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Date Filed: May 26, 2015

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Novartis AG and LTS Lohmann Therapie-Systeme AG

By:

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NOVEN PHARMACEUTICALS INC.
AND MYLAN PHARMACEUTICALS INC.,
Petitioners

v.

NOVARTIS AG AND LTS LOHMANN THERAPIE-SYSTEME AG,
Patent Owners

Inter Partes Review No. 2014-00549[1]

U.S. Patent 6,316,023

PATENT OWNERS' DEMONSTRATIVE EXHIBITS PURSUANT TO 37 C.F.R. § 42.70(b)

[1] Case IPR2015-00265 has been joined with this proceeding.

UNITED STATES PATENT AND TRADEMARK OFFICE

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AND MYLAN PHARMACEUTICALS INC.,
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Patent Owners

Inter Partes Review Nos. 2014-00549, 2014-00265

U.S. Patent 6,316,023

PATENT OWNERS' DEMONSTRATIVE EXHIBITS FOR ORAL HEARING

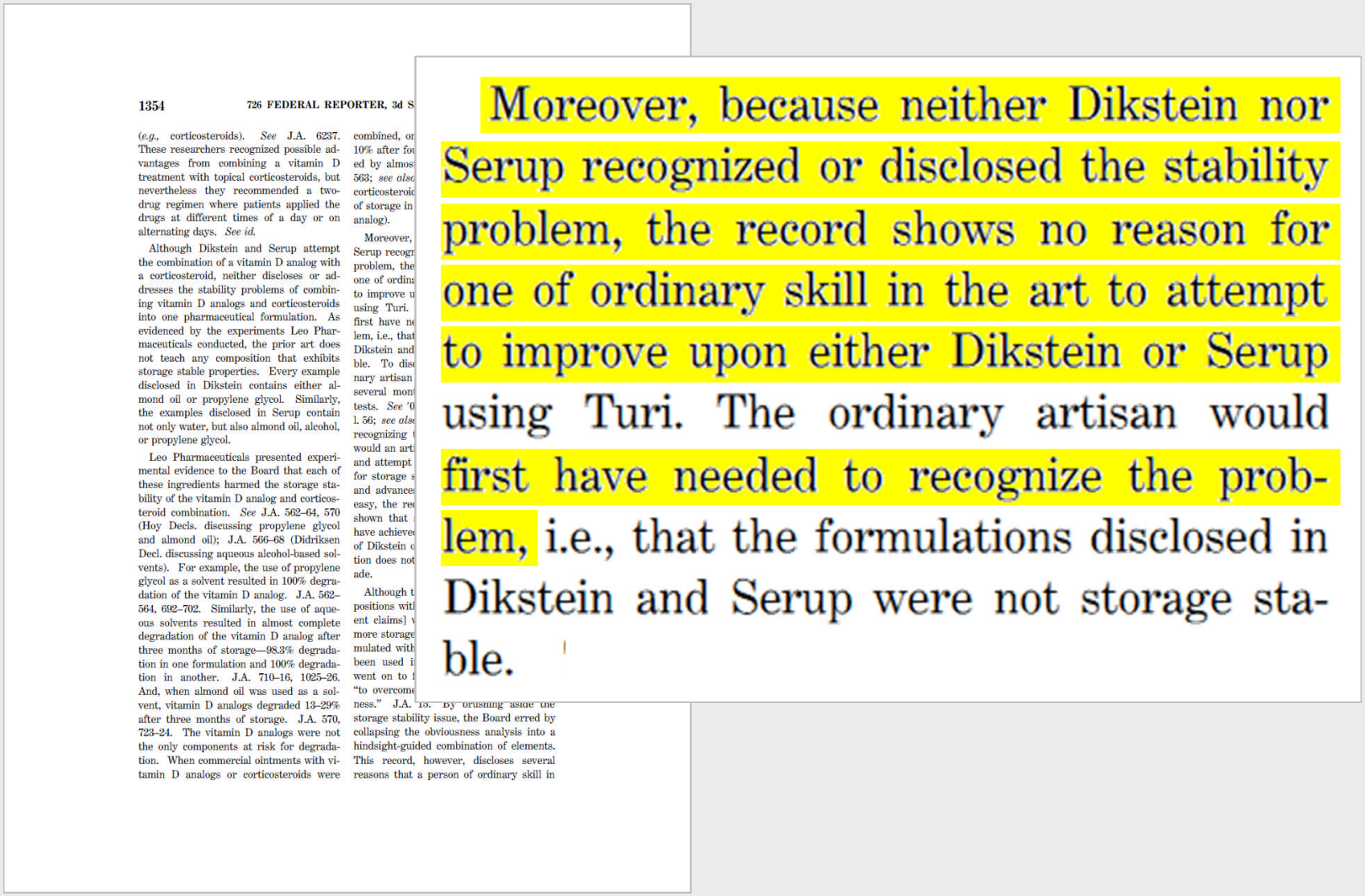
June 2, 2015

Professor Alexander M. Klibanov

- Professor of Chemistry and Bioengineering at M.I.T.
- Elected to the U.S. National Academy of Sciences
- Elected to the U.S. National Academy of Engineering
- Over 45 years as a practicing chemist
- Published over 300 scientific papers
- Given 370 invited lectures

Leo Recognizes That Discovery Of A Problem May Be A Patentable Invention

Paper 25 at 5, 7-8



1354 726 FEDERAL REPORTER, 3d S

(*e.g.*, corticosteroids). *See* J.A. 6237. These researchers recognized possible advantages from combining a vitamin D treatment with topical corticosteroids, but nevertheless they recommended a two-drug regimen where patients applied the drugs at different times of a day or on alternating days. *See id.*

Although Dikstein and Serup attempt the combination of a vitamin D analog with a corticosteroid, neither discloses or addresses the stability problems of combining vitamin D analogs and corticosteroids into one pharmaceutical formulation. As evidenced by the experiments Leo Pharmaceuticals conducted, the prior art does not teach any composition that exhibits storage stable properties. Every example disclosed in Dikstein contains either almond oil or propylene glycol. Similarly, the examples disclosed in Serup contain not only water, but also almond oil, alcohol, or propylene glycol.

Leo Pharmaceuticals presented experimental evidence to the Board that each of these ingredients harmed the storage stability of the vitamin D analog and corticosteroid combination. *See* J.A. 562–64, 570 (Hoy Decls. discussing propylene glycol and almond oil); J.A. 566–68 (Didriksen Decl. discussing aqueous alcohol-based solvents). For example, the use of propylene glycol as a solvent resulted in 100% degradation of the vitamin D analog. J.A. 562–564, 692–702. Similarly, the use of aqueous solvents resulted in almost complete degradation of the vitamin D analog after three months of storage—98.3% degradation in one formulation and 100% degradation in another. J.A. 710–16, 1025–26. And, when almond oil was used as a solvent, vitamin D analogs degraded 13–29% after three months of storage. J.A. 570, 723–24. The vitamin D analogs were not the only components at risk for degradation. When commercial ointments with vitamin D analogs or corticosteroids were combined, or 10% after fo ed by almos 563; *see also* corticosteroid of storage in analog).

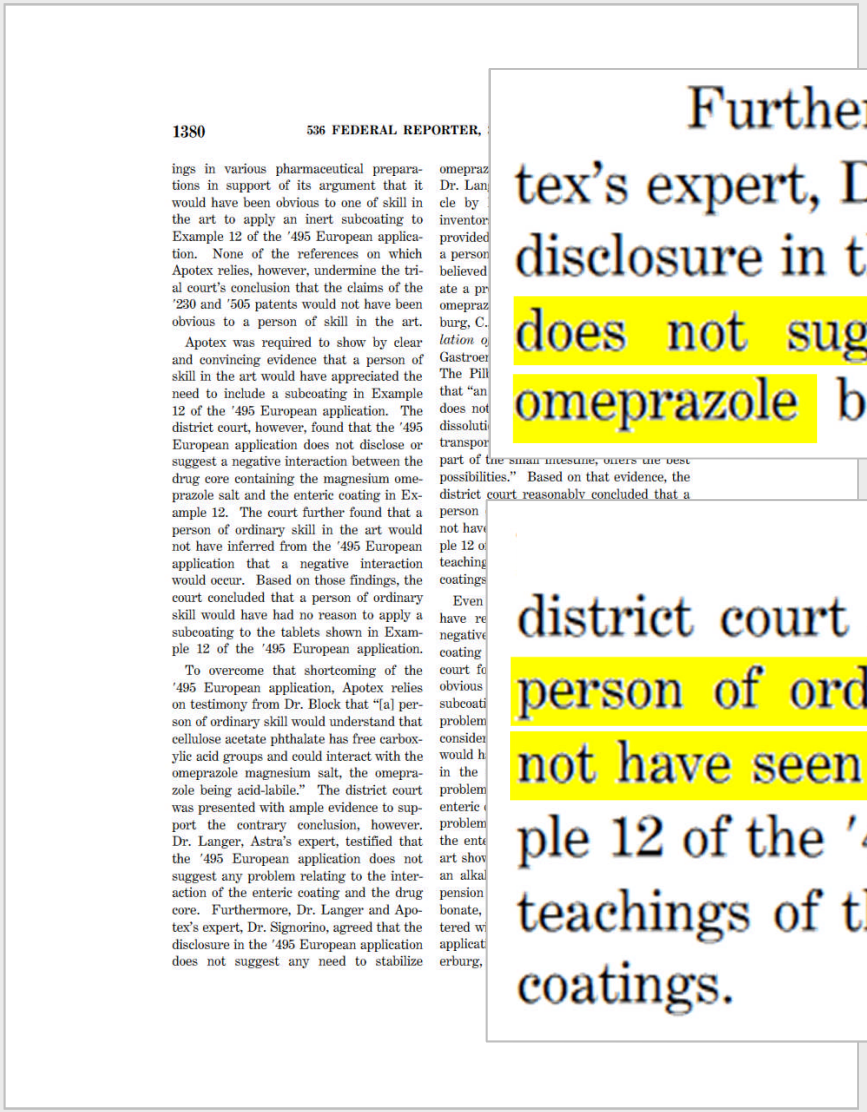
Moreover, Serup recogr problem, the one of ordina to improve u using Turi. first have n lem, i.e., that Dikstein and ble. To dis nary artisan several mon tests. *See* '0 l. 56; *see also* recognizing would an art and attempt for storage and advance easy, the re shown that have achieve of Dikstein tion does not ade.

