into the capsule of a joint, usually to reduce inflammation, as in bursitis. Arthritic or bursitic joints often injected with anti-inflammatory drugs include shoulders, elbows, wrists, ankles, knees, and hips.

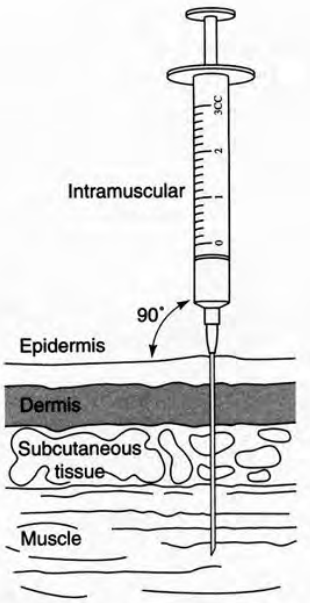

Figure 4.4 Intramuscular injection. Needle is inserted at a 90-degree angle.

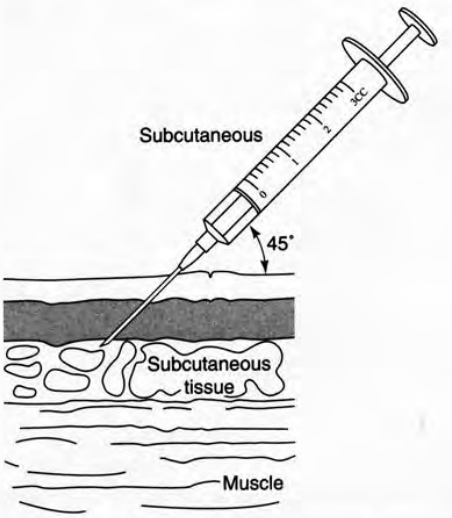

Figure 4.5 Subcutaneous injection. Needle is inserted at a 45-degree angle.

TOPICAL DRUG FORMS

Topical drug forms include drugs for dermal application and drugs for mucosal application. Those for *dermal* application include:

Cream or ointment. A semisolid preparation containing a drug, for external application. **Note:** Creams and ointments are not the same. The dose used differs for each.

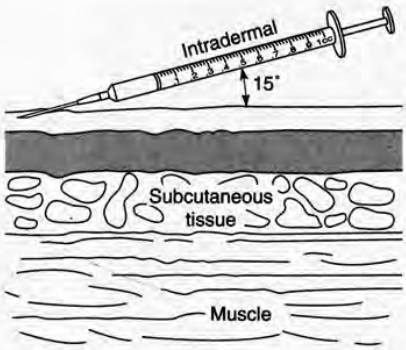

Figure 4.6 Intradermal injection. Needle is inserted just beneath the skin at a 15-degree angle.

Rule of thumb: If skin is wet, use cream, if skin is dry, use ointment.

Lotion. A liquid preparation applied externally for treatment of skin disorders. Unlike hand lotions, medicated lotions (e.g., calamine lotion) should be *patted*, not rubbed, on the affected skin.

Liniment. Preparation for external use that is rubbed on the skin as a counterirritant. As such, the liniment creates a different sensation (e.g., tingling or burning) to mask pain in the skin or muscles.

Dermal patch. Skin patch containing drug molecules that can be absorbed through the skin at varying rates to promote a consistent blood level between application times.

Both the dermal patch and ointment are common forms for administration of nitroglycerin. Nitroglycerin is a vasodilator used for the treatment of angina (chest pain related to narrowing of the coronary arteries). The beauty of the external applications of nitroglycerin is their ability to *prevent* angina by the slow, consistent release of the drug over a period of time. Before the external applications became available, nitroglycerin was primarily available in the form of a sublingual tablet to be taken at the time of an angina attack. Now all three forms are used—the tablet, the ointment, and the patch—with the external forms focusing on the prevention of angina. They are applied at regular intervals, as follows:

Ointment: 1–5 inches applied q8h measured and applied on special Appli-Ruler paper (Fig. 4.7)

Dermal patch: one patch (available in varied doses) q24h*

Other drug preparations considered topical are those that are applied to *mucosal membranes*. Some are administered for local effect (at the site of application) and, in other cases, a systemic effect is desired. The *mucosal drug forms* include:

Eye, ear, and nose drops (gtt). Drugs in sterile liquids to be applied by drops (referred to as instillation of drops).

*See Table 5.1 for common abbreviations.

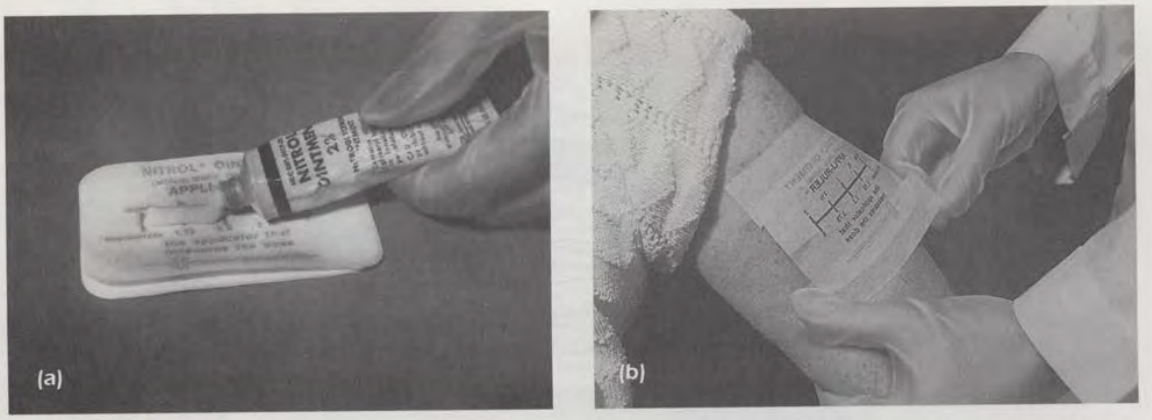

Figure 4.7 Topical administration. Dermal application includes creams and liquids placed on the skin. (a) Nitroglycerin ointment is measured on Appli-Ruler paper. (b) Paper containing ointment is applied to the skin.

Eye ointment. Sterile semisolid preparation, often antibiotic in nature, for ophthalmic use only.

Vaginal creams. Medicated creams, often of antibiotic or antifungal nature, that are to be inserted vaginally with the use of a special applicator.

Rectal and vaginal suppositories. Drug suspended in a substance, such as cocoa butter, that melts at body temperature, for local effect. Some rectal suppositories are also used for systemic effects (Fig. 4.8).

Douche solution. Sterile solution, often an antiseptic such as povidone iodine solution and sterile water, used to irrigate the vaginal canal.

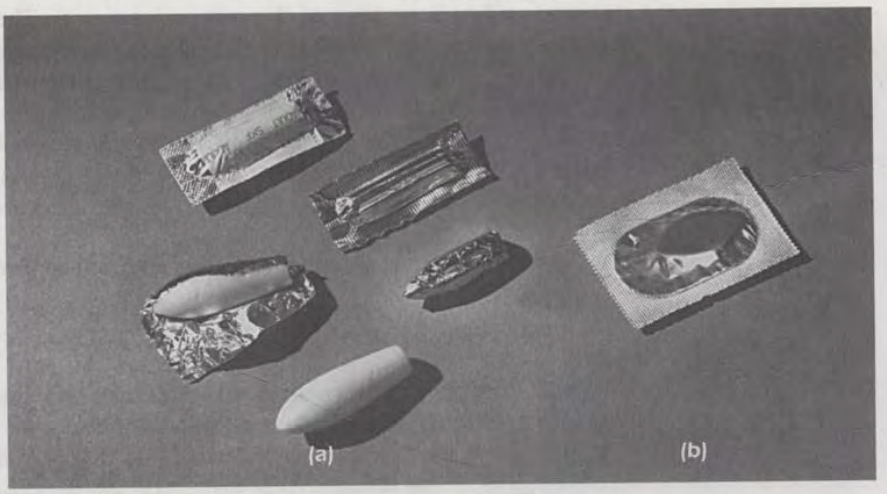

Figure 4.8 Topical administration via mucous membranes. Suppositories come in various shapes and sizes, for example, (a) rectal suppositories, wrapped in foil and unwrapped; and (b) vaginal suppository, wrapped in foil.

Buccal tablet. Tablet that is absorbed *via the buccal mucosa* in the mouth.

- Patient is told *not* to swallow tablet; it is to be placed between the cheek and gums, and allowed to dissolve slowly.
- Not commonly used today.

Sublingual tablet. Tablet that is absorbed via the mucosa under the tongue.

- Patient is told not to swallow tablet; it is to be placed under the tongue and allowed to dissolve slowly.
- The most common sublingual tablet is nitroglycerin. Given for the treatment of angina, this drug reaches the bloodstream immediately via the sublingual capillaries. Angina may be relieved within 1–5 min after sublingual nitroglycerin is administered.

INHALABLE DRUG FORMS

The drug forms used for the inhalation route include:

Spray or mist. Liquid drug forms that may be inhaled as fine droplets via the use of spray bottles, nebulizers, or metered dose inhalers.

- In the hospital setting, respiratory therapists instill a liquid into a chamber of a nebulizer for a patient's breathing treatment. Often the liquid contains a bronchodilator, a mucolytic agent, or sterile saline solution for moisture.
- In the home, the patient may instill sprays via nasal spray bottles, vaporizers, or inhalers. Asthma patients rely on the use of inhalers to keep their bronchioles open by inhaling the mist of a bronchodilator. A mouthpiece, through which the patient inhales, is connected to a container of liquid drug.

Gas. Anesthetics, such as nitrous oxide, that are introduced via the respiratory route for general anesthesia.

Powder. Drug in powder form to reduce bronchial asthma attacks, to be inhaled through a special device called a Spinhaler. The powdered drug, cromolyn sodium (Intal), is inside a capsule that is inserted into the Spinhaler.

Supplies

Considering the variety of drug forms you may be administering, you must become familiar with various supplies to be used (Fig. 4.9):

Medicine cup. Two types of disposable cups are commonly used. Paper cups are used for dispensing tablets and capsules. Plastic 1-oz medicine cups with measurements (ml, tsp, tbsp, dr, or oz) marked on the side are used for dispensing oral liquid medications. (See Table 5.1 for a list of common abbreviations used in medication orders.)

Mortar. Glass cup in which tablets (excluding enteric-coated tablets) may be placed to be crushed. Various other pill-crushing devices are available.

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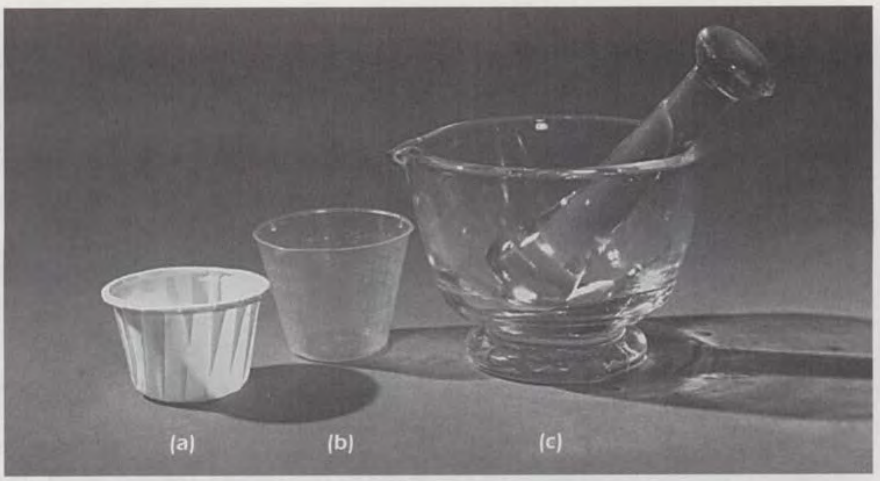

Figure 4.9 Supplies for oral administration. (a) Tablets and capsules are usually administered in paper soufflé cups. (b) Liquids are measured in calibrated plastic cups. (c) A mortar and pestle are used when necessary to crush tablets.

Note: In some areas a physician's order is required for pill crushing. Check the regulations in your area.

Pestle. Club-shaped glass tool used as the crushing device to pulverize tablets.

Finger cot. Rubber coverlet for one finger only, to be applied and lubricated before insertion of a rectal suppository (Fig. 4.10).

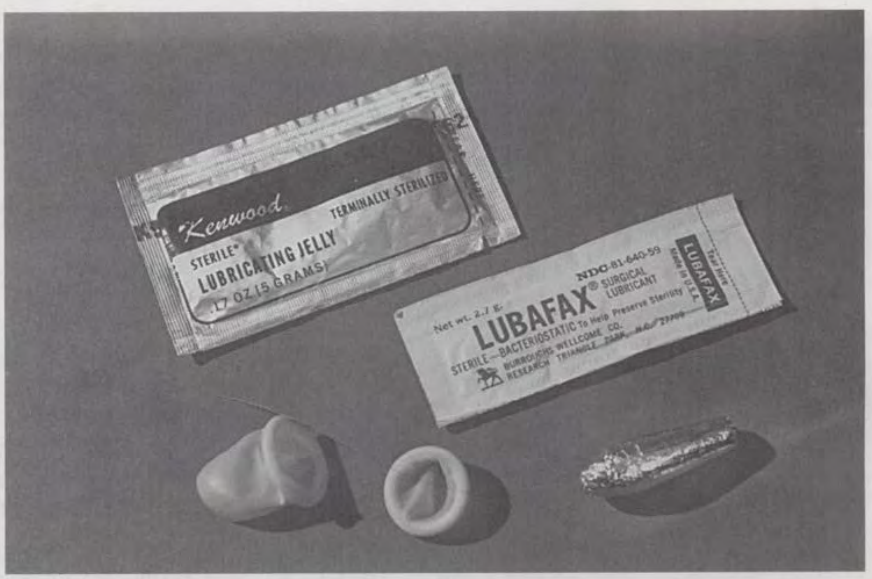

Figure 4.10 Supplies for administration of rectal suppository. A finger cot and small packet of lubricant are required.

Medication for injection is contained in an ampule or vial (Fig. 4.11):

Ampule. Small glass container that holds a single dose of sterile solution for injection. The ampule must be broken at the neck to obtain the solution.

Vial. Glass container sealed at the top by a rubber stopper to enhance sterility of the contents. Contents may be a solution or a powdered drug that needs to be reconstituted. Vials may be multiple dose or unit dose:

- Multiple-dose vials contain large quantities of solution (up to 50 cc) and may repeatedly be entered through the rubber stopper to remove a portion of the contents.
- Unit-dose vials contain small quantities of solution (1–2 cc) that are removed during a single use. Unit-dose vials are widely used today as a means of controlling abuse or removal of excess amounts of solution from a drug vial.

Needles. Needles for injections have two measurements that must be noted (Fig. 4.12):

- Length varies from short (⅜ inch) to medium (1–1½ inch) length for standard injections. Long needles (5 inch) may be used by the physician for intraspinal or intracardiac routes. Needles 2–5 inches long are used by the physician for intra-articular injections (into the joint).
- Gauge is a number that represents the diameter of the needle lumen. Needle gauges vary from 18 (largest) to 27 (smallest), with the higher gauge number representing the smaller lumen.

Syringes. The three most common disposable syringes for parenteral administration of drugs are the standard hypodermic syringe, the tuberculin (TB) syringe, and the insulin syringe (Fig. 4.13).

