

EXHIBIT 3



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(54) **METHOD FOR SOFTENING LINES AND RELAXING THE SKIN WITH ADENOSINE AND ADENOSINE ANALOGUES**
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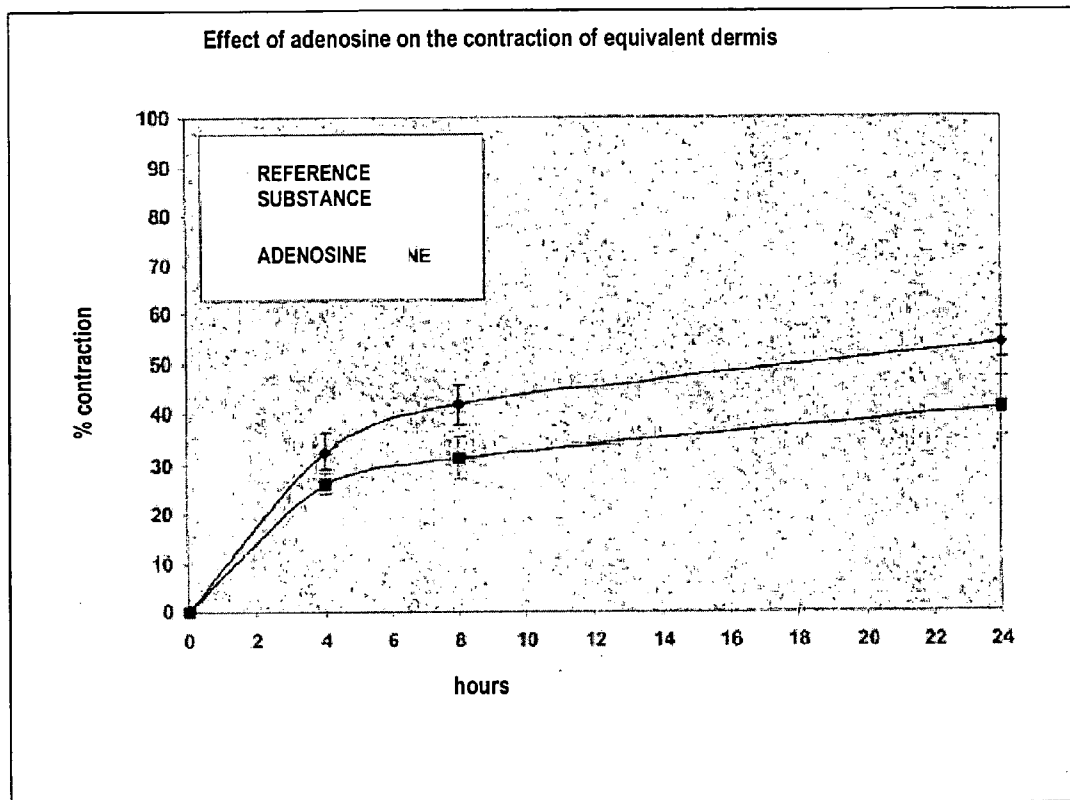
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(57) **ABSTRACT**

The present invention concerns a method for softening lines and/or relaxing the skin with adenosine and/or an analogue of adenosine.



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METHOD FOR SOFTENING LINES AND RELAXING THE SKIN WITH ADENOSINE AND ADENOSINE ANALOGUES

REFERENCE TO PRIOR APPLICATIONS

[0001] This application claims priority to U.S. provisional application 60/432,634 filed Dec. 12, 2002, and to French patent application 0214828 filed Nov. 26, 2002, both incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to a method for softening lines and/or relaxing the skin, and/or relaxing facial features, comprising topical application to the skin of a composition comprising at least one compound selected from the group consisting of adenosine and analogues of adenosine, in a physiologically acceptable medium. Particular uses of the invention composition include the decreasing of wrinkles, the reduction in laugh lines, the reduction in frown lines, etc.

[0003] It also relates to the use of at least one compound as defined above, in a composition suitable for topical application to the skin, as an agent intended to soften lines and/or relax the skin and/or relax facial features.

[0004] Additional advantages and other features of the present invention will be set forth in part in the description that follows and in part will become apparent to those having ordinary skill in the art upon examination of the following or may be learned from the practice of the present invention. The advantages of the present invention may be realized and obtained as particularly pointed out in the appended claims. As will be realized, the present invention is capable of other and different embodiments, and its several details are capable of modifications in various obvious respects, all without departing from the present invention. The description is to be regarded as illustrative in nature, and not as restrictive.