Although positions wit ent claims] more storage mulated with been used went on to "to overcom ness." J.A. 15. By brushing aside the storage stability issue, the Board erred by collapsing the obviousness analysis into a hindsight-guided combination of elements. This record, however, discloses several reasons that a person of ordinary skill in

Moreover, because neither Dikstein nor Serup recognized or disclosed the stability problem, the record shows no reason for one of ordinary skill in the art to attempt to improve upon either Dikstein or Serup using Turi. The ordinary artisan would first have needed to recognize the problem, i.e., that the formulations disclosed in Dikstein and Serup were not storage stable.

Omeprazole Recognizes That Discovery Of A Problem May Be A Patentable Invention

Paper 25 at 5



1380 536 FEDERAL REPORTER,

ings in various pharmaceutical preparations in support of its argument that it would have been obvious to one of skill in the art to apply an inert subcoating to Example 12 of the '495 European application. None of the references on which Apotex relies, however, undermine the trial court's conclusion that the claims of the '230 and '505 patents would not have been obvious to a person of skill in the art.

Apotex was required to show by clear and convincing evidence that a person of skill in the art would have appreciated the need to include a subcoating in Example 12 of the '495 European application. The district court, however, found that the '495 European application does not disclose or suggest a negative interaction between the drug core containing the magnesium omeprazole salt and the enteric coating in Example 12. The court further found that a person of ordinary skill in the art would not have inferred from the '495 European application that a negative interaction would occur. Based on those findings, the court concluded that a person of ordinary skill would have had no reason to apply a subcoating to the tablets shown in Example 12 of the '495 European application.

To overcome that shortcoming of the '495 European application, Apotex relies on testimony from Dr. Block that "[a] person of ordinary skill would understand that cellulose acetate phthalate has free carboxylic acid groups and could interact with the omeprazole magnesium salt, the omeprazole being acid-labile." The district court was presented with ample evidence to support the contrary conclusion, however. Dr. Langer, Astra's expert, testified that the '495 European application does not suggest any problem relating to the interaction of the enteric coating and the drug core. Furthermore, Dr. Langer and Apotex's expert, Dr. Signorino, agreed that the disclosure in the '495 European application does not suggest any need to stabilize

omeprazole beyond using the salt form.

possibilities." Based on that evidence, the district court reasonably concluded that a person

Furthermore, Dr. Langer and Apotex's expert, Dr. Signorino, agreed that the disclosure in the '495 European application does not suggest any need to stabilize omeprazole beyond using the salt form.

Based on that evidence, the district court reasonably concluded that a person of ordinary skill in the art would not have seen any need to apply to Example 12 of the '495 European application the teachings of the references disclosing subcoatings.

Was Rivastigmine Known Or Reasonably Suggested To Have An Oxidative Degradation Problem?

Paper 25 at 11-13, 14-45

The Art Taught That Rivastigmine Was Chemically Stable

- Enz (Ex. 1002)
- Rosin (Ex. 1008)
- Elmalem (Ex. 1009)
- Enz 1991 (Ex. 2026)
- Weinstock 1994 (Ex. 2027)

A POSA Would Not Reasonably Have Predicted That Rivastigmine Would Oxidatively Degrade Based On Its Structure

- Benzylic C-H bond and an adjacent tertiary amine (nicotine)
- Amines (Sasaki) (Ex. 1005)

A POSA Would Not Have Been Motivated To Combine Rivastigmine With An Antioxidant Unless Required

- Ebert (Ex. 1006)
- Handbook of Pharmaceutical Excipients (Ex. 1003)

Prior Art Reported Greater Chemical Stability Of Rivastigmine And RA7 And/Or Did No Add An Antioxidant

Paper 25 at 14-15, 22, 25-26, 28-29, 36-37

Enz (Ex. 1002)	**Did not add an antioxidant** to rivastigmine
Rosin (Ex. 1008)	**Did not add an antioxidant** to RA_7
	RA_7's greater in vivo activity over physostigmine "may be due to . . . **greater chemical stability** . . . ."
Elmalem (Ex. 1009)	RA_7 has "a **greater chemical stability** and longer duration of action than that of physostigmine . . . ."
Enz 1991 (Ex. 2026)	**Did not add an antioxidant** to rivastigmine
	Rivastigmine "appears to have **greater chemical stability** . . . than does physostigmine."
Weinstock 1994 (Ex. 2027)	**Did not add an antioxidant** to rivastigmine
	"In animals and human subjects [rivastigmine] showed **superior chemical stability** . . . than physostigmine."

Ex. 1002 at 19; Ex. 1008 at 3:37-39, 11:21-29; Ex. 1009 at 1; Ex. 2026 at 2; Ex. 2027 at 2-3; Ex. 2012 ¶¶ 47, 54, 68, 72, 74

Prior Art Reported Greater Chemical Stability Of Rivastigmine And RA7 And/Or Did No Add An Antioxidant

Paper 25 at 14-15, 22, 25-26, 28-29, 36-37

Reference	Did Not Add An Antioxidant To Rivastigmine/RA7	Reported Rivastigmine/RA7 Has Greater Chemical Stability Than Physostigmine
Enz (Ex. 1002)	✓	
Rosin (Ex. 1008)	✓	✓
Elmalem (Ex. 1009)		✓
Enz 1991 (Ex. 2026)	✓	✓
Weinstock 1994 (Ex. 2027)	✓	✓

Ex. 1002 at 19; Ex. 1008 at 3:37-39, 11:21-29; Ex. 1009 at 1; Ex. 2026 at 2; Ex. 2027 at 2-3; Ex. 2012 ¶¶ 47, 54, 68, 72, 74

A POSA Would Not Add An Antioxidant Unless Required

Paper 25 at 10-12

Remington's (Ex. 2017):

Obvious sources of pharmaceutical instability include the incompatibility of various ingredients within a formulation. Numerous examples are described in other sections of this book and the literature is replete with illustrations.

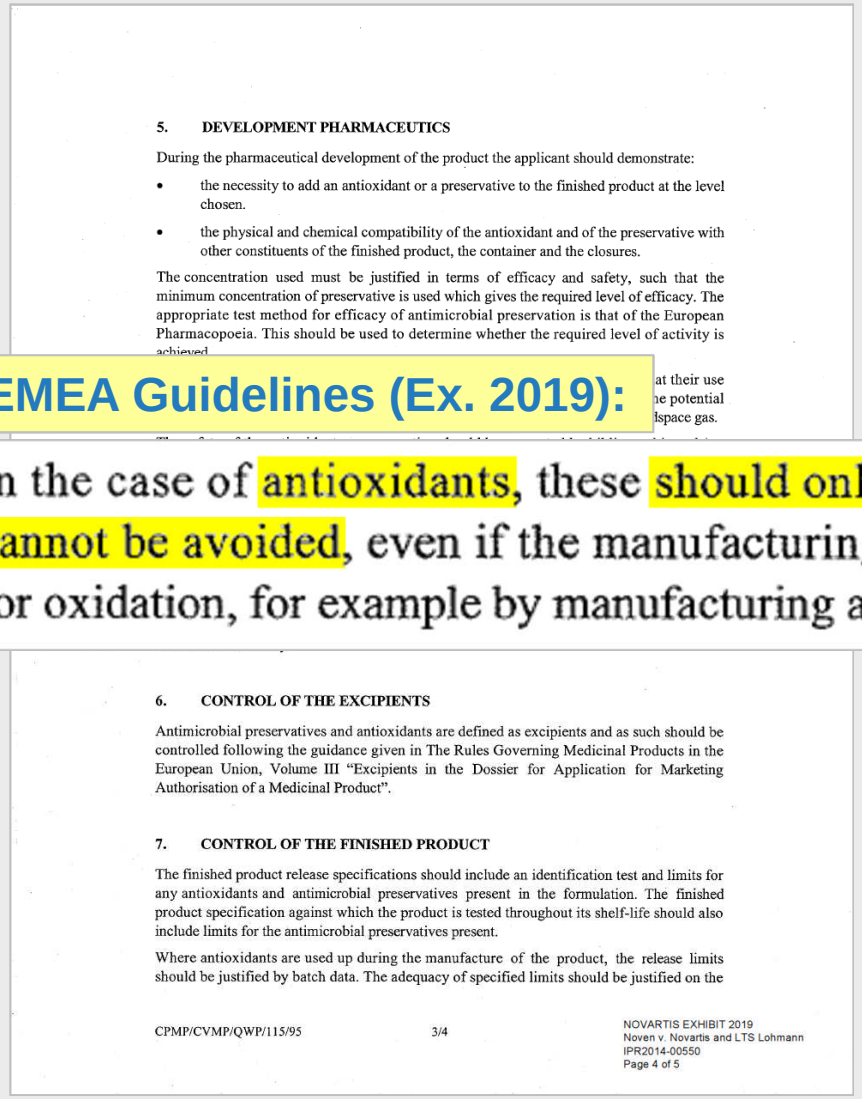
Ansel (Ex. 2020):

The proper use of antioxidants involves their specific application only after appropriate biomedical and pharmaceutical studies. In certain instances other pharmaceutical additives have been found to inactivate a given antioxidant when used in the same formulation. In other cases certain antioxidants have been found to react chemically with the drugs they were intended to stabilize, without a noticeable change in the appearance of the preparation.

Ex. 2017 at 6; Ex. 2020 at 11; Ex. 2012 at ¶¶ 38-39, 41

A POSA Would Not Add An Antioxidant Unless Required

Paper 25 at 11



5. **DEVELOPMENT PHARMACEUTICS**

During the pharmaceutical development of the product the applicant should demonstrate:

- the necessity to add an antioxidant or a preservative to the finished product at the level chosen.
- the physical and chemical compatibility of the antioxidant and of the preservative with other constituents of the finished product, the container and the closures.

The concentration used must be justified in terms of efficacy and safety, such that the minimum concentration of preservative is used which gives the required level of efficacy. The appropriate test method for efficacy of antimicrobial preservation is that of the European Pharmacopoeia. This should be used to determine whether the required level of activity is achieved.