- The standard hypodermic syringe has a capacity of 2–3 cc. Most companies prepackage this type of syringe with a needle attached. Since you

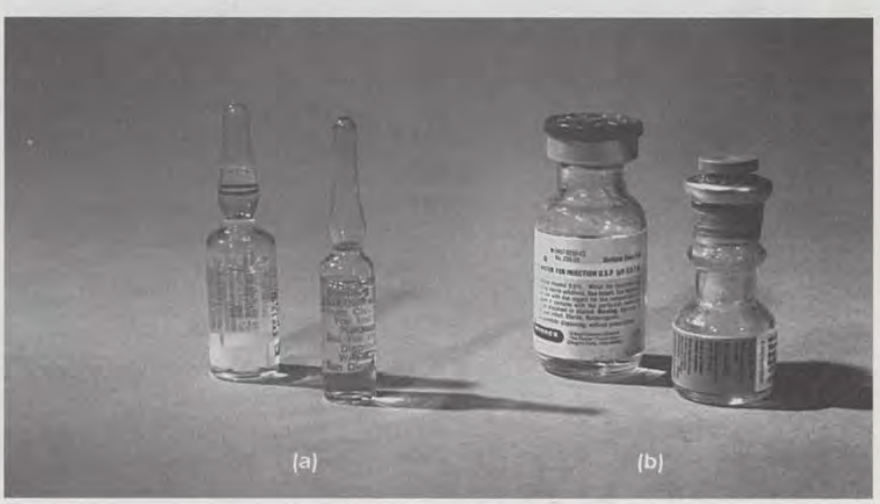

Figure 4.11 Medication for injection. Various premeasured containers include (a) ampules and (b) vials.

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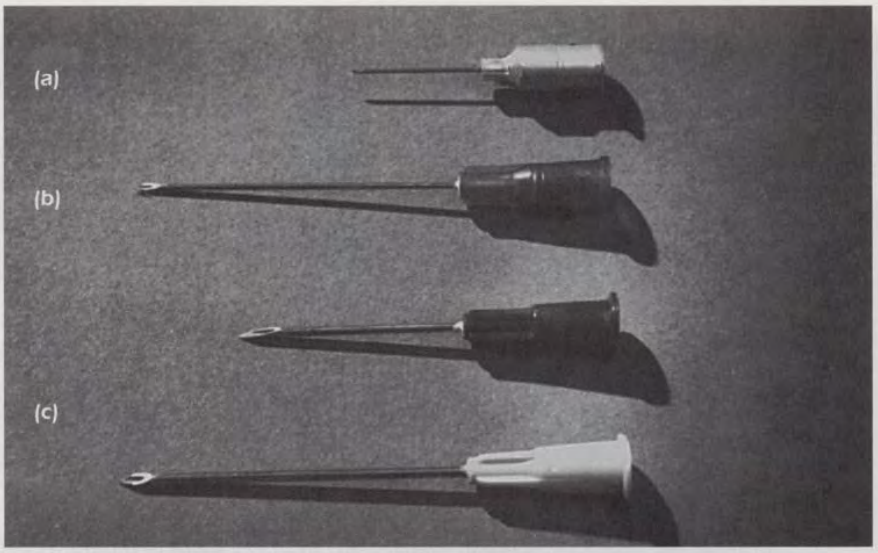


Figure 4.12 Needles commonly used for injections. Sizes vary in length and gauge. (a) 3/8 inch, 27 gauge; (b) 1 ½ inches, 21 gauge; (c) 1 inch and 1 ½ inches, 18 gauge.

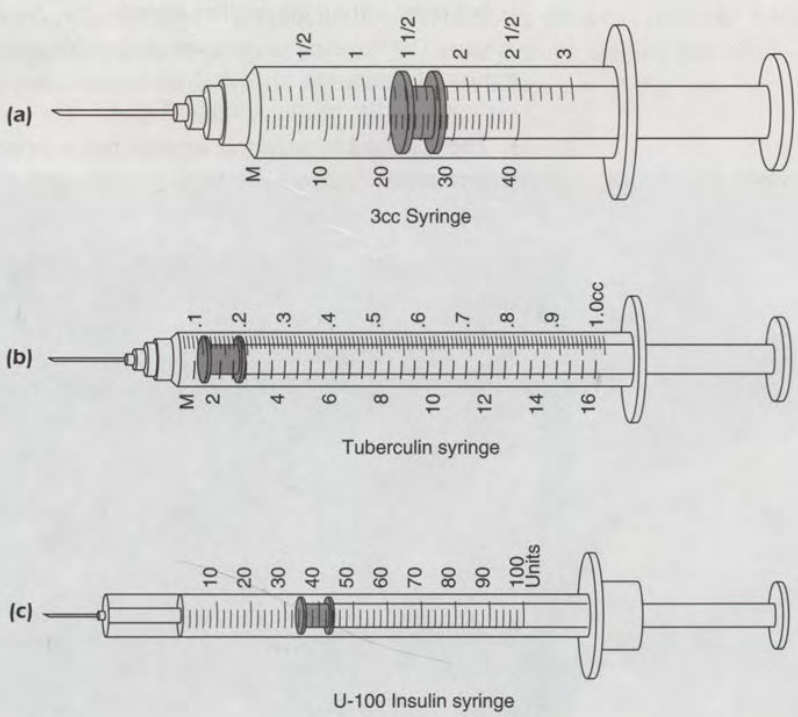


Figure 4.13 Syringes for injection. Type of syringe varies with type and quantity of medication. (a) 3 cc syringe, read at 1.4 cc or 23 minims; (b) tuberculin syringe, read at 0.05 cc; (c) insulin syringe, read at 32 units.

may use this type of syringe for either subcutaneous or intramuscular injections, you must choose the package with the needle length and gauge appropriate for the route and depth of injection you will give. All hypodermic syringes are marked with 10 calibrations per cc. Thus, each small line represents 0.1 cc. When preparing for an injection with this syringe, you must know the amount of solution needed to the nearest 0.1 cc (an additional scale on the syringe shows calibrations in minims, which is discussed later, in Chapter 9).

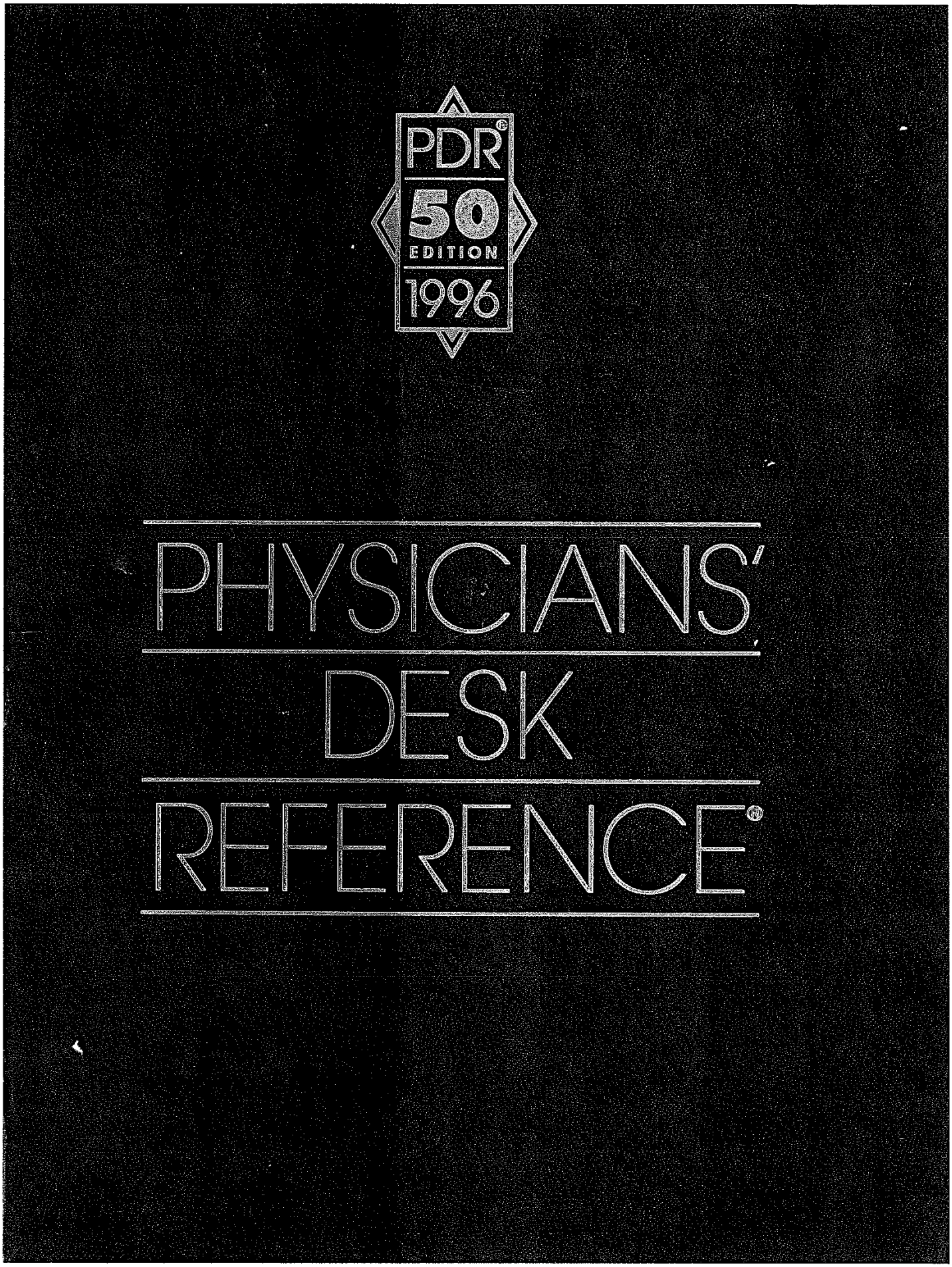
- The TB syringe is very narrow and is finely calibrated. The total capacity is only 1 cc. There are 100 fine calibration lines marking the capacity. Thus, each line represents 0.01 cc. Every tenth line is longer, to indicate 0.1-cc increments. Very precise small amounts of solution may be measured with the TB syringe. It is most commonly used for newborn and pediatric dosages and for intradermal skin tests. When preparing for an injection with this syringe, you must know the amount of solution needed to the nearest 0.01 cc.
- The insulin syringe is used strictly for administering insulin to diabetics. Like the TB syringe, it has only a 1-cc capacity. The 1-cc capacity is marked as 100 units (U) to represent a strength of 100 U of insulin when full. Each group of 10 U is further divided by 5 small lines on an even scale or 5 small lines on an odd scale. Thus, *each line represents 2 U*. A smaller insulin syringe, of only ½-cc capacity, may be used when less than 50 U (½ cc) of insulin is ordered. The smaller insulin syringe has 50 small calibration lines; thus, each represents 1 U of insulin.

It is extremely important that you can interpret the value of the calibrations on each of the syringes. Study the calibrations each time you prepare for an injection to prevent a medication error from negligent misinterpretation.

Oral Syringes. Health care workers should be aware that some oral liquid medications are dispensed from the Pharmacy in disposable plastic syringes with rubber or plastic covers on the tip. These syringes are labeled "Not for injection" or "For oral use only".

Check your knowledge of this chapter before going any further.

TAB 15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signs and the patient's state of consciousness after each local anesthetic administration.

The first step in the management of convulsions consists of immediate attention to the maintenance of a patent airway and assisted or controlled ventilation with oxygen and a delivery system capable of permitting immediate positive airway pressure by mask. Immediately after the institution of these ventilatory measures, the adequacy of the circulation should be evaluated, keeping in mind that drugs used to treat convulsions sometimes depress the circulation when administered intravenously. Should convulsions persist despite adequate respiratory support, and if the status of the circulation permits, small increments of an ultra-short acting barbiturate (such as thiopental or thiamylal) or a benzodiazepine (such as diazepam) may be administered intravenously. The clinician should be familiar, prior to use of local anesthetics, with these anticonvulsant drugs. Supportive treatment of circulatory depression may require administration of intravenous fluids and, when appropriate, a vasopressor as directed by the clinical situation (e.g., ephedrine).

If not treated immediately, both convulsions and cardiovascular depression can result in hypoxia, acidosis, bradycardia, arrhythmias and cardiac arrest. If cardiac arrest should occur, standard cardiopulmonary resuscitative measures should be instituted.

The median lethal dose (LD_{50}) of dyclonine HCl administered orally to female rats is 176 mg/kg and 90 mg/kg in female mice. Intraperitoneally the LD_{50} in female rats is 31 mg/kg and 43 mg/kg in female mice.

DOSAGE AND ADMINISTRATION

As with all local anesthetics, the dosage varies and depends upon the area to be anesthetized, vascularity of the tissues, individual tolerance and the technique of anesthesia. The lowest dosage needed to provide effective anesthesia should be administered.

A maximum dose of 30 mL of 1% Dyclone Topical Solution (300 mg of dyclonine HCl) may be used, although satisfactory anesthesia is usually produced within the range of 4 to 20 mL. For specific techniques and procedures refer to standard textbooks.

Although as much as 300 mg of dyclonine HCl (as a 1% solution) have been tolerated, this dosage as a 0.5% solution has not been administered primarily because satisfactory anesthesia in endoscopic procedures can usually be produced by lesser amounts. For specific techniques for endoscopic procedures refer to standard textbooks.

PROCTOLOGY

Apply pledgets of cotton or sponges moistened with the Dyclone 0.5% Solution to postoperative wounds for the relief of discomfort and pain.

GYNECOLOGY

Apply Dyclone 0.5% Solution as wet compresses or as a spray to relieve the discomfort of episiotomy or perineorrhaphy wounds.

ONCOLOGY-RADIOLOGY

Apply Dyclone 0.5% Solution as a rinse or swab to inflamed or ulcerated mucous membrane of the mouth caused by antineoplastic chemotherapy or radiation therapy. In lesions of the esophagus, 5–15 mL of the anesthetic may be swallowed to relieve pain and allow more comfortable deglutition.

OTORHINOLARYNGOLOGY

To suppress the gag reflex and to facilitate examination of the posterior pharynx or larynx, apply Dyclone 0.5% Solution as a spray or gargle.

Dyclone 0.5% Solution may be applied as a rinse or swab to relieve the discomfort of aphthous stomatitis, herpetic stomatitis, or other painful oral lesions.

DENTISTRY

Dyclone 0.5% Topical Solution is useful to suppress the gag reflex in the positioning of x-ray films, making prosthetic impressions, and doing surgical procedures in the molar areas. It is also useful as a preinjection mucous membrane anesthetic or applied to the gums prior to scaling (prophylaxis). The anesthetic can be applied as a mouthwash or gargle and the excess spit out.

HOW SUPPLIED

Sterile, in one fluid ounce bottles, DYCLONE 0.5% TOPICAL SOLUTION (NDC 0186-3001-01) and DYCLONE 1% TOPICAL SOLUTION (NDC 0186-3002-01). Keep tightly closed. Store at controlled room temperature: 15°–30°C (59°–86°F). Avoid excessive heat (temperatures above 40°C (104°F). Subject to damage by freezing.

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Rev. 8/89 (2)

EMLA®

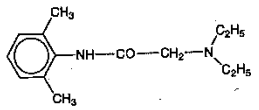
CREAM (lidocaine 2.5% and prilocaine 2.5%)

℞

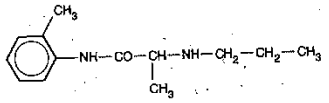
DESCRIPTION

EMLA Cream (lidocaine 2.5% and prilocaine 2.5%) is an emulsion in which the oil phase is a eutectic mixture of lidocaine and prilocaine in a ratio of 1:1 by weight. A eutectic mixture has a melting point below room temperature and therefore both local anesthetics exist as a liquid oil rather than as crystals.

Lidocaine is chemically designated as acetamide, 2-(diethylamino)-N(2,6-dimethylphenyl), has an octanol:water partition ratio of 43 at pH 7.4 and has the following structure:



Prilocaine is chemically designated as propanamide, N-(2-methyl-phenyl)-2-(propylamino), has an octanol:water partition ratio of 25 at pH 7.4, and has the following structure:



Each gram of EMLA Cream contains lidocaine 25 mg, prilocaine 25 mg, polyoxyethylene fatty acid esters (as emulsifiers), carboxypolymethylene (as a thickening agent), sodium hydroxide to adjust to a pH approximating 9, and purified water (about 92%) to 1 gram. EMLA Cream contains no preservative, however it passes the USP antimicrobial effectiveness test due to the pH. The specific gravity of EMLA Cream is 1.00.