BACKGROUND OF THE INVENTION

[0005] Women and, increasingly, men have a tendency to want to appear young for as long as possible, and so they seek to tone down signs of ageing in the skin, primarily wrinkles and fine lines. Thus, advertisements and the fashion industry promote products intended to keep the skin radiant and wrinkle-free, the trade marks of a young skin, for as long as possible. Furthermore, physical appearance has an effect on psyche and/or morale.

[0006] Until now, wrinkles and fine lines have been treated using cosmetic products containing active ingredients that have an effect on the skin, for example by moisturizing it or improving cell renewal, or by encouraging the synthesis of collagen from which cutaneous tissue is formed, or by preventing its degradation.

[0007] Although such treatments can have an effect on wrinkles and fine lines due to chronological or intrinsic ageing, and on those cells due to photo-ageing, they do not have any effect on expression lines.

[0009] More precisely, they are produced by the stress exerted on the skin by the facial muscles which produce facial expressions. Depending on the shape of the face, the frequency of expressions and the existence of any tics, they can appear in childhood. Age and some environmental factors such as exposure to the sun do not have any effect on their genesis but can make them deeper and render them permanent.

[0010] Expression lines are characterized by the presence of furrows at the periphery of the orifices, namely the nose (nasogenic furrows), the mouth (parabuccal lines and bitterness lines) and the eyes (crows feet) around which the facial muscles are located, and also between the eyebrows (glabellar lines or frown lines) and on the forehead.

[0011] Until now, the only routine means for dealing with expression lines are botulinum toxin, which is injected into the glabellar lines (see J. D. Carruthers et al, *J. Dermatol. Surg. Oncol.*, 1992, 18, pp 17-21) and degradable collagen-based, hyaluronic acid-based or polylactic acid-based implants.

[0012] Further, as an alternative to those medical techniques requiring the services of a skilled practitioner, the Applicant has proposed a number of compounds that can provide a myorelaxing effect when topically applied to the skin and which allow expression lines to be dealt with in a different manner. Examples of such compounds that can be cited are antagonists for receptors associated with calcium channels (French application FR-A-2 793 681), and in particular manganese and its salts (FR-A-2 809 005) and alverine (FR-A-798 590); and agonists for receptors associated with the chlorine channel, including glycine (EP-A-0 704 210) and certain extracts of *Iris pallida* (FR-A-2 746 641).

[0013] However, there is still a need for effective compounds for relaxing the skin with a view to smoothing or toning down expression lines.

BRIEF DESCRIPTION OF THE FIGURE

[0014] FIG. 1 illustrates the contraction over time of an equivalent dermis treated with adenosine.

DETAILED DESCRIPTION OF THE INVENTION

[0015] As noted above, the present invention relates to a method for softening lines and/or relaxing the skin, and/or relaxing facial features, comprising topical application to the skin of a composition comprising at least one compound selected from the group consisting of adenosine and analogues of adenosine, in a physiologically acceptable medium. Particular uses of the invention composition include the decreasing of wrinkles, the reduction in laugh lines, the reduction in frown lines, etc.

[0016] The inventor has surprisingly discovered that adenosine and its analogues can satisfy the above need for effective compounds for relaxing the skin with a view to smoothing or toning down expression lines, relaxing the skin, relaxing facial features, decreasing wrinkles, reducing laugh lines, reducing frown lines, etc. More precisely, the inventor has demonstrated that adenosine and its analogues

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believed that the phenotype of certain fibroblasts located along the tension lines created under the effect of contraction of facial muscles when making a facial expression is progressively modified under the effect of said contractions, endowing said fibroblasts with particular contractile properties. Relaxing those cells would thus combat expression lines. Of course, the inventor is not bound by any theory of operation.

[0017] In the pharmaceutical field, adenosine is administered orally or intravenously as a vasodilator and an anti-arrhythmic.

[0018] In the cosmetics field, it has been suggested, in U.S. Pat. No. 6,423,327 and U.S.-2003/044439, that adenosine or an analogue of adenosine be used in a composition that is topically applied to the skin to improve skin condition and in particular to combat lines, skin laxity, skin dryness and pigmentary blemishes. It was indicated that adenosine increases the size of fibroblasts and increases the synthesis of proteins by fibroblasts.