EMEA Guidelines (Ex. 2019):

In the case of antioxidants, these should only be used once it has been shown that their use cannot be avoided, even if the manufacturing process is optimised to minimise the potential for oxidation, for example by manufacturing and filling products under an inert headspace gas.

6. **CONTROL OF THE EXCIPIENTS**

Antimicrobial preservatives and antioxidants are defined as excipients and as such should be controlled following the guidance given in The Rules Governing Medicinal Products in the European Union, Volume III "Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product".

7. **CONTROL OF THE FINISHED PRODUCT**

The finished product release specifications should include an identification test and limits for any antioxidants and antimicrobial preservatives present in the formulation. The finished product specification against which the product is tested throughout its shelf-life should also include limits for the antimicrobial preservatives present.

Where antioxidants are used up during the manufacture of the product, the release limits should be justified by batch data. The adequacy of specified limits should be justified on the

Ex. 2019 at 4; Ex. 2012 at ¶ 40

Petitioners Fail To Consider Elmalem And The Prior Art As A Whole

Paper 25 at 30-31

1060 ESTHER ELMALEM *et al.*

Each of the following drugs, physostigmine, (0.05 and 0.1 mg/kg); RA_6 (0.5 and 1 mg/kg); RA_7 (1 and 2 mg/kg) and RA_{15} (0.25 and 0.5 mg/kg), was injected intravenously (i.v.) with morphine (8 mg/kg) to groups of 6–10 rabbits per drug. Nine other rabbits were given morphine alone with 0.1 ml/kg saline. An additional group of 6 rabbits received morphine

Elmalem (Ex. 1009):

All drugs were made up freshly in sterile saline, which included an equal weight of sodium metabisulphite, to prevent oxidation.

homogenized in phosphate buffer (0.1 M) pH 8, containing 1% Triton. The mixture was centrifuged at 1000 *g* and the supernatant, which contained most of the solubilized enzyme, was used for the determination of the activity of AChE by the method of Ellman, Courtney, Andres and Featherstone (1961). The percentage inhibition of AChE by the drugs was computed by comparison with the pooled mean value for each of the appropriate saline-treated controls.

Estimation of plasma cholinesterase

Blood (0.5 ml) was withdrawn into a heparinized syringe, during the control period and at 5, 15, 30, 60, 90, 120, 150 and 180 min after injection of the AChE inhibitors. The blood was centrifuged at 4°C for 5 min at 1000 *g* and the activity of AChE of the plasma was measured by the method of Ellman *et al.* (1961).

Drugs

The agents tested were RA_6 (*N*-ethyl-3[1-(dimethylamino)ethyl]phenyl carbamate) HCl. RA_7 (*N*-ethyl, *N*-methyl-3[1-(dimethylamino)ethyl] phenyl carbamate HCl. RA_{15} (*N*-propyl-3(1-dimethylamino)-ethyl]-phenyl carbamate HCl. Physostigmine salicylate (Sigma Ltd); Morphine HCl (Teva Pharmaceuticals, Israel). All drugs were made up freshly in sterile saline, which included an equal weight of sodium metabisulphite, to prevent oxidation. All doses are expressed as mg per kg of body weight of the appropriate salt.

RESULTS

Antagonism of the respiratory depressant effect of morphine by antiAChE

Intravenous injection of morphine (8 mg) caused a significant fall in respiration rate of about 50% and a rise in $paCO_2$ of 54% within 15 min, which lasted

n, while the pH fell

at 15–60 min. Mor-

y 70–120 beats per

d caused a small

cholinergic hyperactivity, including salivation, defaecation and slight muscular twitches.

The drug RA_{15} (0.25 mg) significantly reduced the elevation in $paCO_2$ and the fall in respiratory rate after morphine, only at 15 min after injection (Fig. 2). At a dose of 0.5 mg, both the change in $paCO_2$ and in respiration rate, induced by morphine, were significantly antagonised for 3 hr (Fig. 2) but the brady-

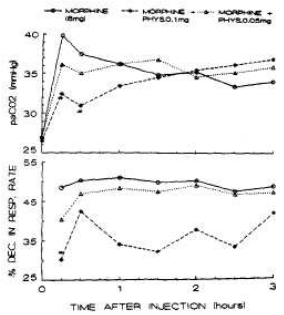


Fig. 1. The influence of physostigmine on the respiratory depressant effect of morphine. Physostigmine was injected intravenously at the same time as morphine. *Significantly different from morphine alone, $P < 0.05$.

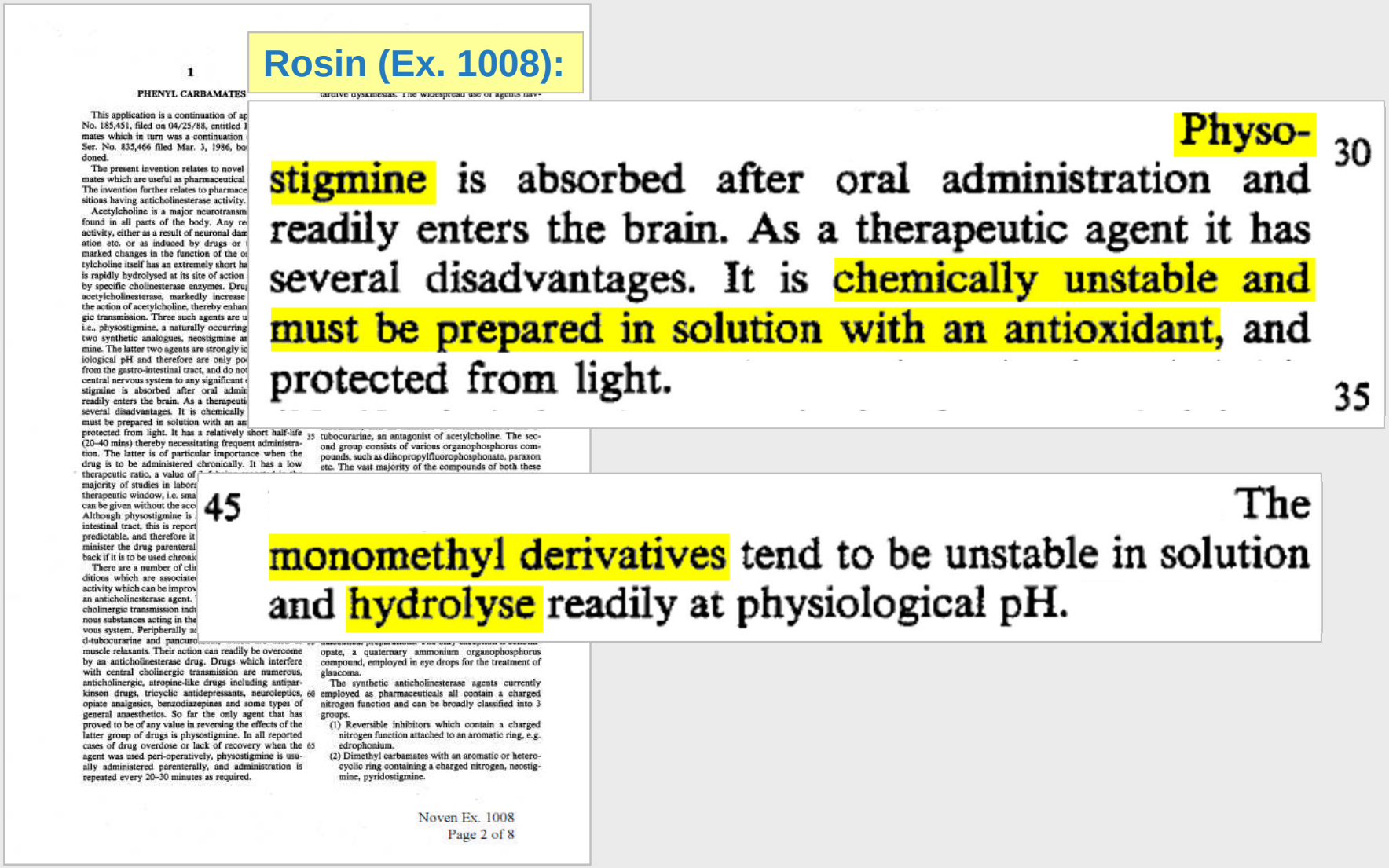
Noven Ex. 1009
Page 2 of 6

Ex. 1009 at 2; Ex. 2012 at ¶¶ 76, 97, 104

Physostigmine Was Known To Undergo Hydrolysis

Paper 25 at 31-32

Rosin (Ex. 1008):



1

PHENYL CARBAMATES

This application is a continuation of ap
No. 185,451, filed on 04/25/88, entitled
mates which in turn was a continuation
Ser. No. 835,466 filed Mar. 3, 1986, bo
doned.

The present invention relates to novel
mates which are useful as pharmaceutical
The invention further relates to pharmace
sitions having anticholinesterase activity.

Acetylcholine is a major neurotransm
found in all parts of the body. Any re
activity, either as a result of neuronal dam
ation etc. or as induced by drugs or
marked changes in the function of the or
tylcholine itself has an extremely short ha
is rapidly hydrolysed at its site of action
by specific cholinesterase enzymes. Dru
acetylcholinesterase, markedly increase
the action of acetylcholine, thereby enhan
gic transmission. Three such agents are u
i.e., physostigmine, a naturally occurring
two synthetic analogues, neostigmine a
mine. The latter two agents are strongly ic
iological pH and therefore are only po
from the gastro-intestinal tract, and do not
central nervous system to any significant
stigmine is absorbed after oral admin
readily enters the brain. As a therapeuti
several disadvantages. It is chemically
must be prepared in solution with an an
protected from light. It has a relatively short half-life
(20–40 mins) thereby necessitating frequent administra-
tion. The latter is of particular importance when the
drug is to be administered chronically. It has a low
therapeutic ratio, a value of
majority of studies in labors
therapeutic window, i.e. sma
can be given without the acc
Although physostigmine is
intestinal tract, this is report
predictable, and therefore it
minister the drug parenteral
back if it is to be used chroni

There are a number of cli
ditions which are associate
activity which can be improv
an anticholinesterase agent.
cholinergic transmission ind
nous substances acting in the
vous system. Peripherally a
d-tubocurarine and pancuro
muscle relaxants. Their action can readily be overcome
by an anticholinesterase drug. Drugs which interfere
with central cholinergic transmission are numerous,
anticholinergic, atropine-like drugs including antipar-
kinson drugs, tricyclic antidepressants, neuroleptics,
opiate analgesics, benzodiazepines and some types of
general anaesthetics. So far the only agent that has
proved to be of any value in reversing the effects of the
latter group of drugs is physostigmine. In all reported
cases of drug overdose or lack of recovery when the
agent was used peri-operatively, physostigmine is usu-
ally administered parenterally, and administration is
repeated every 20–30 minutes as required.

tubocurarine, an antagonist of acetylcholine. The sec-
ond group consists of various organophosphorus com-
pounds, such as diisopropylfluorophosphonate, paraxon
etc. The vast majority of the compounds of both these

opiate, a quaternary ammonium organophosphorus
compound, employed in eye drops for the treatment of
glaucoma.