CLINICAL PHARMACOLOGY

Mechanism of Action: EMLA Cream (lidocaine 2.5% and prilocaine 2.5%), applied to intact skin under occlusive dressing, provides dermal analgesia by the release of lidocaine and prilocaine from the cream into the epidermal and dermal layers of the skin and the accumulation of lidocaine and prilocaine in the vicinity of dermal pain receptors and nerve endings. Lidocaine and prilocaine are amide-type local anesthetic agents. Both lidocaine and prilocaine stabilize neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of impulses, thereby effecting local anesthetic action.

The onset, depth and duration of dermal analgesia provided by EMLA Cream depends primarily on the duration of application. To provide sufficient analgesia for clinical procedures such as intravenous catheter placement and venipuncture, EMLA Cream should be applied under an occlusive dressing for at least 1 hour. To provide dermal analgesia for clinical procedures such as split skin graft harvesting, EMLA Cream should be applied under occlusive dressing for at least 2 hours. Satisfactory dermal analgesia is achieved 1 hour after application, reaches maximum at 2 to 3 hours, and persists for 1 to 2 hours after removal.

Dermal application of EMLA Cream may cause a transient, local blanching followed by a transient, local redness or erythema.

Pharmacokinetics: EMLA Cream is a eutectic mixture of lidocaine 2.5% and prilocaine 2.5% formulated as an oil in water emulsion. As a eutectic mixture, both anesthetics are liquid at room temperature (see DESCRIPTION) and the penetration and subsequent systemic absorption of both prilocaine and lidocaine are enhanced over that which would be seen if each component in crystalline form was applied separately as a 2.5% topical cream.

The amount of lidocaine and prilocaine systemically absorbed from EMLA Cream is directly related to both the duration of application and to the area over which it is applied.

In two pharmacokinetic studies, 60 g of EMLA Cream (1.5 g lidocaine and 1.5 g prilocaine) was applied to 400 cm^2 of intact skin on the lateral thigh and then covered by an occlusive dressing. The subjects were then randomized such that one-half of the subjects had the occlusive dressing and residual cream removed after 3 hours, while the remainder left the dressing in place for 24 hours. The results from these studies are summarized below.

[See Table 1 below.]

When 60 g of EMLA was applied over 400 cm^2 for 24 hours, peak blood levels of lidocaine are approximately 1/20 the systemic toxic level. Likewise, the maximum prilocaine level is about 1/36 the toxic level. The application of EMLA Cream to broken or inflamed skin, or to 2,000 cm^2 or more of skin where more of both anesthetics are absorbed, could result in higher plasma levels that could, in susceptible individuals, produce a systemic pharmacologic response. When each drug is administered intravenously, the steady-state volume of distribution is 1.1 to 2.1 L/kg (mean 1.5, ±0.3 SD, n=13) for lidocaine and is 0.7 to 4.4 L/kg (mean 2.6, ±1.3 SD, n=13) for prilocaine. The larger distribution volume for prilocaine produces the lower plasma concentrations of prilocaine observed when equal amounts of prilocaine and lidocaine are administered. At concentrations produced by application of EMLA Cream, lidocaine is approximately 70% bound to plasma proteins, primarily alpha-1-acid glycoprotein. At much higher plasma concentrations (1 to 4 μg/mL of free base) the plasma protein binding of lidocaine is concentration dependent. Prilocaine is 55% bound to plasma proteins. Both lidocaine and prilocaine cross the placental and blood brain barrier, presumably by passive diffusion.

It is not known if lidocaine or prilocaine are metabolized in the skin. Lidocaine is metabolized rapidly by the liver to a number of metabolites including monoethylglycinexylidide (MEGX) and glycinexylidide (GX), both of which have pharmacologic activity similar to, but less potent than that of lidocaine. The metabolite, 2,6-xylidine, has unknown pharmacologic activity but is carcinogenic in rats (see Carcinogenesis subsection of PRECAUTIONS). Following intravenous administration, MEGX and GX concentrations in serum range from 11 to 36% and from 5 to 11% of lidocaine concentrations, respectively. Prilocaine is metabolized in both the liver and kidneys by amidases to various metabolites including *ortho*-toluidine and N-n-propylalanine. It is not metabolized by plasma esterases. The *ortho*-toluidine metabolite has been shown to be carcinogenic in several animal models (see Carcinogenesis subsection of PRECAUTIONS). In addition, *ortho*-toluidine can produce methemoglobinemia following systemic doses of prilocaine approximating 8 mg/kg (see ADVERSE REACTIONS). Very young patients, patients with glucose-6-phosphate deficiencies and patients taking oxidizing drugs such as antimalarials and sulfonamides are more susceptible to methemoglobinemia (see Methemoglobinemia subsection of PRECAUTIONS).

The half-life of lidocaine elimination from the plasma following IV administration is approximately 65 to 150 minutes (mean 110, ±24 SD, n=13). This half-life may be increased in cardiac or hepatic dysfunction. More than 98% of an absorbed dose of lidocaine can be recovered in the urine as metabolites or parent drug. The systemic clearance is 10 to 20 mL/min/kg (mean 13, ±3 SD, n=13). The elimination half-life of prilocaine is approximately 10 to 150 minutes (mean 70, ±48 SD, n=13). The systemic clearance is 18 to 64 mL/min/kg (mean 38, ±15 SD, n=13). Prilocaine's half-life also may be increased in hepatic or renal dysfunction since both of these organs are involved in prilocaine metabolism.

CLINICAL STUDIES

EMLA Cream application in adults prior to IV cannulation or venipuncture was studied in 200 patients in four clinical studies in Europe. Application for at least 1 hour provided significantly more dermal analgesia than placebo cream or ethyl chloride. EMLA Cream was comparable to subcutaneous lidocaine, but was less efficacious than intradermal lidocaine. Most patients found EMLA Cream treatment preferable to lidocaine infiltration or ethyl chloride spray.

TABLE 1
Absorption of Lidocaine and Prilocaine from EMLA Cream
Normal Volunteers (N=16)

EMLA (g)	Area (cm^2)	Time on (hrs)	Drug Content (mg)	Absorbed (mg)	Cmax (μg/mL)	Tmax (hr)
60	400	3	lidocaine 1500	54	0.12	4
			prilocaine 1500	92	0.07	4
60	400	24*	lidocaine 1500	243	0.28	10
			prilocaine 1500	503	0.14	10

*Maximum recommended duration of exposure is 4 hours.

Continued on next page

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EMLA Cream was compared with 0.5% lidocaine infiltration prior to skin graft harvesting in one open label study in 80 adult patients in England. Application of EMLA Cream for 2 to 5 hours provided dermal analgesia comparable to lidocaine infiltration.

EMLA Cream application in children was studied in seven non-US studies (320 patients) and one US study (100 patients). In controlled studies, application of EMLA Cream for at least 1 hour with or without presurgical medication prior to needle insertion provided significantly more pain reduction than placebo. In children under the age of seven years, EMLA Cream was less effective than in older children or adults.

EMLA Cream was compared with placebo in the laser treatment of facial port-wine stains in 72 pediatric patients (ages 5–16). EMLA Cream was effective in providing pain relief during laser treatment.

Local dermal effects associated with EMLA Cream application in these studies on intact skin included paleness, redness and edema and were transient in nature (see ADVERSE REACTIONS).

Individualization of Dose: The dose of EMLA Cream which provides effective analgesia depends on the duration of the application over the treated area.

All pharmacokinetic and clinical studies employed a thick layer of EMLA Cream (1–2 g/10 cm^2). The duration of application prior to venipuncture was 1 hour. The duration of application prior to taking split thickness skin grafts was 2 hours. Although a thinner application may be efficacious, such has not been studied and may result in less complete analgesia or a shorter duration of adequate analgesia.

The systemic absorption of lidocaine and prilocaine is a side effect of the desired local effect. The amount of drug absorbed depends on surface area and duration of application. The systemic blood levels depend on the amount absorbed and patient size (weight) and rate of systemic drug elimination. Long duration of application, large treatment area, small patients, or impaired elimination may result in high blood levels. The systemic blood levels are typically a small fraction (1/20 to 1/36) of the blood levels which produce toxicity. Table 2 which follows gives maximum recommended application areas for infants and children.

TABLE 2
EMLA CREAM MAXIMUM RECOMMENDED APPLICATION AREA*
For Infants and Children
Based on Application to Intact Skin

Body Weight (kg)	Maximum Application Area (cm^2)**
up to 10 kg	100
10 to 20 kg	600
above 20 kg	2000

* These are broad guidelines for avoiding systemic toxicity in applying EMLA to patients with normal intact skin and with normal renal and hepatic function.

** For more individualized calculation of how much lidocaine and prilocaine may be absorbed, physicians can use the following estimates of lidocaine and prilocaine absorption for children and adults:
The estimated mean (±SD) absorption of lidocaine is 0.045 (±0.016) mg/cm^2/hr.
The estimated mean (±SD) absorption of prilocaine is 0.077 (±0.036) mg/cm^2/hr.

An IV antiarrhythmic dose of lidocaine is 1 mg/kg (70 mg/70 kg) and gives a blood level of about 1 μg/mL. Toxicity would be expected at blood levels above 5 μg/mL. Smaller areas of treatment are recommended in a debilitated patient, a small child or a patient with impaired elimination. Decreasing the duration of application is likely to decrease the analgesic effect.

INDICATION AND USAGE

EMLA Cream (a eutectic mixture of lidocaine 2.5% and prilocaine 2.5%) is indicated as a topical anesthetic for use on **normal intact skin** for local analgesia.

EMLA Cream is not recommended for use on mucous membranes because limited studies show much greater absorption of lidocaine and prilocaine than through intact skin. Safe dosing recommendations for use on mucous membranes cannot be made because it has not been studied adequately.

EMLA Cream is not recommended in any clinical situation in which penetration or migration beyond the tympanic membrane into the middle ear is possible because of the ototoxic effects observed in animal studies (see WARNINGS).

CONTRAINDICATIONS

EMLA Cream (lidocaine 2.5% and prilocaine 2.5%) is contraindicated in patients with a known history of sensitivity to local anesthetics of the amide type or to any other component of the product.

WARNINGS

Application of EMLA Cream to larger areas or for longer times than those recommended could result in sufficient absorption of lidocaine and prilocaine resulting in serious adverse effects (see Individualization of Dose).

Studies in laboratory animals (guinea pigs) have shown that EMLA Cream has an ototoxic effect when instilled into the middle ear. In these same studies, animals exposed to EMLA Cream in the external auditory canal only, showed no abnormality. EMLA Cream should not be used in any clinical situation in which its penetration or migration beyond the tympanic membrane into the middle ear is possible.

Methemoglobinemia: EMLA Cream should not be used in those rare patients with congenital or idiopathic methemoglobinemia and in infants under the age of twelve months who are receiving treatment with methemoglobin-inducing agents.

Very young patients or patients with glucose-6-phosphate deficiencies are more susceptible to methemoglobinemia.

Patients taking drugs associated with drug-induced methemoglobinemia such as sulfonamides, acetaminophen, acetanilid, aniline dyes, benzocaine, chloroquine, dapsone, naphthalene, nitrates and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, para-aminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaquine, quinine, are also at greater risk for developing methemoglobinemia.

A methemoglobinemia value of 28% (of total hemoglobin) developed in a three months old male infant (5.3 kg) who had 5 grams of EMLA Cream under an occlusive dressing applied to the back of the hands and in the cubital regions for 5 hours. The methemoglobinemia was successfully treated with IV methylene blue. The patient was concomitantly receiving trimethoprim (16 mg/day) and sulfamethoxazole (80 mg/day) for a urinary tract infection.

PRECAUTIONS

General: Repeated doses of EMLA Cream may increase blood levels of lidocaine and prilocaine. EMLA Cream should be used with caution in patients who may be more sensitive to the systemic effects of lidocaine and prilocaine including acutely ill, debilitated, or elderly patients.

EMLA Cream coming in contact with the eye should be avoided because animal studies have demonstrated severe eye irritation. Also the loss of protective reflexes can permit corneal irritation and potential abrasion. Absorption of EMLA Cream in conjunctival tissues has not been determined. If eye contact occurs, immediately wash out the eye with water or saline and protect the eye until sensation returns.

Patients allergic to para-aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine and/or prilocaine, however, EMLA Cream should be used with caution in patients with a history of drug sensitivities, especially if the etiologic agent is uncertain.

Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at greater risk of developing toxic plasma concentrations of lidocaine and prilocaine.

Information for Patients: When EMLA Cream is used, the patient should be aware that the production of dermal analgesia may be accompanied by the block of all sensations in the treated skin. For this reason, the patient should avoid inadvertent trauma to the treated area by scratching, rubbing, or exposure to extreme hot or cold temperatures until complete sensation has returned.

Drug Interactions: EMLA Cream should be used with caution in patients receiving Class I antiarrhythmic drugs (such as tocainide and mexiletine) since the toxic effects are additive and potentially synergistic.

Prilocaine may contribute to the formation of methemoglobin in patients treated with other drugs known to cause this condition (see Methemoglobinemia subsection of WARNINGS).

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis: Metabolites of both lidocaine and prilocaine have been shown to be carcinogenic in laboratory animals. In the animal studies reported below, doses or blood levels are compared to the Single Dermal Administration (SDA) of 60 g of EMLA Cream to 400 cm^2 for 3 hours to a small person (50 kg). The typical application for one or two treatments for venipuncture sites (2.5 or 5 g) would be $\frac{1}{24}$ or $\frac{1}{12}$ of that dose in an adult or about the same mg/kg dose in an infant.

A two-year oral toxicity study of 2,6-xylidine, a metabolite of lidocaine, has shown that in both male and female rats 2,6-xylidine in daily doses of 900 mg/m^2 (60 times SDA) resulted in carcinomas and adenomas of the nasal cavity. With daily doses of 300 mg/m^2 (20 times SDA), the increase in incidence of nasal carcinomas and/or adenomas in each sex of the rat were not statistically greater than the control group. In the low dose (90 mg/m^2; 6 times SDA) and control groups, no nasal tumors were observed. A rhabdomyosarcoma, a rare tumor, was observed in the nasal cavity of both male and female rats at the high dose of 900 mg/m^2. In addition, the compound caused subcutaneous fibromas and/or fibrosarcomas in both male and female rats and neoplastic nodules of the liver in the female rats with a significantly positive trend test; pairwise comparisons using Fisher's Exact Test showed significance only at the high dose of 900 mg/m^2. The animal study was conducted at oral doses of 15, 50, and 150 mg/kg/day. The dosages have been converted to mg/m^2 for the SDA calculations above.

Chronic oral toxicity studies of *ortho* -toluidine, a metabolite of prilocaine, in mice (900 to 14,400 mg/m^2; 60 to 960 times SDA) and rats (900 to 4,800 mg/m^2; 60 to 320 times SDA) have shown that *ortho* -toluidine is a carcinogen in both species. The tumors included hepatocarcinomas/adenomas in female mice, multiple occurrences of hemangiosarcomas/hemangiomas in both sexes of mice, sarcomas of multiple organs, transitional-cell carcinomas/papillomas of urinary bladder in both sexes of rats, subcutaneous fibromas/fibrosarcomas and mesotheliomas in male rats, and mammary gland fibroadenomas/adenomas in female rats. The lowest dose tested (900 mg/m^2; 60 times SDA) was carcinogenic in both species. Thus the no-effect dose must be less than 60 times SDA. The animal studies were conducted at 150 to 2,400 mg/kg in mice and at 150 to 800 mg/kg in rats. The dosages have been converted to mg/m^2 for the SDA calculations above.

Mutagenesis: The mutagenic potential of lidocaine HCl has been tested in the Ames Salmonella/mammalian microsome test and by analysis of structural chromosome aberrations in human lymphocytes *in vitro*, and by the mouse micronucleus test *in vivo*. There was no indication in these three tests of any mutagenic effects.