[0019] In the same field, documents WO-A-01/43704, U.S. Pat. No. 3,978,213, U.S. Pat. No. 5,371,089, German patents DE-195 45 107 and DE-200 22 691 disclose compositions with an anti-ageing effect comprising adenosine or an adenosine analogue.

[0020] None of those documents suggests that adenosine could have a relaxing effect on contractile fibroblasts.

[0021] Thus, the present invention provides a method for softening lines and/or relaxing the skin, comprising topical application to the skin of a composition comprising at least one compound selected from adenosine and an analogue of adenosine, in a physiologically acceptable medium.

[0022] It also concerns the use of at least one compound as defined above in a composition adapted for topical application to the skin as an agent for softening lines and/or relaxing the skin.

[0023] The present invention further provides a method for softening lines and/or relaxing the skin, comprising topical application to the skin of an amount of a composition comprising at least one compound selected from the group consisting of adenosine and analogues of adenosine, in a physiologically acceptable medium, effective to provide a relaxing effect on contractile fibroblasts.

[0024] Adenosine analogues that can be used in accordance with the invention and can be cited as particularly useful herein include agonists of adenosine receptors and compounds increasing intra- or extra-cellular adenosine levels.

[0025] Examples of adenosine analogues include: 2'-deoxyadenosine; 2',3'-isopropoylidene adenosine; toyocamycin; 1-methyladenosine, N-6-methyladenosine; adenosine N-oxide; 6-methylmercaptapurine riboside; 6-chloropurine riboside; 5'-adenosine monophosphate; 5'-adenosine diphosphate and 5'-adenosine triphosphate.

[0026] Other adenosine analogues include agonists of adenosine receptors, including phenylisopropyl adenosine (PIA), 1-methylisoguanosine, N⁶-cyclohexyl adenosine (CHA), N⁶-cyclopentyl adenosine (CPA), 2-chloro-N-6-cy-

enosine, 2-p-(2-carboxyethyl)-phenethyl-amino-5'-N-ethylcarboxamido-adenosine (CGS-21680), N-ethylcarboxamido-adenosine (NECA), 5'-(N-cyclopropyl)-carboxamidoadenosine, DPMA (PD 129,944) and metrifudil.

[0027] Other adenosine analogues include compounds which increase the intracellular concentration of adenosine such as erythro-9-(2-hydroxy-3-nonyl) adenine (EHNA) and iodotubercidin.

[0028] Other adenosine analogues include salts and esters of adenosin.

[0029] Adenosine is preferred for use in the present invention. It is commercially available in the form of a powder from PHARMA WALDHOF.

[0030] The composition in accordance with the invention is preferably intended to be applied to zones of the face or forehead marked with expression lines and/or to persons having expression lines.

[0031] The lines concerned are preferably selected from: crow's feet, nasogenic furrows, inter-eyebrow lines and forehead lines.

[0032] The quantity of adenosine and/or adenosine analogue for use in accordance with the invention is a function of the desired effect and can thus vary widely. To provide an order of magnitude, the composition of the invention can comprise 0.001% to 10% by weight, preferably 0.01% to 1% by weight of adenosine and/or adenosine analogue with respect to the total composition weight.

[0033] The composition of the invention is suitable for topical application to the skin and thus it contains a physiologically acceptable medium, i.e. a medium that is compatible with the skin. Such media can comprise water, C1-C8, preferably C1-C4, alcohols, etc.

[0034] This composition can be fluid to a greater or lesser extent and can have the appearance of a white or coloured cream, a pommade, milk, serum, paste or foam. It can also be in the form of a solid, in particular in the form of a stick. It can be used as a skin care product and/or as a skin makeup product.

[0035] The composition of the invention can be in any form, including any of the galenical forms that are normally used in the cosmetics field; in particular, it can be in the form of an aqueous, possibly gelled solution, a lotion type dispersion which may be a two-phased dispersion, an emulsion obtained by dispersing an oily phase in an aqueous phase (O/W) or vice versa (W/O), a triple emulsion (W/O/W or O/W/O) or an ionic and/or nonionic vesicular type dispersion. Said compositions are prepared using the usual methods. Preferably, a composition in the form of an oil-in-water emulsion is used in the present invention.

[0036] When the composition used in the invention is an emulsion, the proportion of oily phase can be from 5% to 80% by weight, preferably 5% to 50% by weight with respect to the total composition weight. Oils, emulsifying agents and co-emulsifying agents used in the composition in the emulsion form are selected from those conventionally

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