The synthetic anticholinesterase agents currently
employed as pharmaceuticals all contain a charged
nitrogen function and can be broadly classified into 3
groups.

(1) Reversible inhibitors which contain a charged
nitrogen function attached to an aromatic ring, e.g.
edrophonium.

(2) Dimethyl carbamates with an aromatic or hetero-
cyclic ring containing a charged nitrogen, neostig-
mine, pyridostigmine.

Noven Ex. 1008
Page 2 of 8

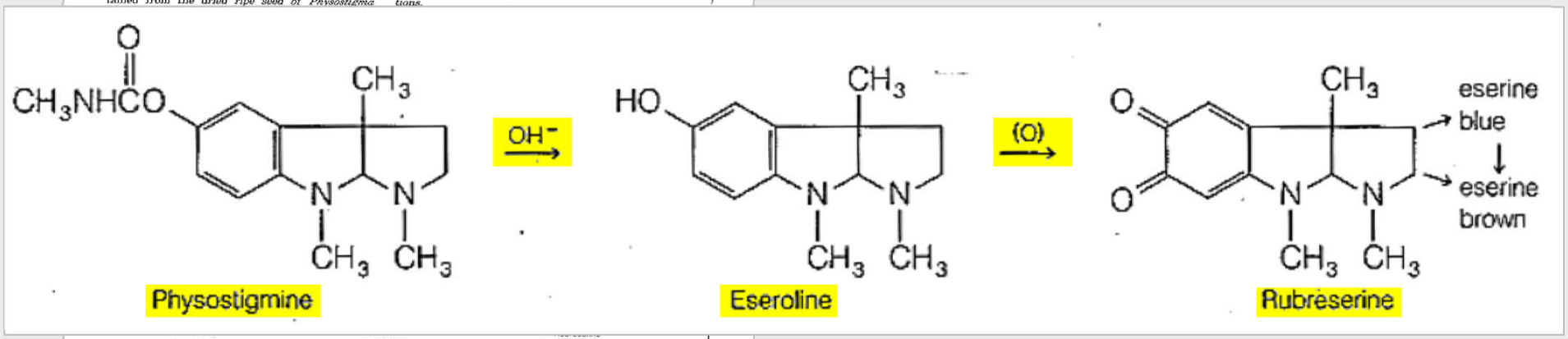
Physo-stigmine is absorbed after oral administration and readily enters the brain. As a therapeutic agent it has several disadvantages. It is chemically unstable and must be prepared in solution with an antioxidant, and protected from light.

The monomethyl derivatives tend to be unstable in solution and hydrolyse readily at physiological pH.

An Antioxidant Prevents The Oxidation Of Physostigmine's Hydrolytic Degradant

Paper 25 at 31-32

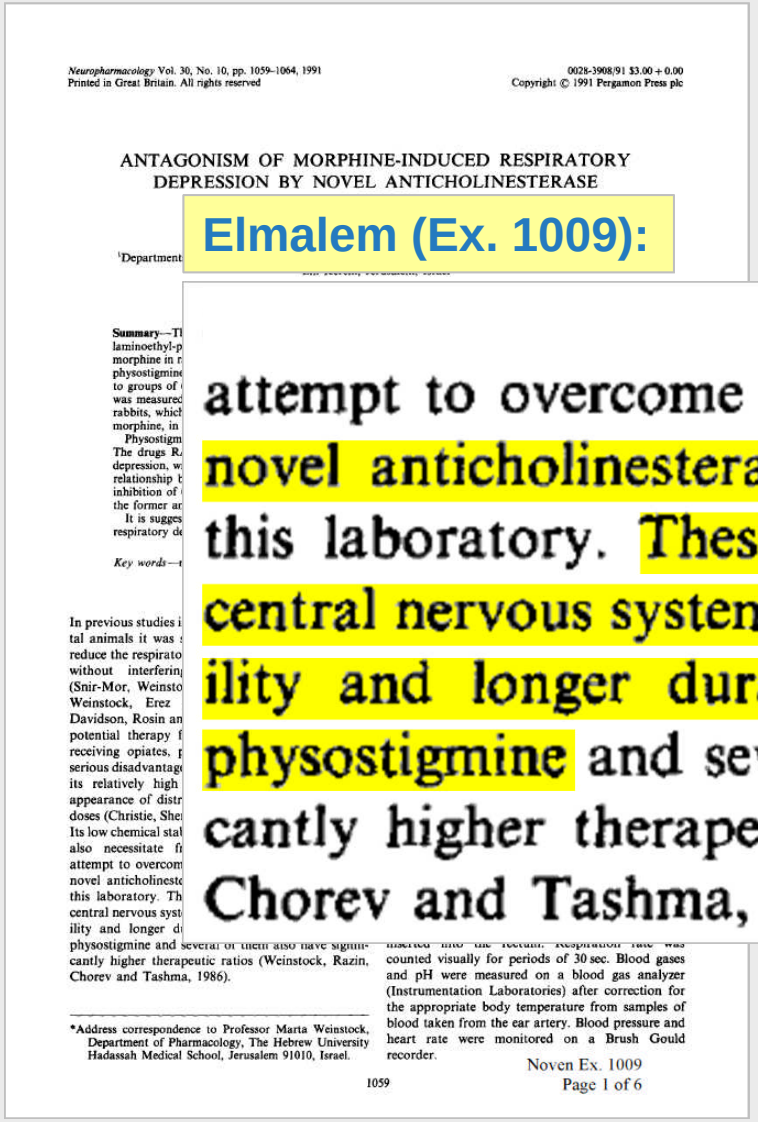
Wilson & Gisvold (Ex. 2038):



The addition of sulfite or ascorbic acid prevents the oxidation of the phenol, eseroline, to rubreserine.

Elmalem States That RA_7 Has Greater Chemical Stability Than Physostigmine

Paper 25 at 28-29



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ANTAGONISM OF MORPHINE-INDUCED RESPIRATORY DEPRESSION BY NOVEL ANTICHOLINESTERASE

Elmalem (Ex. 1009):

In an attempt to overcome these drawbacks, a number of novel anticholinesterase agents were synthesized in this laboratory. These agents readily penetrate the central nervous system, have a greater chemical stability and longer duration of action than that of physostigmine and several of them also have significantly higher therapeutic ratios (Weinstock, Razin, Chorev and Tashma, 1986).

counted visually for periods of 30 sec. Blood gases and pH were measured on a blood gas analyzer (Instrumentation Laboratories) after correction for the appropriate body temperature from samples of blood taken from the ear artery. Blood pressure and heart rate were monitored on a Brush Gould recorder.

Noven Ex. 1009
Page 1 of 6

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Ex. 1009 at 1; Ex. 2012 at ¶¶ 48, 96

Elmalem Quantitatively Compared The Effects Of Different Drugs On Morphine-Induced Respiratory Depression

Neuropharmacology Vol. 30, No. 10, pp. 1059–1064, 1991
Printed in Great Britain.

0028-3908/91 $3.00 + 0.00

ANTAGONISM OF MORPHINE-INDUCED RESPIRATORY DEPRESSION BY NOVEL ANTICHOLINESTERASE AGENTS

MARTA WEINSTOCK[1]*
, School of Pharmacy, Hebrew University,
, Israel

(Accepted 13 May 1991)

Elmalem (Ex. 1009):

Summary—This study compared the effects of 3 novel antiAChE agents (derivatives of dimethylaminoethyl-phenyl carbamate) with that of physostigmine on the respiratory depression induced by morphine in rabbits. Each drug, RA_6, (1 mg i.v., 2 mg s.c.) RA_7 (1 or 2 mg i.v.); RA_{15} (0.25 or 0.5 mg i.v.), physostigmine (0.05 or 0.1 mg i.v.) or saline (1 ml), was injected simultaneously with morphine (8 mg i.v.) to groups of 6–10 rabbits.

Key words—respiratory depression, cholinesterase inhibition in medulla, carbamates, rabbit.

In previous studies in human subjects and experimental animals it was shown that physostigmine could reduce the respiratory depressant effect of morphine, without interfering with the analgesic effect (Snir-Mor, Weinstock, Bahar and Davidson, 1983; Weinstock, Erez and Roll, 1981a; Weinstock, Davidson, Rosin and Schnieden, 1982). However, as potential therapy for concomitant use in patients receiving opiates, physostigmine has a number of serious disadvantages. The most important of these is its relatively high toxicity, which results in the appearance of distressing side effects at therapeutic doses (Christie, Shering, Ferguson and Glenn, 1981). Its low chemical stability and short duration of action also necessitate frequent administration. In an attempt to overcome these drawbacks, a number of novel anticholinesterase agents were synthesized in this laboratory. These agents readily penetrate the central nervous system, have a greater chemical stability and longer duration of action than that of physostigmine and several of them also have significantly higher therapeutic ratios (Weinstock, Razin, Chorev and Tashma, 1986).

*Address correspondence to Professor Marta Weinstock, Department of Pharmacology, The Hebrew University Hadassah Medical School, Jerusalem 91010, Israel.

The purpose of this study was twofold; to compare the abilities of three of these novel anticholinesterase agents with that of physostigmine to antagonize the respiratory depressant effect of morphine and to determine whether there is a correlation between the degree of such antagonism and the amount of inhibition of acetyl-cholinesterase (AChE) in the medulla oblongata.