The mutagenicity of 2,6-xylidine, a metabolite of lidocaine, has been studied in different tests with mixed results. The compound was found to be weakly mutagenic in the Ames test only under metabolic activation conditions. In addition, 2,6-xylidine was observed to be mutagenic at the thymidine kinase locus, with or without activation, and induced chromosome aberrations and sister chromatid exchanges at concentrations at which the drug precipitated out of the solution (1.2 mg/mL). No evidence of genotoxicity was found in the *in vivo* assays measuring unscheduled DNA synthesis in rat hepatocytes, chromosome damage in polychromatic erythrocytes or preferential killing of DNA repair-deficient bacteria in liver, lung, kidney, testes and blood extracts from mice. However, covalent binding studies of DNA from liver and ethmoid turbinates in rats indicate that 2,6-xylidine may be genotoxic under certain conditions *in vivo*.

Ortho -toluidine, a metabolite of prilocaine, (0.5 μg/mL) showed positive results in *Escherichia coli* DNA repair and phage-induction assays. Urine concentrates from rats treated with *ortho* -toluidine (300 mg/kg orally; 300 times SDA) were mutagenic for *Salmonella typhimurium* with metabolic activation. Several other tests on *ortho* -toluidine, including reverse mutations in five different *Salmonella typhimurium* strains with or without metabolic activation and with single strand breaks in DNA of V79 Chinese hamster cells, were negative.

Impairment of Fertility: See Use in Pregnancy.

Use in Pregnancy: Teratogenic Effects: Pregnancy Category B.

Reproduction studies with lidocaine have been performed in rats and have revealed no evidence of harm to the fetus (30 mg/kg subcutaneously; 22 times SDA). Reproduction studies with prilocaine have been performed in rats and have revealed no evidence of impaired fertility or harm to the fetus (300 mg/kg intramuscularly; 188 times SDA). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, EMLA Cream should be used during pregnancy only if clearly needed.

Reproduction studies have been performed in rats receiving subcutaneous administration of an aqueous mixture containing lidocaine HCl and prilocaine HCl at 1:1 (w/w). At 40 mg/kg each, a dose equivalent to 29 times SDA lidocaine and 25 times SDA prilocaine, no teratogenic, embryotoxic or fetotoxic effects were observed.

Labor and Delivery: Neither lidocaine nor prilocaine are contraindicated in labor and delivery. Should EMLA Cream be used concomitantly with other products containing lidocaine and/or prilocaine, total doses contributed by all formulations must be considered.

Nursing Mothers: Lidocaine, and probably prilocaine, are excreted in human milk. Therefore, caution should be exercised when EMLA Cream is administered to a nursing mother since the milk:plasma ratio of lidocaine is 0.4 and is not determined for prilocaine.

Pediatric Use: Controlled studies of EMLA Cream in children under the age of seven years have shown less overall benefit than in older children or adults. These results illustrate the importance of emotional and psychological support of younger children undergoing medical or surgical procedures.

EMLA Cream should be used with care in patients with conditions or therapy associated with methemoglobinemia (see Methemoglobinemia subsection of WARNINGS).
When using EMLA Cream in young children, care must be taken to insure that application of the cream is limited to the intended site (see DOSAGE AND ADMINISTRATION). Accidental ingestion may lead to dose related toxicity.
In children weighing less than 20 kg, the area and duration should be limited (see TABLE 2 in Individualization of Dose).

ADVERSE REACTIONS

Localized Reactions: During or immediately after treatment with EMLA Cream, the skin at the site of treatment may develop erythema or edema or may be the locus of abnormal sensation. In clinical studies involving over 1,300 EMLA Cream-treated subjects, one or more such local reactions were noted in 56% of patients, and were generally mild and transient, resolving spontaneously within 1 or 2 hours. There were no serious reactions which were ascribed to EMLA Cream.
In patients treated with EMLA Cream, local effects observed in the trials included: paleness (pallor or blanching) 37%, redness (erythema) 30%, alterations in temperature sensations 7%, edema 6%, itching 2% and rash, less than 1%.
Allergic Reactions: Allergic and anaphylactoid reactions associated with lidocaine or prilocaine can occur. They are characterized by urticaria, angioedema, bronchospasm, and shock. If they occur they should be managed by conventional means. The detection of sensitivity by skin testing is of doubtful value.
Systemic (Dose Related) Reactions: Systemic adverse reactions following appropriate use of EMLA Cream are unlikely due to the small dose absorbed (see Pharmacokinetics subsection of CLINICAL PHARMACOLOGY). Systemic adverse effects of lidocaine and/or prilocaine are similar in nature to those observed with other amide local anesthetic agents including CNS excitation and/or depression (light-headedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression and arrest). Excitatory CNS reactions may be brief or not occur at all, in which case the first manifestation may be drowsiness merging into unconsciousness. Cardiovascular manifestations may include bradycardia, hypotension and cardiovascular collapse leading to arrest.

OVERDOSAGE

Peak blood levels following a 60 g application to 400 cm^2 for 3 hours are 0.05 to 0.16 μg/mL for lidocaine and 0.02 to 0.10 μg/mL for prilocaine. Toxic levels of lidocaine (>5 μg/mL) and/or prilocaine (> 6 μg/mL) cause decreases in cardiac output, total peripheral resistance and mean arterial pressure. These changes may be attributable to direct depressant effects of these local anesthetic agents on the cardiovascular system. In the absence of massive topical overdose or oral ingestion, evaluation should include evaluation of other etiologies for the clinical effects or overdosage from other sources of lidocaine, prilocaine or other local anesthetics. Consult the package inserts for parenteral Xylocaine (lidocaine HCl) or Citanest (prilocaine HCl) for further information for the management of overdose.

DOSAGE AND ADMINISTRATION

A thick layer of EMLA Cream is applied to intact skin and covered with an occlusive dressing:
Minor Dermal Procedures: For minor procedures such as intravenous cannulation and venipuncture, apply 2.5 grams of EMLA Cream (½ the 5 g tube) over 20 to 25 cm^2 of skin surface for at least 1 hour. In controlled clinical trials, two sites were usually prepared in case there was a technical problem with cannulation or venipuncture at the first site.
Major Dermal Procedures: For more painful dermatological procedures involving a larger skin area such as split thickness skin graft harvesting, apply 2 grams of EMLA Cream per 10 cm^2 of skin and allow to remain in contact with the skin for at least 2 hours.
Dermal analgesia can be expected to increase for up to 3 hours under occlusive dressing and persist for 1 to 2 hours after removal of the cream. The amount of lidocaine and prilocaine absorbed during the period of application can be estimated from the information in Table 2, ** footnote, in Individualization of Dose.
A single application of EMLA Cream in a child weighing less than 10 kg should not be applied over an area larger than 100 cm^2. A single application of EMLA Cream in children weighing between 10 kg and 20 kg should not be applied over an area larger than 600 cm^2 (see Table 2 in Individualization of Dose).
When applying EMLA Cream to young children, care must be taken to maintain careful observation of the child to prevent accidental ingestion of EMLA Cream or the occlusive dressing. A secondary protective covering to prevent inadvertent disruption of the application site may be useful.
EMLA Cream should not be used in infants under the age of one month nor in infants, under the age of twelve months, who are receiving treatment with methemoglobin-inducing agents (see Methemoglobinemia subsection of WARNINGS).
When EMLA Cream (lidocaine 2.5% and prilocaine 2.5%) is used concomitantly with other products containing local anesthetic agents, the amount absorbed from all formulations must be considered (see Individualization of Dose). The amount absorbed in the case of EMLA Cream is determined by the area over which it is applied and the duration of application under occlusion (see Table 2, ** footnote, in Individualization of Dose).
Although the incidence of systemic adverse reactions with EMLA Cream is very low, caution should be exercised, particularly when applying it over large areas and leaving it on for longer than 2 hours. The incidence of systemic adverse reactions can be expected to be directly proportional to the area and time of exposure (see Individualization of Dose).

HOW SUPPLIED

EMLA Cream is available as the following:
NDC 0186-1515-01 5 gram tube, box of 1, contains 2 Tegaderm® dressings (6 cm × 7 cm)
NDC 0186-1515-03 5 gram tube, box of 5, contains 12 Tegaderm® dressings (6 cm × 7 cm)
NDC 0186-1516-01 30 gram tube, box of 1
NOT FOR OPHTHALMIC USE.
KEEP CONTAINER TIGHTLY CLOSED AT ALL TIMES WHEN NOT IN USE.
Store at controlled room temperature 15°–30°C (59°–86°F).
Manufactured by:
Astra Pharmaceutical Production, AB
Sodertalje, Sweden
Manufactured for: Astra USA, Inc. 000425R05 Iss. 3/94
Westborough, MA 01581
Shown in Product Identification Guide, page 305

EPINEPHRINE ℞

[ep-ĕ-nef'-rin]
Injection, USP
1:10,000 (0.1 mg/mL)
Adult Strength

(For details of indications, dosage and administration, precautions, and adverse reactions, see circular in package.)

HOW SUPPLIED

Epinephrine Injection, USP, 1:10,000, is supplied in 10 mL prefilled syringes with a 21 G $^{15}/_{16}$" needle. (NDC 0186-0653-01) The solution should be stored at controlled room temperature 15°-30°C (59°-86°F) and should be protected from light by storage in the original carton until use.
021883R03 Rev. 7/91 (3)

FENTANYL CITRATE* and DROPERIDOL INJECTION ℂ ℞

***WARNING May be habit forming.**
FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY.

The two components of Fentanyl Citrate and Droperidol Injection, fentanyl citrate and droperidol, have different pharmacologic actions. Before administering Fentanyl Citrate and Droperidol Injection, the user should become familiar with the special properties of each drug, particularly the widely differing durations of action.

(For details of indication, dosage and administration, precautions, and adverse reactions, see circular in package.)

HOW SUPPLIED

Each mL of Fentanyl Citrate and Droperidol Injection contains fentanyl citrate (WARNING: May be habit forming) equivalent to 0.05 mg (50 mcg) of fentanyl base, droperidol 2.5 mg and lactic acid to adjust pH and is available in the following dosage forms:
Ampules
NDC 0186-1230-03, 2 mL ampule in packages of 10
NDC 0186-1231-03, 5 mL ampule in packages of 10
Vials
NDC 0186-1232-13, 2 mL single dose vial in packages of 10
NDC 0186-1233-13, 5 mL single dose vial in packages of 10
(FOR INTRAVENOUS USE BY HOSPITAL PERSONNEL SPECIFICALLY TRAINED IN THE USE OF OPIOID ANALGESICS.)
Protect from light. Store at controlled room temperature 15°–30°C (59°–86°F).
021881R03 Rev. 12/94

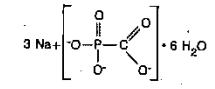
FOSCAVIR® ℞

[fos-ka-vēer]
(foscarnet sodium) Injection

RENAL IMPAIRMENT IS THE MAJOR TOXICITY OF FOSCAVIR, AND OCCURS TO SOME DEGREE IN MOST PATIENTS. CONSEQUENTLY, CONTINUAL ASSESSMENT OF A PATIENT'S RISK AND FREQUENT MONITORING OF SERUM CREATININE WITH DOSE ADJUSTMENT FOR CHANGES IN RENAL FUNCTION ARE IMPERATIVE.
FOSCAVIR HAS BEEN SHOWN TO CAUSE ALTERATIONS IN PLASMA MINERALS AND ELECTROLYTES THAT HAVE LED TO SEIZURES. THEREFORE, PATIENTS MUST BE MONITORED FREQUENTLY FOR SUCH CHANGES AND THEIR POTENTIAL SEQUELAE.
FOSCAVIR IS INDICATED FOR USE ONLY IN THE TREATMENT OF CMV RETINITIS AND MUCOCUTANEOUS ACYCLDVIR-RESISTANT HSV INFECTIONS IN IMMUNOCOMPROMISED PATIENTS. (See INDICATIONS section.)

DESCRIPTION

FOSCAVIR is the brand name for foscarnet sodium. The chemical name of foscarnet sodium is phosphonoformic acid, trisodium salt. Foscarnet sodium is a white, crystalline powder containing 6 equivalents of water of hydration with an empirical formula of $Na_3CO_5P \cdot 6\ H_2O$ and a molecular weight of 300.1. The structural formula is:



FOSCAVIR has the potential to chelate divalent metal ions, such as calcium and magnesium, to form stable coordination compounds. FOSCAVIR INJECTION is a sterile, isotonic aqueous solution for intravenous administration only. The solution is clear and colorless. Each milliliter of FOSCAVIR contains 24 mg of foscarnet sodium hexahydrate in Water for Injection, USP. Hydrochloric acid and/or sodium hydroxide may have been added to adjust the pH of the solution to 7.4. FOSCAVIR INJECTION contains no preservatives.

CLINICAL PHARMACOLOGY

Microbiology: *Mechanism of Action:* FOSCAVIR is an organic analogue of inorganic pyrophosphate that inhibits replication of all known herpesviruses *in vitro* including cytomegalovirus (CMV), herpes simplex virus types 1 and 2 (HSV-1, HSV-2), human herpesvirus 6 (HHV-6), Epstein-Barr virus (EBV), and varicella-zoster virus (VZV).
FOSCAVIR exerts its antiviral activity by a selective inhibition at the pyrophosphate binding site on virus-specific DNA polymerases and reverse transcriptases at concentrations that do not affect cellular DNA polymerases. FOSCAVIR does not require activation (phosphorylation) by thymidine kinase or other kinases, and therefore is active *in vitro* against HSV TK deficient mutants and CMV UL97 mutants. Thus, HSV strains resistant to acyclovir or CMV strains resistant to ganciclovir may be sensitive to FOSCAVIR. However, acyclovir or ganciclovir resistant mutants with alterations in the viral DNA polymerase may be resistant to FOSCAVIR and may not respond to therapy with FOSCAVIR.
Antiviral Activity: The quantitative relationship between the *in vitro* susceptibility of human cytomegalovirus (CMV) or mucocutaneous herpes simplex virus 1 and 2 (HSV-1 and HSV-2) to FOSCAVIR and clinical response to therapy has not been clearly established in man and virus sensitivity testing has not been standardized. Sensitivity test results, expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell culture (IC_{50}), vary greatly depending on the assay method used, cell type employed and the laboratory performing the test. A number of sensitive viruses and their IC_{50} values are listed below.

[See Table 1 at top of next column.]

Clinical isolates of CMV taken from patients show different sensitivities to FOSCAVIR *in vitro*. Statistically significant decreases in positive CMV cultures from blood and urine have been demonstrated in two studies (FOS-03 and ACTG-015/915) of patients treated with FOSCAVIR. Although median time to progression of CMV retinitis was increased in patients treated with the drug, reductions in positive blood or urine cultures have not been shown to correlate with clinical efficacy in individual patients.

[See Table 2 at top of next column.]

Continued on next page

ACTIONS AND USES
Aquaphor Healing Ointment is specially formulated for faster healing of severely dry skin, cracked skin and minor burns. It is recommended for patients suffering from severe skin chapping and from skin disorders that result in severely dry skin. This formula is also indicated as a follow-up skin treatment for patients undergoing radiation therapy or other drying/burning medical therapies. It is preservative-free, fragrance-free and hypoallergenic.[1].

ADMINISTRATION AND DOSAGE
Use Aquaphor Healing Ointment whenever a mild healing agent is needed. Apply liberally to affected areas two to three times a day. In the case of minor wounds, clean area prior to application.

PRECAUTIONS
For external use only. Avoid contact with the eyes. Not to be applied over third degree burns, deep or puncture wounds, infections or lacerations. If condition worsens or does not improve within seven days, patient should consult a physician.

HOW SUPPLIED
1.75 oz. tube
1. Data on file, BDF Inc

EUCERIN® OTC
[ū'sir-in]
Dry Skin Therapy Cleansing Bar

INDICATIONS
Use with warm water to cleanse skin.

ACTIVE INGREDIENT
Eucerite®

CONTAINS
Disodium Lauryl Sulfosuccinate, Sodium Cocoyl Isethionate, Cetearyl Alcohol, Corn Starch, Glyceryl Stearate, Paraffin, Water, Titanium Dioxide, Octyldodecanol, Cyclopentadecanolide, Lanolin Alcohol, Bisabolol.

ACTIONS AND USES
Eucerin® Cleansing Bar has been specially formulated for use on sensitive skin. The formulation contains Eucerite®, a special blend of ingredients that closely resemble the natural oils of the skin, thus providing excellent moisturizing properties. This formulation is fragrance-free and non-comedogenic. Additionally, the pH value of Eucerin Cleansing Bar is neutral so as not to affect the skin's normal acid mantle.

DIRECTIONS
Use during shower, bath, or regular cleansing.

HOW SUPPLIED
3 ounce bar.
List number 3852

EUCERIN® Creme OTC
[ū'sir-in]
Original Moisturizing Creme
NDC Numbers—10356-090-01
10356-090-05
10356-090-04
10356-090-07

INDICATIONS
Use daily to help relieve dry and very dry skin.

COMPOSITION
Triple Purified Water, Petrolatum, Mineral Oil, Ceresin, Lanolin Alcohol, Methylchloroisothiazolinone, Methylisothiazolinone.

ACTIONS AND USES
A gentle, non-comedogenic, fragrance-free water-in-oil emulsion. Eucerin can be used as a treatment for dry skin associated with eczema, psoriasis, chapped or chafed skin, sunburn, windburn and itching associated with dryness.[1].

ADMINISTRATION AND DOSAGES
Apply freely to affected areas of the skin as often as necessary.

PRECAUTIONS
For external use only. Discontinue use if signs of irritation occur.

HOW SUPPLIED
16 oz. jar—List Number 0090
8 oz. jar—List Number 3774
4 oz. jar—List Number 3797
2 oz. tube—List Number 3868
1. Data on File.

EUCERIN® FACIAL MOISTURIZING LOTION SPF 25 OTC
NDC Number—10356-972-01

INDICATIONS
Use daily to help relieve dry skin and provide broad spectrum sun protection.

COMPOSITION
Active Ingredients: Octyl Methoxycinnamate, Octyl Salicylate, Titanium Dioxide.
Other Ingredients: Water, Octyldodecyl Neopentanoate, Dioctyl Malate, Glycerin, Petrolatum, Zinc Oxide, Cetearyl Alcohol, DEA-Cetyl Phosphate, PEG-40 Castor Oil, Glyceryl Stearate, Sodium Hyaluronate, Lactic Acid, Lanolin Alcohol, Sodium Cetearyl Sulfate, Xanthan Gum, Methicone, Dimethicone, EDTA, Sodium Hydroxide, Methylchloroisothiazolinone, Methylisothiazolinone.

ACTIONS AND USES
Eucerin Facial Moisturizing Lotion SPF 25 is fragrance-free and non-comedogenic, with a unique sun screen (titanium dioxide) to protect skin from UVA and UVB light. It is specially formulated for dry, sensitive skin or for those undergoing therapies which irritate delicate facial skin. This light, oil-in-water formula is non-greasy and is easily absorbed into the skin.

ADMINISTRATION AND DOSAGE
Apply Eucerin Facial Moisturizing Lotion SPF 25 twice a day (especially in the morning), to nourish and moisture skin and protect it from harmful UVA and UVB rays.

PRECAUTIONS
For external use only. Avoid contact with eyes. Keep out of the reach of children. Discontinue use if signs of irritation occur.

HOW SUPPLIED
4-oz. bottle.—List No. 03972

EUCERIN® Lotion OTC
[ū'sir-in]
Original Moisturizing Lotion
NDC Numbers—10356-793-01
10356-793-04

INDICATIONS
Use daily to help relieve dry skiu.

COMPOSITION
Water, Mineral Oil, Isopropyl Myristate, PEG-40 Sorbitan Peroleate, Glyceryl Lanoleate, Sorbitol, Propylene Glycol, Cetyl Palmitate, Magnesium Sulfate, Aluminum Stearate, Lanolin Alcohol, BHT, Methylchloroisothiazolinone, Methylisothiazolinone.

ACTIONS AND USES
Eucerin Lotion is a non-comedogenic, fragrance-free, unique water-in-oil formulation that will help to alleviate and soothe dry skin, and provide long-lasting moisturization.

ADMINISTRATION AND DOSAGE
Use daily on dry skin.

PRECAUTIONS
For external use only. Discontinue use if signs of irritation occur.

HOW SUPPLIED
8 fluid oz. plastic bottle—List Number 3793
16 fluid oz. plastic bottle—List number 3794

EUCERIN PLUS CREME OTC
Moisturizing Alphahydroxy Creme
NDC 10356-036-01

INDICATIONS
Use daily to help relieve severely dry, flaky skin.

COMPOSITION
Water, Mineral Oil, Urea, Magnesium Stearate, Ceresin, Polyglyceryl-3 Diisostearate, Sodium Lactate, Isopropyl Palmitate, Benzyl Alcohol, Panthenol, Bisabolol, Lanolin Alcohol, Magnesium Sulfate.

CAUTION
For external use only. Avoid contact with eyes and areas where skin is inflamed or cracked. Discontinue use if signs of irritation occur. Keep out of reach of children.

ACTION AND USES
Eucerin Plus Creme is a unique alpha-hydroxy acid moisturizing creme (2.5% sodium lactate, 10% urea) that is clinically proven to relieve severely dry, flaky skin conditions[1]. Unlike other alpha-hydroxy acid mositurizers, Eucerin Plus Creme has low irritation potential, is fragrance-free and non-comedogenic.

ADMINISTRATION AND DOSAGE
Use daily on severely dry, scaly skin.

PRECAUTIONS
Avoid contact with eyes or areas where skin is inflamed or cracked. Discontinue use if signs of irritation occur. For external use only. Keep ont of reach of children.

HOW SUPPLIED
4 oz. jar—List No. 03611
1. Data on file.

EUCERIN PLUS LOTION OTC
Alphahydroxy Moisturizing Lotion
NDC 10356-967-01

INDICATIONS
Use daily to help relieve severely dry, flaky skin.

COMPOSITION
Water, Mineral Oil, PEG-7 Hydrogenated Castor Oil, Isohexadecane, Sodium Lactate 5%, Urea 5%, Glycerin, Isopropyl Palmitate, Panthenol, Ozokerite, Magnesium Sulfate, Lanolin Alcohol, Bisabolol, Methylchloroisothiazolinone, Methylisothiazolinone.

ACTION AND USES
Eucerin Plus Lotion in a unique alpha-hydroxy acid moisturizing lotion (5% Sodium Lactate, 5% Urea) that is clinically proven to relieve severely dry, flaky skin conditions.[1] Unlike other alpha-hydroxy acid moisturizing lotions, Eucerin Plus has low irritation potential, is fragrance free and non-comedogenic.

ADMINISTRATION AND DOSAGE
Use daily on severely dry, flaky skin.

PRECAUTIONS
Avoid contact with eyes or areas where skin is inflamed or cracked. Discontinue use if signs of irritation occur. For external use only. Keep out of reach of children.

HOW SUPPLIED
6 oz bottle—List No. 03967
1. Data on File.

Berlex Laboratories
300 FAIRFIELD ROAD
WAYNE, NJ 07470

Direct Inquiries to:
(201) 694-4100

For Medical Information and to report drug adverse events Contact:
Department of Epidemiology and Medical Affairs
300 Fairfield Road
Wayne, NJ 07470
(800) 888-2407

Betaseron for SC Injection Only: (Medical Information Only)
15049 San Pablo Avenue
Richmond, CA 94809-0099
(800) 888-4112

Fludara for Injection Only: (Medical Information Only)
15049 San Pablo Avenue
Richmond, CA 94809-0099
(800) 888-4112

BETAPACE® ℞
[bā'-tăh-pāce'']
(sotalol HCl)

DESCRIPTION
BETAPACE® (sotalol hydrochloride), is an antiarrhythmic drug with Class II (beta-adrenoreceptor blocking) and Class

Continued on next page

Information on the Berlex products appearing here is based on the most current information available at the time of publication closing. Further information for these and other products may be obtained from the Medical Affairs Department, Berlex Laboratories, 300 Fairfield Road, Wayne, New Jersey 07470, 1-800-888-2407. Information on Betaseron and Fludara may be obtained from Berlex Laboratories, 15049 San Pablo Avenue, Richmond, California 94804-0016, 1-800-888-4112.

cle of purified water, carbomer 940, sodium hydroxide, docusate sodium, fragrance and alcohol 14%
Benzoyl peroxide is an antibacterial and keratolytic agent.

HOW SUPPLIED

5 & 10 Benzagel® are available in 1.5 oz (42.5 g) and 3 oz (85 g) plastic tubes; 5 Benzagel® contains 50 mg benzoyl peroxide per gram and 10 Benzagel® contains 100 mg benzoyl peroxide per gram.
5-Benzagel 1.5 oz NDC 0066-0430-15
5-Benzagel 3.0 oz NDC 0066-0430-30
10-Benzagel 1.5 oz NDC 0066-0431-15
10 Benzagel 3.0 oz NDC 0066-0431-30

BENZAMYCIN® Topical Gel ℞

[ben'za-mi"sin]
(erythromycin—benzoyl peroxide)

PRODUCT OVERVIEW

KEY FACTS

Benzamycin® is a topical gel containing 3% erythromycin and 5% benzoyl peroxide. Erythromycin is an antibiotic and benzoyl peroxide is an antibacterial and keratolytic agent.

MAJOR USES

Benzamycin® is indicated for the topical control of acne vulgaris.

SAFETY INFORMATION

Benzamycin® is contraindicated in patients with a history of hypersensitivity to erythromycin, benzoyl peroxide, or any of the other listed ingredients. Avoid contact with eyes and mucous membranes. Concomitant topical acne therapy should be used with caution. Adverse reactions may include dryness, erythema, and pruritus.

PRESCRIBING INFORMATION

BENZAMYCIN® Topical Gel ℞

[ben'za-mi"sin]
(erythromycin—benzoyl peroxide)

Reconstitute Before Dispensing

DESCRIPTION

Each gram of Benzamycin® (erythromycin—benzoyl peroxide) topical gel contains, as dispensed, 30 mg (3%) of erythromycin and 50 mg (5%) of benzoyl peroxide in a gel vehicle of purified watar, carbomer 940, alcohol 20%, sodium hydroxide, docusate sodium and fragrance.
Erythromycin ($C_{37}H_{67}NO_{13}$) is produced by a strain of *Streptomyces erythraeus* and belongs to the macrolide group of antibiotics.
Benzoyl peroxide ($C_{14}H_{10}O_4$), is an antibacterial and keratolytic agent.

CLINICAL PHARMACOLOGY

Erythromycin is a bacteriostatic macrolide antibiotic, but may be bactericidal in high concentrations. Although the mechanism by which erythromycin acts in reducing inflammatory lesions of acne vulgaris is unknown, it is presumably due to its antibiotic action. Antagonism has been demonstrated between clindamycin and erythromycin.
Benzoyl peroxide is an antibacterial agent which has been shown te be effective against *Propionibacterium acnes*, an anaerobe found in sebaceous follicles and comedones. The antibacterial action of benzoyl peroxide is believed to be due to the release of active oxygen. Benzoyl peroxide has a keratolytic and desquamative effect which may also contribute to its efficacy.
Benzoyl peroxide has been shown to be absorbed by the skin where it is converted to benzoic acid.

INDICATIONS AND USAGE

Benzamycin® Topical Gel is indicated for the topical control of acne vulgaris.

CONTRAINDICATIONS

Benzamycin® Topical Gel is contraindicated in tbose patients with a history of hypersensitivity to erythromycin, benzoyl peroxide or any of the other listed ingredients.

PRECAUTIONS

General—For external use only. Not for ophthalmic use. Avoid contact with eyes and mucous membranes. Concomitant topical acne therapy should be used with caution because a possible cumulative irritancy effect may occur, especially with peeling, desquamating or abrasive agents. If severe irritation develops, discontinue use and institute appropriate therapy.
The use of antibiotic agents may be associated with the overgrowth of antibiotic-resistant organisms. If this occurs, administration of this drug should be discontinued and appropriate measures taken.
Information for Patients—Patients using Benzamycin® Topical Gel should receive the following information and instructions:

BENZAMYCIN® Topical Gel

Size (Net Weight)	NDC 0066-	Benzoyl Peroxide Gel	Active Erythromycin Powder (In Plastic Vial)	Ethyl Alcohol (70%) To Be Added
23.3 grams (as dispensed)	0510-23	20 grams	0.8 grams	3 mL
46.6 grams (as dispensed)	0510-46	40 grams	1.6 grams	6 mL

1. Benzamycin® Topical Gel is for external use only. Avoid contact with the eyes and mucous membranes.
2. Patients should not use any other topical acne preparation unless otherwise directed by physician.
3. Benzamycin® Topical Gel may bleach bair or colored fabric.
4. If excesive irritation or dryness should occur, patient should discontinue medication and consult physician.
5. Discard product after 3 months and obtain fresh material.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term studies in animals bave not been performed to evaluate carcinogenic potential or the effect on fertility.
Pregnancy Category C: Animal reproduction studies have not been conducted with Benzamycin® Topical Gel. It is also not known whether Benzamycin® Topical Gel can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Benzamycin® Topical Gel should be given to a pregnant woman only if clearly needed.
Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Benzamycin® Topical Gel is administered to a nursing woman.
Pediatric Use: Safety and effectiveness in children under the age of 12 bave not been established.

ADVERSE REACTIONS

Adverse reactions which may occur include dryness, erythema and pruritus. Of a total of 153 patients treated with Benzamycin® Topical Gel during clinical trials, 4 patients experienced adverse reactions, of whom three experienced dryness and one an urticarial reaction which responded well to aymptomatic treatment.

DOSAGE AND ADMINISTRATION

Benzamycin® Topical Gel should be applied twice daily, morning and evening, or as directed by physician, to affected areas after the skin is thoroughly washed, rinsed with warm water and gently patted dry.

How Supplied and Compounding Directions:
[See table above.]
Prior to dispensing, tap vial until all powder flows freely. Add the indicated amount of ethyl alcohol (70%) to vial (to the mark) and immediately shake to completely dissolve erythromycin. Add this solution to gel and stir until homogeneous in appearance (1 to 1½ minutes). Benzamycin Topical Gel should then be stored under refrigeration. Do not freeze. Place a 3-month expiration dato on the label.
Note: Prior to reconstitution, store at room temperature. After reconstitution, store under refrigeration. Do not freeze. Keep tightly closed. Keep out of the reach of children.
Caution: Federal (U.S.A.) law prohibits dispensing without prescription.
U.S. Patent Nos. 4,387,107 and 4,497,794.

DRITHOCREME® ℞

(anthralin) 0.1%, 0.25%, 0.5%, 1.0% (HP)

DESCRIPTION

Drithocreme® is a pale yellow topical cream containing 0.1%, 0.25%, 0.5% or 1.0% (HP) anthralin USP in a base of white petrolatum, sodium lauryl sulfate, cetostearyl alcohol, ascorbic acid, salicylic acid, chlorocresol and purified water.

CLINICAL PHARMACOLOGY

Although the precise mechanism of anthralin's anti-psoriatic action is not fully understood, *in vitro* evidence auggests that its antimitotic effect results from inhibition of DNA synthesis. Additionally, the chemically reducing properties of anthralin may upset oxidative metabolic processes, providing a further slowing down of epidermal mitosis.
Absorption in man has not been finally determined, but in a limited clinical study of Drithocreme, no traces of anthraquinone metabolites were detected in the urine of aubjects treated; however, caution is advised in patients with renal disease.

INDICATIONS AND USAGE

An aid in the topical treatment of quiescent or chronic psoriasis. Treatment should be continued until the skin is entirely clear, *i.e.*, when there is nothing to feel with the fingers and the texture is normal.

CONTRAINDICATIONS

Do not use Drithocreme on the face, or for acute or actively inflamed psoriatic eruptions. Do not use if sensitive to any of the ingredients.

WARNINGS

Avoid contact with the eyes or mucous membranes. Drithocreme should not normally be applied to intertriginous skin areas and high strengths should not be used on these sites. Remove any unintended residue which may be deposited behind the ears. Avoid applying to the folds and creases of the akin. Discontinue use if a sensitivity reaction occurs or if excessive irritation develops on uninvolved skin areas. Keep out of the reach of children.