METHODS

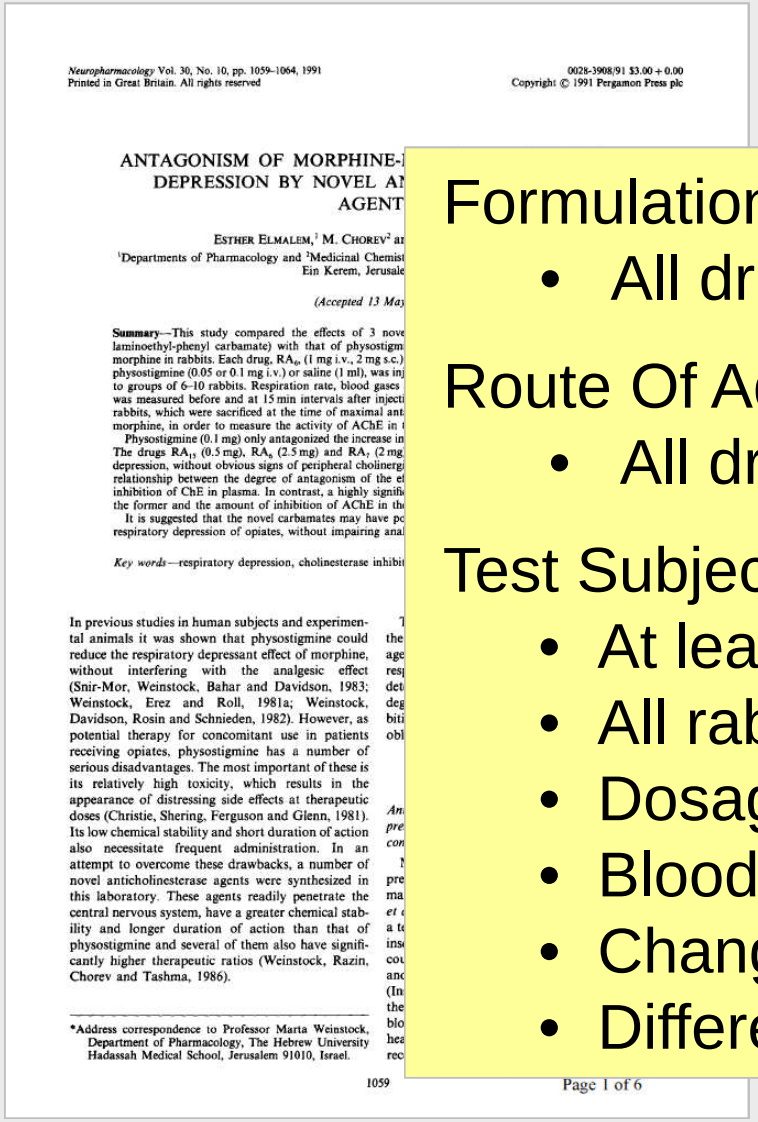
Antagonism of the cardiovascular and respiratory depressant effects of morphine by the anticholinesterase compounds

Male and female rabbits, weighing 2.5–3 kg, were prepared with catheters in the central ear artery and marginal ear vein, as previously described (Weinstock *et al.*, 1981a). Rectal temperature was monitored on a telethermometer with the aid of a thermistor probe inserted into the rectum. Respiration rate was counted visually for periods of 30 sec. Blood gases and pH were measured on a blood gas analyzer (Instrumentation Laboratories) after correction for the appropriate body temperature from samples of blood taken from the ear artery. Blood pressure and heart rate were monitored on a Brush Gould recorder.

Noven Ex. 1009
Page 1 of 6

Elmalem Was A Well-Controlled Study

Paper 25 at 29, 32-33



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ANTAGONISM OF MORPHINE-
DEPRESSION BY NOVEL A
AGENT

ESTHER ELMALEM,[1] M. CHOREV[2] a

[1]Departments of Pharmacology and [2]Medicinal Chemist
Ein Kerem, Jerusale

(Accepted 13 Ma

Summary—This study compared the effects of 3 nove
laminoethyl-phenyl carbamate) with that of physostigm
morphine in rabbits. Each drug, RA_n (1 mg i.v., 2 mg s.c.)
physostigmine (0.05 or 0.1 mg i.v.) or saline (1 ml), was inj
to groups of 6–10 rabbits. Respiration rate, blood gases
was measured before and at 15 min intervals after injecti
rabbits, which were sacrificed at the time of maximal ant
morphine, in order to measure the activity of AChE in
Physostigmine (0.1 mg) only antagonized the increase in
The drugs RA_{13} (0.5 mg), RA_8 (2.5 mg) and RA_7 (2 mg
depression, without obvious signs of peripheral cholinergi
relationship between the degree of antagonism of the el
inhibition of ChE in plasma. In contrast, a highly signifi
the former and the amount of inhibition of AChE in th
It is suggested that the novel carbamates may have po
respiratory depression of opiates, without impairing anal

Key words—respiratory depression, cholinesterase inhibit

In previous studies in human subjects and experimental animals it was shown that physostigmine could reduce the respiratory depressant effect of morphine, without interfering with the analgesic effect (Snir-Mor, Weinstock, Bahar and Davidson, 1983; Weinstock, Erez and Roll, 1981a; Weinstock, Davidson, Rosin and Schnieden, 1982). However, as potential therapy for concomitant use in patients receiving opiates, physostigmine has a number of serious disadvantages. The most important of these is its relatively high toxicity, which results in the appearance of distressing side effects at therapeutic doses (Christie, Shering, Ferguson and Glenn, 1981). Its low chemical stability and short duration of action also necessitate frequent administration. In an attempt to overcome these drawbacks, a number of novel anticholinesterase agents were synthesized in this laboratory. These agents readily penetrate the central nervous system, have a greater chemical stability and longer duration of action than that of physostigmine and several of them also have significantly higher therapeutic ratios (Weinstock, Razin, Chorev and Tashma, 1986).

*Address correspondence to Professor Marta Weinstock, Department of Pharmacology, The Hebrew University Hadassah Medical School, Jerusalem 91010, Israel.

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Page 1 of 6

Formulation Controls:

- All drugs formulated with an antioxidant

Route Of Administration Controls:

- All drugs administered by injection

Test Subject Controls:

- At least 4 rabbits/treatment
- All rabbits similar size (2.5 to 3 kg)
- Dosages calculated per kg body weight
- Blood samples analyzed before treatment
- Changes in body temperature monitored
- Differences in respiration rates normalized

Weinstock 1994 Did Not Suggest That Rivastigmine Requires An Antioxidant In Any Formulation

Paper 25 at 36

Weinstock 1994 (Ex. 2027):

J Neural Transm (1994) [Suppl] 43: 219–225

Pharmacological evaluation of phenyl-carbamates as CNS-selective acetylcholinesterase inhibitors

M. Weinstock[1], M. Razin[1], M. Chorev[2], and A. Enz[3]

esterase. If memory impairments in AD are related to a lack of cholinergic activity in cortical and hippocampal brain areas, SDZ ENA 713 should produce significant symptomatic improvement.

Introduction

Summary. The pharmacological and clinical properties of a novel phenyl carbamate acetylcholinesterase (AChE) inhibitor, SDZ ENA 713 are described. In animals and human subjects this compound showed superior chemical stability, oral bioavailability and a longer duration of action than physostigmine.

Ex. 2027 at 2; Ex. 2012 at ¶¶ 47, 74

Petitioners' Reading Of Elmalem Adds A Variable To The Well-Controlled Study

Paper 25 at 33-34

Elmalem (Ex. 1009):

1060

Each of the following drugs, physostigmine, (0.05 and 0.1 mg/kg); RA_6 (0.5 and 1 mg/kg); RA_7 (1 and 2 mg/kg) and RA_{15} (0.25 and 0.5 mg/kg), was injected intravenously (i.v.) with morphine (8 mg/kg) to groups of 6–10 rabbits per drug. Nine other rabbits were given morphine alone with 0.1 ml/kg saline.

All drugs were made up freshly in sterile saline, which included an equal weight of sodium metabisulphite, to prevent oxidation.

Measurement of anticholine
areas of the brain of rabbit

Rabbits were injected i
physostigmine or each of
doses designated, or with R
4 animals was used for e
stated times after the inj
sacrificed by air embolism
were injected with saline or
sacrificed at the same times
the anticholinesterases, i.e.
each after 15 and 30 min. T
the frontal cortex, hippoca
rapidly dissected out on ice,
homogenized in phosphat
containing 1% Triton. The
at 1000 *g* and the supernata
of the solubilized enzyme, was used for the determination of the activity of AChE by the method of Ellman, Courtney, Andres and Featherstone (1961). The percentage inhibition of AChE by the drugs was computed by comparison with the pooled mean value for each of the appropriate saline-treated controls.

Estimation of plasma cholin

Blood (0.5 ml) was with
syringe, during the control
90, 120, 150 and 180 min af
inhibitors. The blood was
5 min at 1000 *g* and the
plasma was measured by th
(1961).

Drugs

The agents tested were RA
amino)ethyl]phenyl carbamate) HCl. RA_7 (*N*-ethyl, *N*-methyl-3[1-(dimethylamino)ethyl] phenyl carbamate HCl. RA_{15} (*N*-propyl-3(1-dimethylamino)-ethyl]-phenyl carbamate HCl. Physostigmine salicylate (Sigma Ltd); Morphine HCl (Teva Pharmaceuticals, Israel). All drugs were made up freshly in sterile saline, which included an equal weight of sodium metabisulphite, to prevent oxidation. All doses are expressed as mg per kg of body weight of the appropriate salt.

elevation in $paCO_2$ and the fall in respiratory rate after morphine, only at 15 min after injection (Fig. 2). At a dose of 0.5 mg, both the change in $paCO_2$ and in respiration rate, induced by morphine, were significantly antagonised for 3 hr (Fig. 2) but the brady-

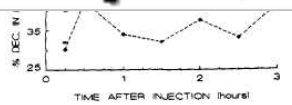


Fig. 1. The influence of physostigmine on the respiratory depressant effect of morphine. Physostigmine was injected intravenously at the same time as morphine. *Significantly different from morphine alone, $P < 0.05$.