PRECAUTIONS

For external use only. To prevent the possibility of staining clothing or bed linen while gaining experience in using Drithocreme, it may be advisable to use protective dressings. To prevent the possibility of discoloration, particularly where Drithocreme HP (1.0%) has been used, always rinse the bath/shower with hot water immediately after washing/showering and then use a suitable cleanser to remove any deposit on the surface of the bath or shower. Contact with fabrics, plastics and other materials may cause staining and should be avoided. Always wash hands thoroughly after use.
Long-term studies in animals have not been performed to evaluate the carcinogenic potential of the drug. Although anthralin has been found to have tumor-promoting properties on mouse skin, there have been no reports to suggest carcinogenic effects in humans after many years of clinical use.
As long-term use of topical corticosteroids may destabilize psoriasis, and withdrawal may also give rise to a 'rebound' phenomenon, an interval of at least one week should be allowed between the discontinuance of such steroids and the commencement of Drithocreme therapy. Petrolatum or a suitably bland emollient may usefully be applied during the intervening period.

PREGNANCY

Pregnancy Category C. Animal reproduction studies have not been conducted with Dritbocreme. It is also not known whether Drithocreme can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Drithocreme® should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in milk and because of the potential for tumorigenicity shown for anthralin in animal studies, a decision ahould be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in children have not been specifically established.

ADVERSE REACTIONS

Very few instances of contact allergic reactions to anthralin have been reported. However, transient primary irritation of normal skin or uninvolved skin surrounding the treated lesions is more frequently seen and may occasionally be severe. Application of Drithocreme must be restricted to the psoriatic lesions. If the initial treatment produces excessive soreness or if the lesions spread, reduce frequency of application and, in extreme cases, discontinue use and consult physician. Some temporary discoloration of hair and fingernails may arise during the period of treatment but should be minimized by careful application.

DOSAGE AND ADMINISTRATION

Generally, it is recommended that Drithocreme be applied once a day or as directed by a physician. Anthralin is known to be a potential skin irritant. The irritant potential of anthralin is directly related to the strength being used and each patient's individual tolerance. Therefore, where the response to anthralin treatment has not previously been established, always commence treatment for at least one week using 0.1% Drithocreme. Increase to the 0.25%, 0.5% and 1.0% (HP) strengths when directed by a physician.
To open the tube, unscrew the cap and invert to pierce membrane. Apply as directed and remove by washing or showering. The optimal period of contact will vary according to the strength used and the patient's response to treatment.

Continued on next page

Dermik Laboratories—Cont.

For the Skin
Apply sparingly only to the psoriatic lesions and rub gently and carefully into the skin until absorbed. It is most important to avoid applying an excessive quantity which may cause unnecessary soiling and staining of the clothing and/or bed linen. At the end of each period of treatment, a bath or shower should be taken to remove any surplus cream (which may have become red/brown in color). The margins of the lesions may gradually become stained purple/brown as treatment progresses, but this will disappear after cessation of treatment.

For the Scalp
Comb the hair to remove scalar debris and, after suitably parting, rub the cream well into the lesions. Keep Drithocreme away from the eyes. Care should be taken to avoid application of the cream to uninvolved scalp margins. Remove any unintended residue which may be deposited behind the ears. At the end of each period of contact, wash the hair and scalp to remove any surplus cream (which may have become red/brown in color). Keep tightly capped when not in use.
Store at controlled room temperature, 15°–30°C (59°–88°F).

HOW SUPPLIED
50g tubes
Drithocreme 0.1% NDC 0088-7200-50
Drithocreme 0.25% NDC 0066-7201-50
Drithocreme 0.5% NDC 0056-7202-50
Drithocreme HP 1% NDC 0086-7203-50

DRITHO-SCALP® ℞
(anthralin) 0.25%, 0.5%

DESCRIPTION
Dritho-Scalp® is a pale yellow topical cream containing 0.25 or 0.5% anthralin USP in a base of white petrolatum, mineral oil, sodium lauryl sulfate, cetostearyl alcohol, ascorbic acid, salicylic acid, chlorocresol and purified water.

CLINICAL PHARMACOLOGY
Although the precise mechanism of anthralin's antipsoriatic action is not fully understood, *in vitro* evidence suggests that its antimitotic effect results from inhibition of DNA synthesis. Additionally, the chemically reducing properties of anthralin may upset oxidative metabelic processes, providing a further slowing down of epidermal mitosis.
Absorption in man has not been finally determined, but in a limited clinical study of anthralin cream, no traces of anthraquinone metabolites were detected in the urine of subjects treated; however, caution is advised in patients with renal disease.

INDICATIONS AND USAGE
An aid in the topical treatment of quiescent or chronic psoriasis of the scalp. Treatment should be continued until the skin is entirely clear, *i.e.*, when there is nothing to feel with the fingers and the texture is normal.

CONTRAINDICATIONS
In patients with acute psoriatic eruptions or a history of hypersensitivity to any of the ingredients.

WARNINGS
Avoid contact with the eyes or mucous membranes. Dritho-Scalp should not normally be applied to intertriginous skin area and high strengths should not he used on these sites. Remove any unintended residue which may be deposited behind the ears. Avoid applying to the folds and creases of the skin. Discontinue use if a sensitivity reaction occurs or if excessive irritation develops on uninvolved skin areas. Keep out of the reach of children.

PRECAUTIONS
For external use only. Dritho-Scalp may stain the hair and should be applied sparingly and carefully to psoriatic lesions only. Contact with fabrics, plastics and other materiala may cause staining and should be avoided. To prevent the possibility of discoloration, always rinse the bath/shower with hot water immediately after washing/showering and then use a suitable cleanser to remove any deposit on the surface of the bath or shower. Always wash hands thoroughly after use.
Long-term studies in animals have not been performed to evaluate the carcinogenic potential of the drug. Although anthralin has been found to have tumor-promoting properties on mouse skin, there have been no reports to suggest carcinogenic effects in humans after many years of clinical use.
As long-term use of topical corticosteroids may destabilize psoriasis, and withdrawal may also give rise to a 'rebound' phenomenon, an interval of at least one week should be allowed between the discontinuance of such steroids and the commencement of Dritho-Scalp therapy. Petrolatum or a suitably bland emollient may usefully be applied during the intervening period.

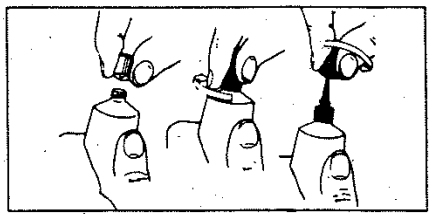
Pregnancy
Pregnancy Category C. Animal reproduction studies have not been conducted with Dritho-Scalp. It is also not known whether Dritho-Scalp can cause fetal harm when administered to a pregnant women or can affect reproduction capacity. Dritho-Scalp should be given to a pregnant woman only if clearly needed.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in milk and because of the potential for tumorigenicity shown for anthralin in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness in children have not been specifically established.

ADVERSE REACTIONS
Very few instances of contact allergic reactions to anthralin have been reported. However, transient primary irritation of uninvolved skin surrounding the treated lesions is more frequently seen and may occasionally be severe. Application of Dritho-Scalp® must be restricted to the psoriatic lesions. If the initial treatment produces excessive soreness or if the lesions spread, reduce frequency of application and, in extreme cases, discontinue use and consult physician. Some temporary discoloration of hair and fingernails may arise during the period of treatment but should be minimized by careful application.

DOSAGE AND ADMINISTRATION
Generally, it is recommended that Dritho-Scalp be applied once a day or as directed by a physician. Anthralin is known to be a potential skin irritant. The irritant potential of anthralin is directly related to the strength being used and each patient's individual tolerance. Therefore, where the response to anthralin treatment has not previously been established, always commence treatment for at least one week using 0.25% Dritho-Scalp. Increase to the 0.5% strength only when directed by a physician.
Before initial use, the tube membrane should be pierced by inverting the white cap, which should then be discarded. The black applicator should then be screwed firmly onto the tube. This applicator includes a black cap which should always be replaced between treatments (see illustration).



Apply as directed and remove by washing or showering. The optimal period of contact will vary according to the strength used and the patient's response to treatment.
Comb the hair to remove scalar debris and, after suitably parting, apply Dritho-Scalp only to the lesions and rub in well, taking care to prevent the cream spreading onto the forehead.

Keep Dritho-Scalp well away from the eyes.
Avoid application of the cream to uninvolved scalp margins. Remove any unintended residue which may be deposited behind the ears. At the end of each period of contact, wash the hair and scalp to remove any surplus cream (which may have become red/brown in color).

Always wash hands thoroughly after use.
Store at controlled room temperature, 15°–30°C (59°–85°F).

HOW SUPPLIED
50 g tube with special applicator
Dritho-Scalp 0.25% NDC 0066-7204-50
Dritho-Scalp 0.5% NDC 0055-7205-50

FLORONE® ℞
[flōr-ōhn]
(brand of diflorasone diacetate cream and diflorasone diacetate ointment 0.05%)
FLORONE E® ℞
(brand of diflorasone diacetate emollient cream 0.05%)
Not For Ophthalmic Use

PRODUCT OVERVIEW

KEY FACTS
Florone is a topical corticosteroid containing 0.05% diflorasone diacetate in an emulsified, hydrophilic cream and in an ointment with an emollient, occlusive base. Florone Ointment contains no propylene glycol. Florone E Emollient Cream contains 0.5 mg diflorasone diacetate in a hydrophilic, vanishing cream base.

MAJOR USES
These products are indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

SAFETY INFORMATION
The Florone products are contraindicated in patients with a history of hypersensitivity to any of their components. Systemic absorption of topical corticosteroids has produced reversible HPA axis suppression. Therefore, patients receiving a large dose applied to a large area or under an occlusive dressing should be evaluated periodically. The most common adverse reactions are burning, itching, irritation, and dryness.

PRESCRIBING INFORMATION

FLORONE® ℞
[flōr-ōhn]
(brand of diflorasone diacetate cream and diflorasone diacetate ointment 0.05%)
FLORONE E® ℞
(brand of diflorasone diacetate emollient cream 0.05%)
Not For Ophthalmic Use

DESCRIPTION
Each gram of FLORONE Cream and FLORONE Ointment contains 0.5 mg diflorasone diacetate in a cream or ointment base respectively. Each gram of Florone E Emollient Cream contains 0.5 mg diflorasone diacetate in an emollient cream base.
Chemically, diflorasone diacetate is: 6α, 9α-difluoro-11β, 17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21 diacetate.
FLORONE Cream contains diflorasone diacetate in an emulsified and hydrophilic cream base consisting of propylene glycol, stearic acid, polysorbate 60, sorbitan monostearate and monooleate, sorbic acid, citric acid and water. The corticosteroid is formulated as a solution in the vehicle using 15 percent propylene glycol to optimize drug delivery.
FLORONE Ointment contains diflorasone diacetate in an emollient, occlusive base consisting of polyoxypropylene 15-stearyl ether, stearic acid, lanolin alcohol and white petrolatum.
Florone E Emollient Cream contains diflorasone diacetate in a hydrophilic, vanishing cream base of propylene glycol, stearyl alcohol, cetyl alcohol, sorbitan monostearate, polysorbate 60, mineral oil and water.

CLINICAL PHARMACOLOGY
Topical corticosteroids share anti-inflammatory, antipruritic and vasoconstrictive actions.
The mechanism of anti-inflammatory activity of the topical corticosteroids is unclear. Various laboratory methods, including vasoconstrictor assays, are used to compare and predict potencies and/or clinical efficacies of the topical corticosteroids. There is some evidence to suggest that a recognizable correlation exists between vasoconstrictor potency and therapeutic efficacy in man.
Pharmacokinetics: The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier and the use of occlusive dressings.
Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids. Thus, occlusive dressings may be a valuable therapeutic adjunct for treatment of resistant dermatoses. (See DOSAGE AND ADMINISTRATION.)
Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. They are metabolized primarily in the liver and are then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

THYROLAR® Tablets Name	Composition (T_3/T_4 per tablet)	Color	Armacode®
Thyrolar®—¼(0456-0040-01)	3.1 mcg/12.5 mcg	Violet/White	YC
Thyrolar®—½(0456-0045-01)	6.25 mcg/25 mcg	Peach/White	YD
Thyrolar®—1 (0456-0050-01)	12.5 mcg/50 mcg	Pink/White	YE
Thyrolar®—2 (0456-0055-01)	25 mcg/100 mcg	Green/White	YF
Thyrolar®—3 (0456-0060-01)	37.5 mcg/150 mcg	Yellow/White	YH

ZONE-A CREAM 1% ℞

[zōn 'ā]

DESCRIPTION

A topical preparation containing Hydrocortisone acetate 1% and Pramoxine HCl 1% in a hydrophilic cream base containing stearic acid, cetyl alcohol, aquaphor, isopropyl palmitate, polyoxyl 40 stearato, propylene glycol, potassium sorbate 0.1%, sorbic acid 0.1%, triethanolamine lauryl sulfate and water.

HOW SUPPLIED

1 oz. tube NDC 0785-5505-04

Fujisawa USA, Inc.
PARKWAY NORTH CENTER
3 PARKWAY NORTH
DEERFIELD, IL 60015-2548

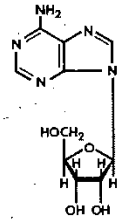
For Medical Information Contact:
Generally:
Medical and Scientific Information
(800) 727-7003
In Emergencies:
Medical and Scientific Information
(800) 727-7003

ADENOCARD® ℞

(adenosine)
For Rapid Bolus Intravenous Use

DESCRIPTION

Adenosine is an endogenous nucleoside occurring in all cells of the body. It is chemically 6-amino-9-β-D-ribofuranosyl-9-H-purine and has the following structural formula:



$C_{10}H_{13}N_5O_4$ 267.24

Adenosine is a white crystalline powder. It is soluble in water and practically insoluble in alcohol. Solubility increases by warming and lowering the pH. Adenosine is not chemically related to other antiarrhythmic drugs.

Adenocard® (adenosine) is a sterile solution for rapid bolus intravenous injection. Each mL contains 3 mg adenosine and 9 mg sodium chloride in Water for Injection. The pH of the solution is between 5.5 and 7.5.

CLINICAL PHARMACOLOGY

Mechanism of Action

Adenocard (adenosine) slows conduction time through the A-V node, can interrupt the reentry pathways through the A-V node and can restore normal sinus rhythm in patients with paroxysmal supraventricular tachycardia (PSVT), including PSVT associated with Wolff-Parkinson-White Syndrome.

Adenocard is antagonized competitively by methylxanthines such as caffeine and theophylline and potentiated by blockers of nucleoside transport such as dipyridamole. Adenocard is not blocked by atropine.

Hemodynamics

The usual intravenous bolus dose of 6 or 12 mg Adenocard (adenosine) will have no systemic hemodynamic effects. When larger doses are given by infusion, adenosine decreases blood pressure by decreasing peripheral resistance.

Pharmacokinetics

Intravenously administered Adenocard (adenosine) is removed from the circulation very rapidly. Following an intravenous bolus, adenosine is taken up by erythrocytes and vascular endothelial cells. The half-life of intravenous adenosine is estimated to be less than 10 seconds. Adenosine enters the body pool and is primarily metabolized to inosine and adenosine monophosphate (AMP).

Hepatic and Renal Failure

Hepatic and renal failure should have no effect on the activity of a bolus Adenocard (adenosine) injection. Since Adenocard (adenosine) has a direct action, hepatic and renal function are not required for the activity or the metabolism of a bolus adenosine injection.

Clinical Trial Results

In controlled studies in the United States, bolus doses of 3, 6, 9, and 12 mg were studied. A cumulative 60% of patients with paroxysmal supraventricular tachycardia had converted to normal sinus rhythm within one minute after an intravenous bolus dose of 6 mg Adenocard (some converted on 3 mg and failures were given 6 mg), and a cumulative 92% converted after a bolus dose of 12 mg. Seven to sixteen percent of patients converted after 1–4 placebo bolus injections. Similar responses were seen in a variety of patient subsets, including those using or not using digoxin, those with Wolff-Parkinson-White Syndrome, males, females, Blacks, Caucasians, and Hispanics.

Adenosine is not effective in converting rhythms other than PSVT, such as atrial flutter, atrial fibrillation, or ventricular tachycardia, to normal sinus rhythm. To date, such patients have not had adverse consequences following administration of adenosine.

INDICATIONS AND USAGE

Intravenous Adenocard (adenosine) is indicated for the following.

Conversion to sinus rhythm of paroxysmal supraventricular tachycardia (PSVT), including that associated with accessory bypass tracts (Wolff-Parkinson-White Syndrome). When clinically advisable, appropriate vagal maneuvers (e.g., Valsalva maneuver), should be attempted prior to Adenocard administration.

It is important to be sure the Adenocard solution actually reaches the systemic circulation (see **DOSAGE AND ADMINISTRATION**).

Adenocard does not convert atrial flutter, atrial fibrillation, or ventricular tachycardia to normal sinus rhythm. In the presence of atrial flutter or atrial fibrillation, a transient modest slowing of ventricular response may occur immediately following Adenocard administration.

CONTRAINDICATIONS

Intravenous Adenocard (adenosine) is contraindicated in:

1. Second- or third-degree A-V block (except in patients with a functioning artificial pacemaker).
2. Sick sinus syndrome (except in patients with a functioning artificial pacemaker).
3. Known hypersensitivity to adenosine.

WARNINGS

Heart Block

Adenocard (adenosine) exerts its effect by decreasing conduction through the A-V node and may produce a short-lasting first-, second- or third-degree heart block. In extreme cases, transient asystole may result (one case has been reported in a patient with atrial flutter who was receiving carbamazepine). Appropriate therapy should be instituted as needed. Patients who develop high-level block on one dose of Adenocard should not be given additional doses. Because of the very short half-life of adenosine, these effects are generally self-limiting.

Rarely, ventricular fibrillation has been reported following Adenocard administration, including both resuscitated and fatal events. In most instances, these cases were associated with the concomitant use of digoxin. Although no causal relationship or drug-drug interaction has been established, Adenocard should be used with caution in patients receiving digoxin. Appropriate resuscitative measures should be available.

Arrhythmias at Time of Conversion

At the time of conversion to normal sinus rhythm, a variety of new rhythms may appear on the electrocardiogram. They generally last only a few seconds without intervention, and may take the form of premature ventricular contractions, atrial premature contractions, sinus bradycardia, sinus tachycardia, skipped beats, and varying degrees of A-V nodal block. Such findings were seen in 55% of patients.

PRECAUTIONS

Drug Interactions

Intravenous Adenocard (adenosine) has been effectively administered in the presence of other cardioactive drugs, such as quinidine, beta-adrenergic blocking agents, calcium-channel blocking agents, and angiotensin-converting enzyme inhibitors, without any change in the adverse reaction profile. The use of Adenocard in patients receiving digitalis may be rarely associated with ventricular fibrillation (see **WARNINGS**).

The effects of adenosine are antagonized by methylxanthines such as caffeine and theophylline. In the presence of these methylxanthines, larger doses of adenosine may be required or adenosine may not be effective.

Adenosine effects are potentiated by dipyridamole. Thus, smaller doses of adenosine may be effective in the presence of dipyridamole. Carbamazepine has been reported to increase the degree of heart block produced by other agents. As the primary effect of adenosine is to decrease conduction through the A-V node, higher degrees of heart block may be produced in the presence of carbamazepine.

Asthma

Most patients with asthma who have received intravenous Adenocard (adenosine) have not experienced exacerbation of their asthma. Cases of bronchospasm have been reported rarely in both asthmatic and non-asthmatic patients. Inhaled adenosine has been reported to induce bronchoconstriction in asthmatic patients, but not in normal individuals.

Carcinogenesis, Mutagenesis

Studies in animals have not been performed to evaluate the carcinogenic potential of Adenocard (adenosine). Adenosine tested negative for mutagenic potential in the Salmonella/Mammalian Microsome Assay (Ames Test).

Adenosine, like other nucleosides at millimolar concentrations present for several doubling times of cells in culture, is known to produce a variety of chromosomal alterations. In rats and mice, adenosine administered intraperitoneally once a day for 5 days at 50, 100, and 150 mg/kg caused decreased spermatogenesis and increasod numbers of abnormal sperm, a reflection of the ability of adenosine to produce chromosomal damage.

Pregnancy Category C

Animal reproduction studies have not been conducted with adenosine; nor have studies been performed in pregnant women. As adenosine is a naturally occurring material, widely dispersed throughout the body, no fetal effects would be anticipated. However, since it is not known whether Adenocard can cause fetal harm when administered to pregnant women, Adenocard should be used during pregnancy only if clearly needed.

Pediatrics

No controlled studies have been conducted in pediatric patients.

ADVERSE REACTIONS

The following reactions were reported with intravenous Adenocard (adenosine) used in controlled U.S. clinical trials. The placebo group had a less than 1% rate of all of these reactions.

Cardiovascular	Facial flushing (18%), headache (2%), sweating, palpitations, chest pain, hypotension (less than 1%)
Respiratory	Shortness of breath/dyspnea (12%), chest pressure (7%), hyperventilation, head pressure (less than 1%)
Central Nervous System	Lightheadedness (2%), dizziness, tingling in arms, numbness (1%), apprehension, blurred vision, burning sensation, heaviness in arms, neck and back pain (less than 1%)
Gastrointestinal	Nausea (3%), metallic taste, tightness in throat, pressure in groin (less than 1%)

In post-market clinical experience with Adenocard, cases of prolonged asystole, ventricular tachycardia, ventricular fibrillation, transient increase in blood pressure, and bronchospasm, in association with Adenocard use, have been reported.

OVERDOSAGE

The half-life of Adenocard (adenosine) is less than 10 seconds. Thus, adverse effects are generally rapidly self-limiting. Treatment of any prolonged adverse effects should be individualized and be directed toward the specific effect. Methylxanthines, such as caffeine and theophylline, are competitive antagonists of adenosine.

DOSAGE AND ADMINISTRATION

For rapid bolus intravenous use only.

Adenocard (adenosine) Injection should be given as a rapid bolus by the peripheral intravenous route. To be certain the solution reaches the systemic circulation, it should be administered either directly into a vein or, if given into an IV line, it should be given as close to the patient as possible and followed by a rapid saline flush.

The dose recommendation is based on clinical studies with peripheral venous bolus dosing. Central venous (CVP or other) administration of Adenocard has not been systematically studied.

Continued on next page

Fujisawa—Cont.

The recommended intravenous doses for adults are as follows:

Initial dose: 6 mg given as a rapid intravenous bolus (administered over a 1–2 second period).

Repeat administration: If the first dose does not result in elimination of the supraventricular tachycardia within 1–2 minutes, 12 mg should be given as a rapid intravenous bolus. This 12 mg dose may be repeated a second time if required.

Doses greater than 12 mg are not recommended.

NOTE: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

HOW SUPPLIED

Adenocard® (adenosine) Injection is supplied as a sterile solution in normal saline.

NDC 0469-0871-02 Product Code 87102 6 mg/2 mL (3 mg/mL) in 2 mL flip-top vials, packaged in 10's

NDC 0469-7234-12 Product Code 723412 6 mg/2 mL (3 mg/mL) in a 2 mL disposable syringe, in a package of five.

NDC 0469-7234-14 Product Code 723414 12 mg/4 mL (3 mg/mL) in a 5 mL disposable syringe, in a package of five.

Store at controlled room temperature 15°–30°C (59°–86°F).

DO NOT REFRIGERATE as crystallization may occur. If crystallization has occurred, dissolve crystals by warming to room temperature. The solution must be clear at the time of use.

Contains no preservatives. Discard unused portion.

CAUTION: Federal law prohibits dispensing without prescription.

Fujisawa USA, Inc., Deerfield, IL 60015
Under license from Medco Research, Inc.
Research Triangle Park, NC 27709
45514E
Revised: November 1994

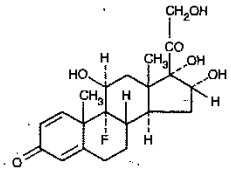
ARISTOCORT®

[a-ris-tō-cort]
(triamcinolone)
TABLETS

DESCRIPTION

ARISTOCORT triamcinolone is a synthetic adrenocorticosteroid. The tablets contain triamcinolone, 9-Fluoro-11β, 16α, 17,21-tetrahydroxypregna-1,4-diene-3,20-dione.

Its structural formula is:



ARISTOCORT Triamcinolone Tablets contain 1, 2, 4, or 8 mg triamcinolone and the following inactive ingredients: Corn Starch, Dibasic Calcium Phosphate, Docusate Sodium, Lactose, Magnesium Stearate, Microcrystalline Cellulose, Red 30, Sodium Benzoate, Sodium Starch Glycolate and Yellow 10.

ACTION

ARISTOCORT is primarily glucocorticoid in action and has potent anti-inflammatory, hormonal and metabolic effects common to cortisone-like drugs. It is essentially devoid of mineralocorticoid activity when administered in therapeutic doses, causing little or no sodium retention, with potassium excretion minimal or absent. The body's immune responses to diverse stimuli are also modified by its action.

INDICATIONS

1. Endocrine Disorders:
   Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the first choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy mineralocorticoid supplementation is of particular importance).
   Congenital adrenal hyperplasia.
   Nonsuppurative thyroiditis.
   Hypercalcemia associated with cancer.
2. Rheumatic Disorders:
   As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:
   Psoriatic arthritis.
   Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy).
   Ankylosing spondylitis.
   Acute and subacute bursitis.
   Acute nonspecific tenosynovitis.
   Acute gouty arthritis.
   Posttraumatic osteoarthritis.
   Synovitis of osteoarthritis.
   Epicondylitis.
3. Collagen Diseases:
   During an exacerbation or as maintenance therapy in selected cases of—
   Systemic lupus erythematosus.
   Acute rheumatic carditis.
4. Dermatologic Diseases:
   Pemphigus.
   Bullous dermatitis herpetiformis.
   Severe erythema multiforme (Stevens-Johnson syndrome).
   Exfoliative dermatitis.
   Mycosis fungoides.
   Severe psoriasis.
   Severe seborrheic dermatitis.
5. Allergic States:
   Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment:
   Seasonal or perennial allergic rhinitis.
   Bronchial asthma.
   Contact dermatitis.
   Atopic dermatitis.
   Serum sickness.
   Drug hypersensitivity reactions.
6. Ophthalmic Diseases:
   Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as—
   Allergic conjunctivitis.
   Keratitis.
   Allergic corneal marginal ulcers.
   Herpes zoster ophthalmicus.
   Iritis and iridocyclitis.
   Chorioretinitis.
   Anterior segment inflammation.
   Diffuse posterior uveitis and choroiditis.
   Optic neuritis.
   Sympathetic ophthalmia.
7. Respiratory Diseases:
   Symptomatic sarcoidosis.
   Loeffler's syndrome not manageable by other means.
   Berylliosis.
   Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy.
   Aspiration pneumonitis.
8. Hematologic Disorders:
   Idiopathic thrombocytopenic purpura in adults.
   Secondary thrombocytopenia in adults.
   Acquired (autoimmune) hemolytic anemia.
   Erythroblastopenia (RBC anemia).
   Congenital (erythroid) hypoplastic anemia.
9. Neoplastic Diseases:
   For palliative management of:
   Leukemias and lymphomas in adults.
   Acute leukemia of childhood.
10. Edematous States:
    To induce a diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus.
11. Gastrointestinal Diseases:
    To tide the patient over a critical period of the disease in:
    Ulcerative colitis.
    Regional enteritis.
12. Nervous System:
    Acute exacerbations of multiple sclerosis.
13. Miscellaneous:
    Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy.
    Trichinosis with neurologic or myocardial involvement.

CONTRAINDICATIONS

Systemic fungal infections.
Sensitivity to the drug or any of its components.

WARNINGS

In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation is indicated.

Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Usage in Pregnancy: Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy, nursing mothers or women of childbearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with ARISTOCORT triamcinolone except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

While on Corticosteroid Therapy Patients Should Not Be Vaccinated Against Smallpox. Other Immunization Procedures Should Not Be Undertaken in Patients Who Are on Corticosteroids, Especially on High Doses, Because of Possible Hazards of Neurological Complications and Lack of Antibody Response.

The use of triamcinolone in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in nonimmune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

PRECAUTIONS

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted.

Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

There is an enhanced effect of corticosteroids on patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

The lowest possible dose of corticosteroids should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction should be gradual.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Steroids should be used with caution in nonspecific ulcerative colitis if there is a probability of impending perforation, abscess or other pyogenic infection, diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis they do not show that they affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. (See DOSAGE AND ADMINISTRATION.)

Since complications of treatment with glucocorticoid are dependent on the size of the dose and the duration of treatment a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

Information for Patients

Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and should also be advised that if they are exposed, medical advice should be sought without delay.

Geigy—Cont.

Lioresal®
Lopressor®
Lopressor HCT®
PB2®
PB2-SR®
Tofranil®
Tofranil-PM®
Voltaren®

GenDerm Corporation

600 KNIGHTSBRIDGE PARKWAY
LINCOLNSHIRE, IL 60069

Direct Inquiries to:
Medical Information Department
(708) 634-7373

DOLORAC™ OTC

(capsaicin) cream, 0.25%
TOPICAL ANALGESIC CREAM

PRODUCT OVERVIEW

KEY FACTS

Dolorac is a highly concentrated cream formulation of capsaicin shown to have greater analgesic efficacy and a more rapid onset of action than conventional strengths of capsaicin cream.

MAJOR USES

Dolorac applied twice daily has been shown to be clinically effective in controlling pain from arthritis.

SAFETY INFORMATION

Patients are likely to experience a burning sensation at the site of Dolorac application, but the severity and duration of this effect are similar to those of lower strength capsaicin creams. Inhalation of airborne material from dried cream residue can cause coughing, sneezing or respiratory irritation and should be avoided. Patients should be instructed to wash hands after applying Dolorac. If applying to hands wait at least 30 minutes, then wash hands to avoid spreading cream to contact lenses, eyes, mouth or other sensitive mucous membranes.

PRESCRIBING INFORMATION

DOLORAC™ OTC

(capsaicin) cream, 0.25%
TOPICAL ANALGESIC CREAM

DESCRIPTION

Dolorac contains capsaicin, in an emollient base containing benzyl alcohol, cetyl alcohol, glyceryl monostearate, isopropyl myristate, PEG-100 stearate, purified water, sorbitol solution, and white petrolatum.

ACTION

Although the precise mechanism of action of capsaicin is not fully understood, current evidence suggests that capsaicin renders skin and joints insensitive to pain by depleting and preventing reaccumulation of substance P in peripheral sensory neurons. Substance P is thought to be the principal chemomediator of pain impulses from the periphery to the central nervous system. In addition, substance P has been shown to be released into joint tissues and activate inflammatory mediators involved in the pathogenesis of rheumatoid arthritis.

INDICATIONS

For the temporary relief of pain from arthritis. For use in painful neuralgias, consult a physician.

WARNINGS

FOR EXTERNAL USE ONLY. Avoid contact with eyes and broken (open) or irritated skin. Avoid inhaling airborne material from dried residue. Contact a physician immediately if difficulty breathing or swallowing occurs. Do not bandage tightly. If condition worsens, or does not improve after 7 days, discontinue use of this product and consult your physician. **Keep this and all drugs out of the reach of children.** In case of accidental ingestion, seek professional assistance or contact a Poison Control Center immediately.