Noven Ex. 1009
Page 2 of 6

Ex. 1009 at 2; Ex. 2012 at ¶ 110

Antioxidant Amount Is Not Calculated Based On The Amount Of Drug

Paper 43 at 9-10; *see also* Paper 25 at 33-34

Dr. Kydonieus (Ex. 1049):

Q. And Dr. Kydonieus, I'm asking you when the Handbook of Pharmaceutical Excipients refers to a percent weight by weight, it is a percent -- percentage based on the total weight of the pharmaceutical composition, correct?

A. Yes, in --

MR. COULSON: Objection to form.

A. Excuse me.

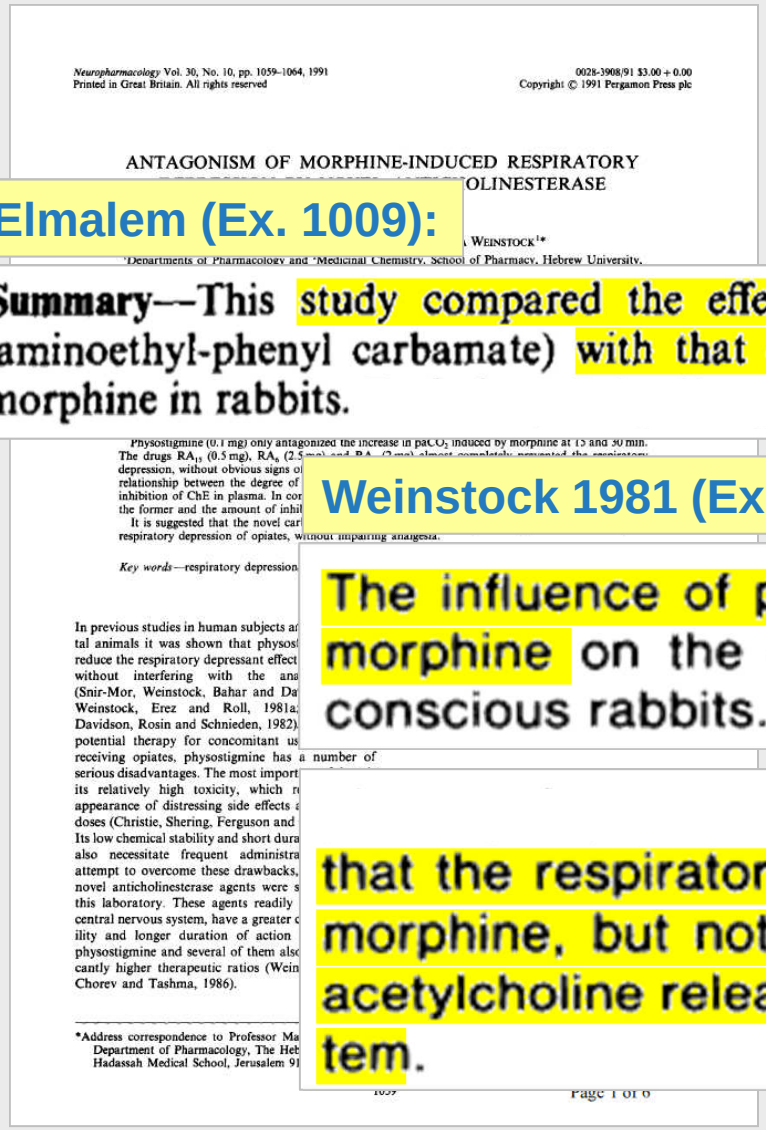
MR. COULSON: Objection. Form.

A. In the -- if you want, I can read it for you, but I believe it is on the total weight.

Ex. 1049 at 59:9-20; *see also* Ex. 2012 at ¶ 110

Elmalem And Weinstock 1981 Studies Were Conducted For Different Purposes

Paper 25 at 35 n.7



Neuropharmacology Vol. 30, No. 10, pp. 1059–1064, 1991
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ANTAGONISM OF MORPHINE-INDUCED RESPIRATORY
OLINESTERASE

WEINSTOCK[1]*

[1]Departments of Pharmacology and [2]Medicinal Chemistry, School of Pharmacy, Hebrew University,

Elmalem (Ex. 1009):

Summary—This study compared the effects of 3 novel antiAChE agents (derivatives of dimethylaminoethyl-phenyl carbamate) with that of physostigmine on the respiratory depression induced by morphine in rabbits.

Physostigmine (0.1 mg) only antagonized the increase in $paCO_2$ induced by morphine at 15 and 30 min. The drugs RA_{15} (0.5 mg), RA_8 (2.5 mg) and RA (2 mg) almost completely prevented the respiratory depression, without obvious signs of relationship between the degree of inhibition of ChE in plasma. In cor the former and the amount of inhi It is suggested that the novel car respiratory depression of opiates, without impairing analgesia.

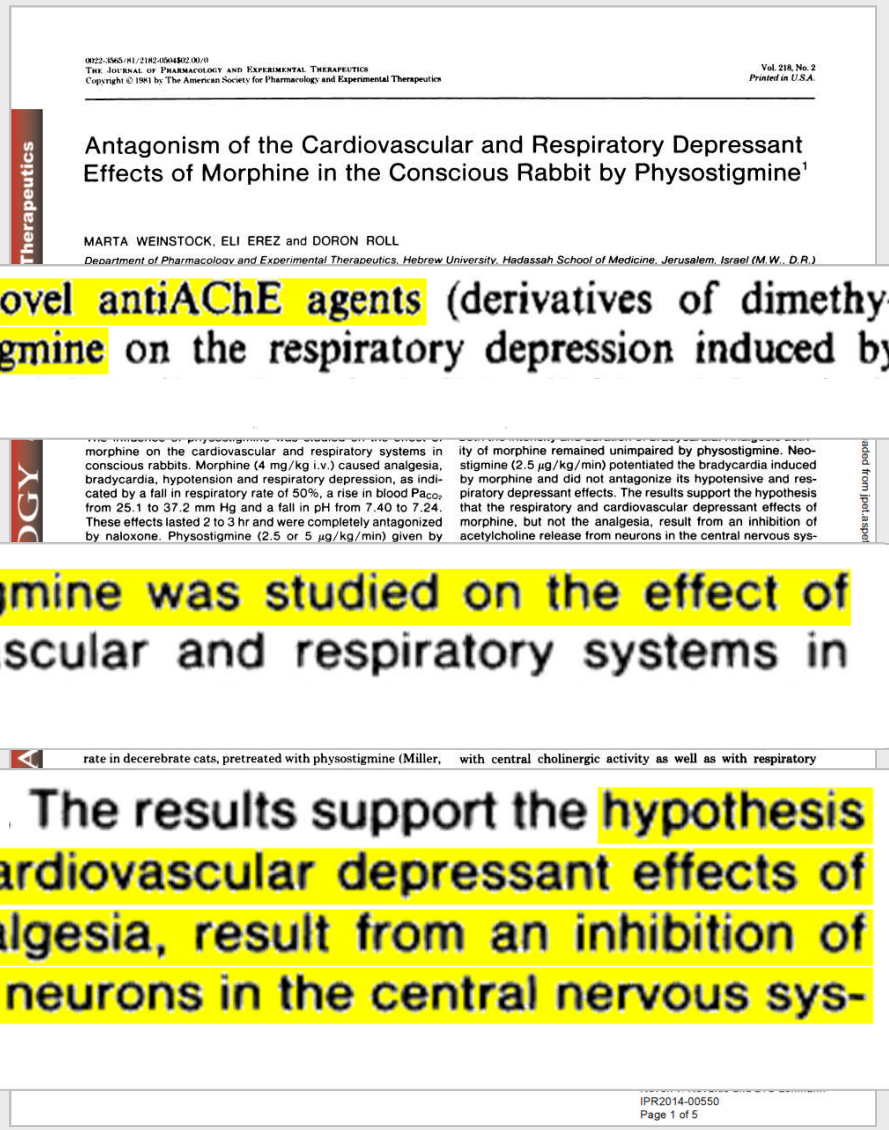
Key words—respiratory depression

In previous studies in human subjects a tal animals it was shown that physos reduce the respiratory depressant effect without interfering with the ana (Snir-Mor, Weinstock, Bahar and Da Weinstock, Erez and Roll, 1981a; Davidson, Rosin and Schnieden, 1982). potential therapy for concomitant us receiving opiates, physostigmine has a number of serious disadvantages. The most import its relatively high toxicity, which r appearance of distressing side effects a doses (Christie, Shering, Ferguson and Its low chemical stability and short dura also necessitate frequent administra attempt to overcome these drawbacks, novel anticholinesterase agents were s this laboratory. These agents readily central nervous system, have a greater c ility and longer duration of action physostigmine and several of them also cantly higher therapeutic ratios (Wein Chorev and Tashma, 1986).

*Address correspondence to Professor Ma Department of Pharmacology, The Heb Hadassah Medical School, Jerusalem 91

1059

Page 1 of 6



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THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
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Vol. 218, No. 2
Printed in U.S.A.

Antagonism of the Cardiovascular and Respiratory Depressant Effects of Morphine in the Conscious Rabbit by Physostigmine[1]

MARTA WEINSTOCK, ELI EREZ and DORON ROLL

Department of Pharmacology and Experimental Therapeutics, Hebrew University, Hadassah School of Medicine, Jerusalem, Israel (M.W., D.R.)

Weinstock 1981 (Ex. 2046):

The influence of physostigmine was studied on the effect of morphine on the cardiovascular and respiratory systems in conscious rabbits.

morphine on the cardiovascular and respiratory systems in conscious rabbits. Morphine (4 mg/kg i.v.) caused analgesia, bradycardia, hypotension and respiratory depression, as indicated by a fall in respiratory rate of 50%, a rise in blood Pa_{CO_2} from 25.1 to 37.2 mm Hg and a fall in pH from 7.40 to 7.24. These effects lasted 2 to 3 hr and were completely antagonized by naloxone. Physostigmine (2.5 or 5 μg/kg/min) given by

ity of morphine remained unimpaired by physostigmine. Neostigmine (2.5 μg/kg/min) potentiated the bradycardia induced by morphine and did not antagonize its hypotensive and respiratory depressant effects. The results support the hypothesis that the respiratory and cardiovascular depressant effects of morphine, but not the analgesia, result from an inhibition of acetylcholine release from neurons in the central nervous sys-

rate in decerebrate cats, pretreated with physostigmine (Miller,

with central cholinergic activity as well as with respiratory

The results support the hypothesis that the respiratory and cardiovascular depressant effects of morphine, but not the analgesia, result from an inhibition of acetylcholine release from neurons in the central nervous system.