DIRECTIONS

For adults and children 12 years of age and older: apply a thin film of Dolorac to affected area 2 times daily. For children under 12 years of age: consult with a physician. Substantial burning initially occurs at the site of application, but generally subsides after several days of use as directed. Application schedules of less than 2 times a day may cause this burning sensation to persist lo... and may not provide optimum pain relief. **Wash hands after applying Dolorac. If applying to hands wait at least 30 minutes, then wash hands.**

HOW SUPPLIED

Dolorac™
1.0 oz (28 g) tube (NDC 52761-571-30)
Store at room temperature 15°–30°C (59°–86°F)
U.S. Patent Nos. 4486450 and 4536404

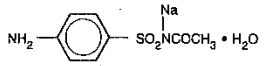
NOVACET® LOTION ℞

[nov'a set]
(Sodium Sulfacetamide 10% and Sulfur 5%)
ACNE MEDICATION

DESCRIPTION

Each gram of Novacet Lotion (sodium sulfacetamide 10% and sulfur 5%) contains 100 mg of sodium sulfacetamide and 50 mg of sulfur in a lotion containing propylene glycol, isopropyl myristate, propylene glycol stearate, cetyl alcohol, PEG-8 stearate, benzyl alcohol, sodium thiosulfate, EDTA disodium, buffering agent, emulsifying wax, and purified water.

Sodium sulfacetamide is a sulfonamide with antibacterial activity while sulfur acts as a keratolytic agent. Chemically sodium sulfacetamide is N'-[(4-aminophenyl) sulfonyl]-acetamide, monosodium salt, monohydrate. The structural formula is:



CLINICAL PHARMACOLOGY

The most widely accepted mechanism of action of sulfonamides is the Woods-Fildes theory which is based on the fact that sulfonamides act as competitive antagonists to para-aminobenzoic acid (PABA), an essential component for bacterial growth. While absorption through intact skin has not been determined, sodium sulfacetamide is readily absorbed from the gastrointestinal tract when taken orally and excreted in the urine, largely unchanged. The biological half-life has variously been reported as 7 to 12.8 hours.

The exact mode of action of sulfur in the treatment of acne is unknown, but it has been reported that it inhibits the growth of **P. acnes** and the formation of free fatty acids.

INDICATIONS

Novacet Lotion is indicated in the topical control of acne vulgaris, acne rosacea and seborrheic dermatitis.

CONTRAINDICATIONS

Novacet Lotion is contraindicated for use by patients having known hypersensitivity to sulfonamides, sulfur or any other component of this preparation. Novacet Lotion is not to be used by patients with kidney disease.

WARNINGS

Although rare, sensitivity to sodium sulfacetamide may occur. Therefore, caution and careful supervision should be observed when prescribing this drug for patients who may be prone to hypersensitivity to topical sulfonamides. Systemic toxic reactions such as agranulocytosis, acute hemolytic anemia, purpura hemorrhagica, drug fever, jaundice, and contact dermatitis indicate hypersensitivity to sulfonamides. Particular caution should be employed if areas of denuded or abraded skin are involved.

PRECAUTIONS

General—If irritation develops, use of the product should be discontinued and appropriate therapy instituted. For external use only. Keep away from eyes. Patients should be carefully observed for possible local irritation or sensitization during long-term therapy. The object of this therapy is to achieve desquamation without irritation, but sodium sulfacetamide and sulfur can cause reddening and scaling of epidermis. These side effects are not unusual in the treatment of acne vulgaris, but patients should be cautioned about the possibility. Keep out of the reach of children.

Carcinogenesis, Mutagenesis and Impairment of Fertility—Long-term studies in animals have not been performed to evaluate carcinogenic potential.

Pregnancy—Category C. Animal reproduction studies have not been conducted with Novacet Lotion. It is also not known whether Novacet Lotion can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

Novacet Lotion should be given to a pregnant woman only if clearly needed.

Nursing Mothers—It is not known whether sodium sulfacetamide is excreted in the human milk following topical use of Novacet Lotion. However, small amounts of orally administered sulfonamides have been reported to be eliminated in human milk. In view of this and because many drugs are excreted in human milk, caution should be exercised when Novacet Lotion is administered to a nursing woman.

Pediatric Use—Safety and effectiveness in children under the age of 12 have not been established.

ADVERSE REACTIONS

Although rare, sodium sulfacetamide may cause local irritation.

DOSAGE AND ADMINISTRATION

Apply a thin film of Novacet Lotion to affected areas 1 to 3 times daily.

HOW SUPPLIED

30 g tubes (NDC 52761-530-30) and 60 g tubes (NDC 52761-530-60)
Store at controlled room temperature 15°–30°C (59°–86°F).

CAUTION

Federal law prohibits dispensing without prescription.

OCCLUSAL®-HP OTC

[ō-kloo'sal]
Salicylic Acid, USP, 17%
Wart Remover
FOR EXTERNAL USE ONLY

DESCRIPTION

Occlusal-HP is a topical wart remover preparation containing 17% salicylic acid, in a polyacrylic vehicle containing ethyl acetate, isopropyl alcohol, butyl acetate, polyvinyl butyral, dibutyl phthalate, acrylates copolymer and nitrocellulose. The pharmacologic activity of Occlusal-HP is generally attributed to the keratolytic action of salicylic acid. The structural formula of salicylic acid is:

CLINICAL PHARMACOLOGY

Although the exact mode of action of salicylic acid in the treatment of warts is not known, its activity appears to be associated with its keratolytic action which results in mechanical removal of epidermal cells infected with wart viruses.

INDICATIONS AND USAGE

Occlusal-HP is indicated for the treatment and removal of common and plantar warts. The common wart is easily recognized by the rough 'cauliflower-like' appearance of the surface. The plantar wart is recognized by its location only on the bottom of the foot, its tenderness, and the interruption of the footprint pattern.

WARNINGS

Occlusal-HP is for external use only. Occlusal-HP is flammable and should be kept away from fire or flame. Keep bottle tightly capped and store at room temperature away from heat when not in use.

Occlusal-HP should not be used on irritated skin, on any area that is infected or reddened, if you are a diabetic or if you have poor blood circulation. Occlusal-HP should not be used on moles, birthmarks, warts with hair growing from them, genital warts, or warts on the face or mucous membranes. Do not permit Occlusal-HP to contact eyes or mucous membranes. If contact with eyes or mucous membranes occurs, immediately flush with water for 15 minutes. Occlusal-HP should not be allowed to contact normal skin surrounding warts. Treatment should be discontinued if excessive irritation occurs. If discomfort persists, see your doctor. Avoid inhaling vapors.

Keep this and all drugs out of the reach of children. In case of accidental ingestion, seek professional assistance or contact a Poison Control Center immediately.

ADVERSE REACTIONS

A localized irritant reaction may occur if Occlusal-HP is applied to the normal skin surrounding the wart. Any irritation may normally be controlled by temporarily discontinuing use of Occlusal-HP, and by applying the medication only to the wart site when treatment is resumed.

DIRECTIONS

Prior to application of Occlusal-HP, may soak wart in warm water for five minutes. Remove any loosened tissue by rubbing with a brush, wash cloth, or emery board. Dry area thoroughly. Using the brush applicator supplied, apply small amount at a time with brush to sufficiently cover each wart. Let dry and repeat application. Be careful not to apply to surrounding skin.

Repeat this procedure once or twice daily as needed (until wart is removed) for up to 12 weeks.

You should see improvement in 1 to 2 weeks. Maximum resolution may be expected after 4 to 6 weeks of daily

TAB 16

From:	Tamar Lusztig
To:	Ashkenazi, Isaac S.; Mowery, Katharine Lester; "bfarnan@farnanlaw.com"; ""mfarnan@farnanlaw.com" (mfarnan@farnanlaw.com)"; Bill Carmody; Justin A. Nelson; Beatrice Franklin
Cc:	Cottrell, Fred; Moyer, Jeffrey L.; Modi, Naveen; Palys, Joseph E.; Murray, Katherine F.; PH-UMASS v. L'Oreal USDC; Dittmann, Eric W.; Tymoczko, Nicholas; Kasaraneni, Karthik; Mowery, Katharine Lester
Subject:	RE: University of Massachusetts v. L"Oreal USA, Inc., C.A. No. 17-868-CFC-SRF
Date:	Friday, February 7, 2020 2:05:00 PM

Isaac,

Depositions following expert claim construction declarations are routine. Nothing you have pointed to in the scheduling order prevents us from taking one. We intend to argue in our reply brief that Dr. Kasting's declaration should be stricken because you have refused to provide him for a deposition, which has prejudiced us and violates basic principles of fairness.

-Tamar

From: Ashkenazi, Isaac S. <isaacashkenazi@paulhastings.com>
Sent: Friday, February 7, 2020 1:10 PM
To: Tamar Lusztig <TLusztig@susmangodfrey.com>; Mowery, Katharine Lester <Mowery@rlf.com>; 'bfarnan@farnanlaw.com' <bfarnan@farnanlaw.com>; ''mfarnan@farnanlaw.com' (mfarnan@farnanlaw.com)' <mfarnan@farnanlaw.com>; Bill Carmody <bcarmody@SusmanGodfrey.com>; Justin A. Nelson <jnelson@SusmanGodfrey.com>; Beatrice Franklin <BFranklin@susmangodfrey.com>
Cc: Cottrell, Fred <Cottrell@RLF.com>; Moyer, Jeffrey L. <moyer@RLF.com>; Modi, Naveen <naveenmodi@paulhastings.com>; Palys, Joseph E. <josephpalys@paulhastings.com>; Murray, Katherine F. <katherinemurray@paulhastings.com>; PH-UMASS v. L'Oreal USDC <PH-UMass-LOreal-USDC@paulhastings.com>; Dittmann, Eric W. <ericdittmann@paulhastings.com>; Tymoczko, Nicholas <nicholastymoczko@paulhastings.com>; Kasaraneni, Karthik <karthikkasaraneni@paulhastings.com>; Mowery, Katharine Lester <Mowery@rlf.com>
Subject: RE: University of Massachusetts v. L'Oreal USA, Inc., C.A. No. 17-868-CFC-SRF

Counsel,

Although the Scheduling Order contemplates expert declarations (such as the one submitted by Dr. Kasting), it does not provide for expert depositions as part of claim construction briefing. (*See, e.g.,* D.I. 46 at 16.) Requiring a deposition before Plaintiffs' next brief, as you propose, would be particularly unworkable given the tight time frames provided for the claim construction briefing schedule. *See, e.g.*, *Pharmacyclics LLC and Janssen Biotech, Inc. v. Alvogen Pine Brook LLC and Natco Pharma Ltd.*, No. 19-434 (Oral Order, Nov. 6, 2019) (denying a party's request to depose an expert declarant in connection with claim construction proceedings). In any event, Dr. Kasting has significant teaching obligations and is unavailable for deposition over the next 10 days, as you demand.

Regards,
Isaac

From: Tamar Lusztig <TLusztig@susmangodfrey.com>
Sent: Thursday, February 6, 2020 8:04 PM
To: Mowery, Katharine Lester <Mowery@rlf.com>; 'bfarnan@farnanlaw.com' <bfarnan@farnanlaw.com>; ''mfarnan@farnanlaw.com' (mfarnan@farnanlaw.com)' <mfarnan@farnanlaw.com>; Bill Carmody <bcarmody@SusmanGodfrey.com>; Justin A. Nelson <jnelson@SusmanGodfrey.com>; Beatrice Franklin <BFranklin@susmangodfrey.com>
Cc: Cottrell, Fred <Cottrell@RLF.com>; Moyer, Jeffrey L. <moyer@RLF.com>; Modi, Naveen <naveenmodi@paulhastings.com>; Palys, Joseph E. <josephpalys@paulhastings.com>; Murray, Katherine F. <katherinemurray@paulhastings.com>; PH-UMASS v. L'Oreal USDC <PH-UMass-LOreal-USDC@paulhastings.com>; Dittmann, Eric W. <ericdittmann@paulhastings.com>; Ashkenazi, Isaac S. <isaacashkenazi@paulhastings.com>; Tymoczko, Nicholas <nicholastymoczko@paulhastings.com>; Kasaraneni, Karthik <karthikkasaraneni@paulhastings.com>; Mowery, Katharine Lester <Mowery@rlf.com>
Subject: [EXT] RE: University of Massachusetts v. L'Oreal USA, Inc., C.A. No. 17-868-CFC-SRF

Counsel, we're still waiting to hear back about this. We are permitted to depose Dr. Kasting for the purposes of our reply brief, and given the short turn-around time, need to hear back about this as soon as possible. Please provide a date (on or before 2/17, so we may incorporate his testimony into our reply brief), or we will ask the court to disregard his testimony on the basis that we were not able to examine him about his opinions.

-Tamar

From: Tamar Lusztig <TLusztig@susmangodfrey.com>
Sent: Wednesday, February 5, 2020 9:22 PM
To: Mowery, Katharine Lester <Mowery@rlf.com>; 'bfarnan@farnanlaw.com' <bfarnan@farnanlaw.com>; ''mfarnan@farnanlaw.com' (mfarnan@farnanlaw.com)' <mfarnan@farnanlaw.com>; Bill Carmody <bcarmody@SusmanGodfrey.com>; Justin A. Nelson <jnelson@SusmanGodfrey.com>; Beatrice Franklin <BFranklin@susmangodfrey.com>
Cc: Cottrell, Fred <Cottrell@RLF.com>; Moyer, Jeffrey L. <moyer@RLF.com>; Modi, Naveen <naveenmodi@paulhastings.com>; Palys, Joseph E. <josephpalys@paulhastings.com>; Murray, Katherine F. <katherinemurray@paulhastings.com>; ph-umass-loreal-usdc@paulhastings.com; Dittmann, Eric W. <ericdittmann@paulhastings.com>; Ashkenazi, Isaac S. <isaacashkenazi@paulhastings.com>; Tymoczko, Nicholas <nicholastymoczko@paulhastings.com>; Kasaraneni, Karthik <karthikkasaraneni@paulhastings.com>; Mowery, Katharine Lester <Mowery@rlf.com>
Subject: Re: University of Massachusetts v. L'Oreal USA, Inc., C.A. No. 17-868-CFC-SRF

Thanks. Could you please let us know when and where Dr. Kasting will be available for us to depose him before our reply brief is due?

From: Mowery, Katharine Lester <Mowery@rlf.com>
Sent: Wednesday, February 5, 2020 6:01:26 PM

To: 'bfarnan@farnanlaw.com' <bfarnan@farnanlaw.com>; ''mfarnan@farnanlaw.com' (mfarnan@farnanlaw.com)' <mfarnan@farnanlaw.com>; Bill Carmody <bcarmody@SusmanGodfrey.com>; Justin A. Nelson <jnelson@SusmanGodfrey.com>; Tamar Lusztig <TLusztig@susmangodfrey.com>; Beatrice Franklin <BFranklin@susmangodfrey.com>
Cc: Cottrell, Fred <Cottrell@RLF.com>; Moyer, Jeffrey L. <moyer@RLF.com>; Modi, Naveen <naveenmodi@paulhastings.com>; Palys, Joseph E. <josephpalys@paulhastings.com>; Murray, Katherine F. <katherinemurray@paulhastings.com>; ph-umass-loreal-usdc@paulhastings.com <ph-umass-loreal-usdc@paulhastings.com>; Dittmann, Eric W. <ericdittmann@paulhastings.com>; Ashkenazi, Isaac S. <isaacashkenazi@paulhastings.com>; Tymoczko, Nicholas <nicholastymoczko@paulhastings.com>; Kasaraneni, Karthik <karthikkasaraneni@paulhastings.com>; Mowery, Katharine Lester <Mowery@rlf.com>
Subject: University of Massachusetts v. L'Oreal USA, Inc., C.A. No. 17-868-CFC-SRF

Counsel,

Attached is a PDF and word version of L'Oréal USA's opening position for the claim construction brief and a PDF of Dr. Kasting's Declaration. For your convenience, PDFs of the non-patent documents referenced in Dr. Kasting's Declaration may be accessed via the FTP site below. As with Plaintiffs' opening position, we will update the appendix citations in both our opening position and Dr. Kasting's Declaration once the appendix has been set.

*****

Secure FTP Information:
Link: https://securetransport-us1.phextranet.com (Chrome recommended)
User Name: **PHST-US18t**
Password: Kh5#vW9*2zX^

Best regards,

Katharine Lester Mowery
Richards, Layton & Finger, P.A.
One Rodney Square
920 North King Street
Wilmington, DE 19801
Direct Dial: 302.651.7623
Email: mowery@rlf.com

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