IPR2014-00550
Page 1 of 5

Elmalem And Weinstock 1981 Used Different Experimental Designs

Paper 25 at 35 n.7; Paper 43 at 10-11

Elmalem (Ex. 1009):

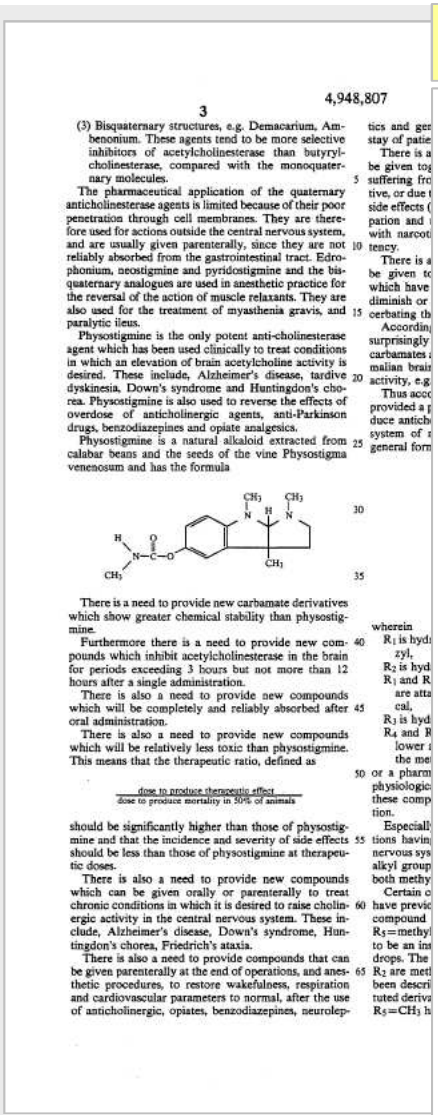
All drugs were made up freshly in sterile saline, which included an equal weight of sodium metabisulphite, to prevent oxidation.

Weinstock 1981 (Ex. 2046):

Morphine and physostigmine were made up freshly for each experiment in sterile saline which included an equal weight of ascorbic acid to prevent oxidation.

Rosin Discloses Millions Of "Compounds Of The Invention"

Paper 25 at 24-25



3 4,948,807

(3) Bisquaternary structures, e.g. Demacarium, Ambenonium. These agents tend to be more selective inhibitors of acetylcholinesterase than butyrylcholinesterase, compared with the monoquaternary molecules.

The pharmaceutical application of the quaternary anticholinesterase agents is limited because of their poor penetration through cell membranes. They are therefore used for actions outside the central nervous system, and are usually given parenterally, since they are not reliably absorbed from the gastrointestinal tract. Edrophonium, neostigmine and pyridostigmine and the bisquaternary analogues are used in anesthetic practice for the reversal of the action of muscle relaxants. They are also used for the treatment of myasthenia gravis, and paralytic ileus.

Physostigmine is the only potent anti-cholinesterase agent which has been used clinically to treat conditions in which an elevation of brain acetylcholine activity is desired. These include, Alzheimer's disease, tardive dyskinesia, Down's syndrome and Huntingdon's chorea. Physostigmine is also used to reverse the effects of overdose of anticholinergic agents, anti-Parkinson drugs, benzodiazepines and opiate analgesics.

Physostigmine is a natural alkaloid extracted from calabar beans and the seeds of the vine Physostigma venenosum and has the formula

There is a need to provide new carbamate derivatives which show greater chemical stability than physostigmine.

Furthermore there is a need to provide new compounds which inhibit acetylcholinesterase in the brain for periods exceeding 3 hours but not more than 12 hours after a single administration.

There is also a need to provide new compounds which will be completely and reliably absorbed after oral administration.

There is also a need to provide new compounds which will be relatively less toxic than physostigmine. This means that the therapeutic ratio, defined as

$$\frac{\text{dose to produce therapeutic effect}}{\text{dose to produce mortality in 50\% of animals}}$$

should be significantly higher than those of physostigmine and that the incidence and severity of side effects should be less than those of physostigmine at therapeutic doses.

There is also a need to provide new compounds which can be given orally or parenterally to treat chronic conditions in which it is desired to raise cholinergic activity in the central nervous system. These include, Alzheimer's disease, Down's syndrome, Huntingdon's chorea, Friedrich's ataxia.

There is also a need to provide compounds that can be given parenterally at the end of operations, and anesthetic procedures, to restore wakefulness, respiration and cardiovascular parameters to normal, after the use of anticholinergic, opiates, benzodiazepines, neurolep-

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R_2 are met
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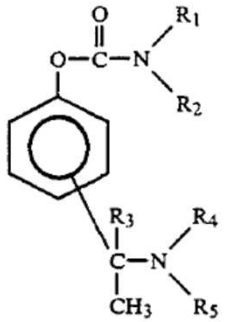
tuted deriva
R_5=CH_3 h

Rosin (Ex. 1008):

Thus according to the present invention there is now provided a pharmaceutical composition adapted to produce anticholinesterase activity in the central nervous system of mammals comprising a compound of the general formula I



I

wherein

R_1 is hydrogen, lower alkyl, cyclohexyl, allyl or benzyl,

R_2 is hydrogen, methyl, ethyl or propyl, or

R_1 and R_2 together with the nitrogen to which they are attached form a morpholino or piperidino radical,

R_3 is hydrogen or lower alkyl,

R_4 and R_5 are the same dr different and each is a lower alkyl, and the dialkylaminoalkyl group is in the meta, ortho or para position,

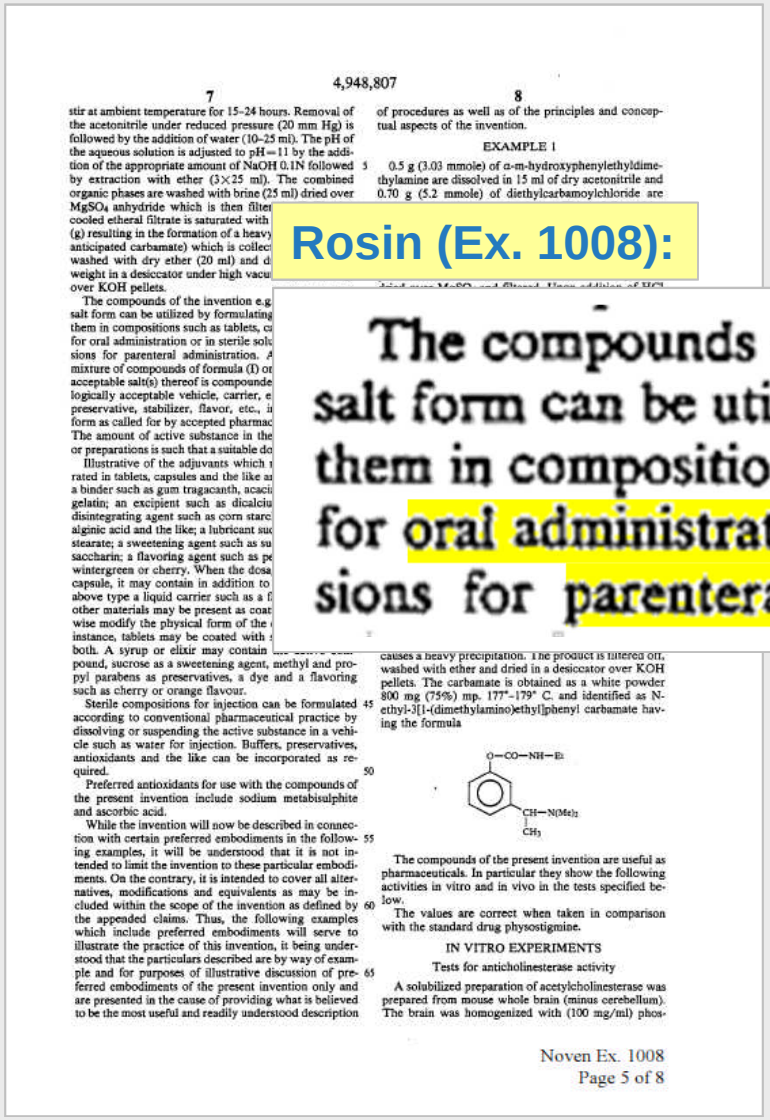
or a pharmacologically acceptable salt thereof and a physiologically acceptable carrier therefor. Hereinafter these compounds are called compounds of the invention.

Hereinafter these compounds are called compounds of the invention.

Ex. 1008 at 4:21-53; Ex. 2012 at ¶ 63

Rosin Discloses Compositions For Oral And Parenteral Administration

Paper 25 at 25



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stir at ambient temperature for 15-24 hours. Removal of the acetonitrile under reduced pressure (20 mm Hg) is followed by the addition of water (10-25 ml). The pH of the aqueous solution is adjusted to pH=11 by the addition of the appropriate amount of NaOH 0.1N followed by extraction with ether (3×25 ml). The combined organic phases are washed with brine (25 ml) dried over $MgSO_4$ anhydride which is then filter cooled etheral filtrate is saturated with (g) resulting in the formation of a heavy anticipated carbamate) which is collec washed with dry ether (20 ml) and d weight in a desiccator under high vacu over KOH pellets.

The compounds of the invention e.g salt form can be utilized by formulating them in compositions such as tablets, c for oral administration or in sterile sol sions for parenteral administration. A mixture of compounds of formula (I) o acceptable salt(s) thereof is compounde logically acceptable vehicle, carrier, e preservative, stabilizer, flavor, etc., i form as called for by accepted pharmac The amount of active substance in the or preparations is such that a suitable do

Illustrative of the adjuvants which rated in tablets, capsules and the like a a binder such as gum tragacanth, acaci gelatin; an excipient such as dicalciu disintegrating agent such as corn starc alginic acid and the like; a lubricant suc stearate; a sweetening agent such as su saccharin; a flavoring agent such as pe wintergreen or cherry. When the dosa capsule, it may contain in addition to above type a liquid carrier such as a f other materials may be present as coat wise modify the physical form of the instance, tablets may be coated with both. A syrup or elixir may contain pound, sucrose as a sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange flavour.

Sterile compositions for injection can be formulated according to conventional pharmaceutical practice by dissolving or suspending the active substance in a vehicle such as water for injection. Buffers, preservatives, antioxidants and the like can be incorporated as required.

Preferred antioxidants for use with the compounds of the present invention include sodium metabisulphite and ascorbic acid.

While the invention will now be described in connection with certain preferred embodiments in the following examples, it will be understood that it is not intended to limit the invention to these particular embodiments. On the contrary, it is intended to cover all alternatives, modifications and equivalents as may be included within the scope of the invention as defined by the appended claims. Thus, the following examples which include preferred embodiments will serve to illustrate the practice of this invention, it being understood that the particulars described are by way of example and for purposes of illustrative discussion of preferred embodiments of the present invention only and are presented in the cause of providing what is believed to be the most useful and readily understood description of procedures as well as of the principles and conceptual aspects of the invention.

EXAMPLE 1

0.5 g (3.03 mmole) of α-m-hydroxyphenylethyldimethylamine are dissolved in 15 ml of dry acetonitrile and 0.70 g (5.2 mmole) of diethylcarbamoylchloride are

causes a heavy precipitation. The product is filtered off, washed with ether and dried in a desiccator over KOH pellets. The carbamate is obtained as a white powder 800 mg (75%) mp. 177°-179° C. and identified as N-ethyl-3[1-(dimethylamino)ethyl]phenyl carbamate having the formula

The compounds of the present invention are useful as pharmaceuticals. In particular they show the following activities in vitro and in vivo in the tests specified below.

The values are correct when taken in comparison with the standard drug physostigmine.

IN VITRO EXPERIMENTS

Tests for anticholinesterase activity

A solubilized preparation of acetylcholinesterase was prepared from mouse whole brain (minus cerebellum). The brain was homogenized with (100 mg/ml) phos-

Noven Ex. 1008
Page 5 of 8

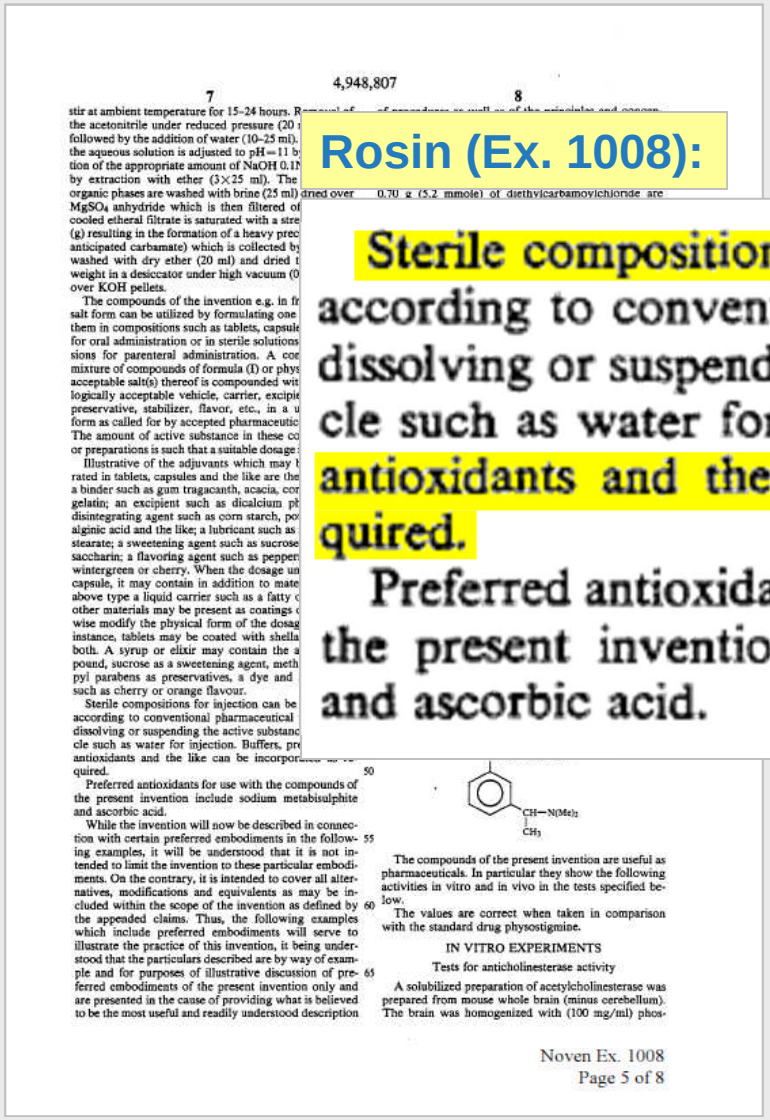
Rosin (Ex. 1008):

The compounds of the invention e.g. in free form or salt form can be utilized by formulating one or more of them in compositions such as tablets, capsules or elixirs for oral administration or in sterile solutions or suspensions for parenteral administration.

Ex. 1008 at 7:15-19; Ex. 2012 at ¶ 69

Rosin Discloses Use Of Antioxidants In Sterile Compositions For Injection Only As Required

Paper 25 at 25-26



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Rosin (Ex. 1008):

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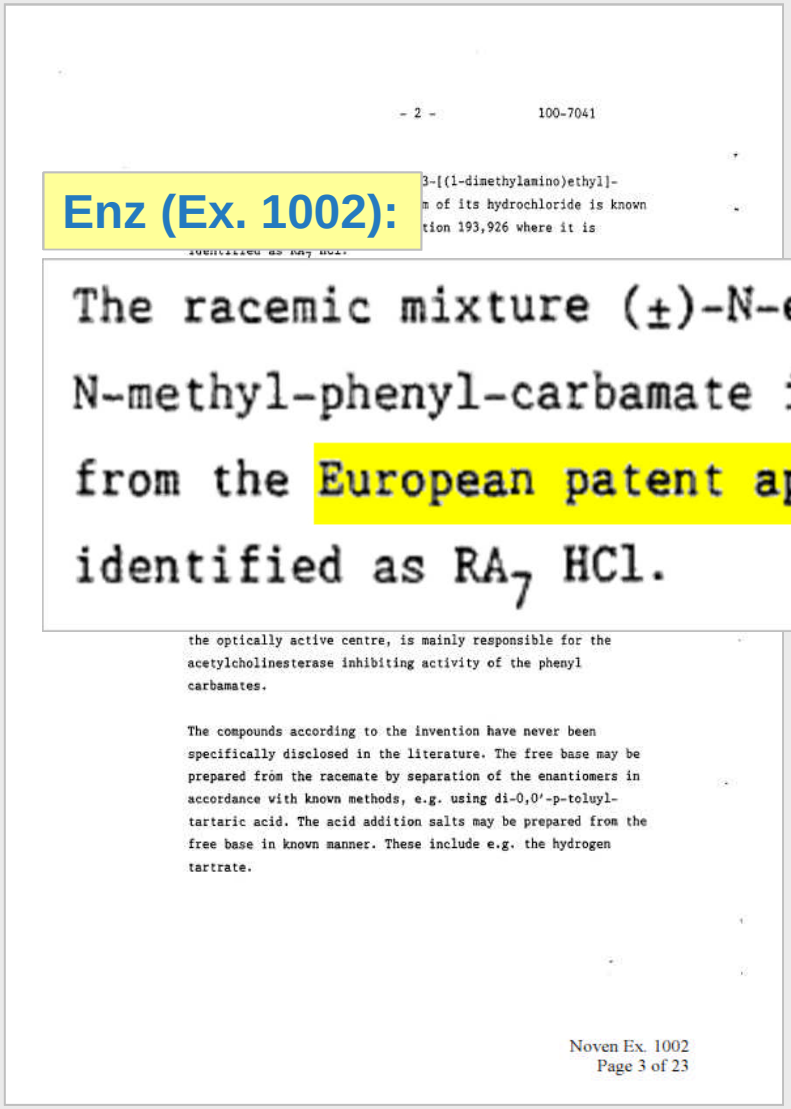
Preferred antioxidants for use with the compounds of the present invention include sodium metabisulphite and ascorbic acid.

Noven Ex. 1008
Page 5 of 8

Ex. 1008 at 7:45-53; Ex. 2012 at ¶¶ 64-67

Enz Confirms That Rosin Does Not Suggest An Oxidative Degradation Problem For RA_7

Paper 25 at 26-27



- 2 - 100-7041

3-[(1-dimethylamino)ethyl]-
m of its hydrochloride is known
tion 193,926 where it is

identified as RA_7 HCl.

the optically active centre, is mainly responsible for the acetylcholinesterase inhibiting activity of the phenyl carbamates.

The compounds according to the invention have never been specifically disclosed in the literature. The free base may be prepared from the racemate by separation of the enantiomers in accordance with known methods, e.g. using di-O,O'-p-toluyl-tartaric acid. The acid addition salts may be prepared from the free base in known manner. These include e.g. the hydrogen tartrate.

Noven Ex. 1002
Page 3 of 23

Enz (Ex. 1002):

The racemic mixture (±)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methyl-phenyl-carbamate in form of its hydrochloride is known from the European patent application 193,926 where it is identified as RA_7 HCl.

Rosin Discloses Millions Of "Compounds Of The Invention"

Paper 25 at 24-25

(3) Bisquaternary structures, e.g. Demacarium, Ambenonium. These agents tend to be more selective inhibitors of acetylcholinesterase than butyrylcholinesterase, compared with the monoquaternary molecules.

The pharmaceutical application of the quaternary anticholinesterase agents is limited because of their poor penetration through cell membranes. They are therefore used for actions outside the central nervous system, and are usually given parenterally, since they are not reliably absorbed from the gastrointestinal tract. Edrophonium, neostigmine and pyridostigmine and the bisquaternary analogues are used in anesthetic practice for the reversal of the action of muscle relaxants. They are also used for the treatment of myasthenia gravis, and paralytic ileus.

Physostigmine is the only potent anti-cholinesterase agent which has been used clinically to treat conditions in which an elevation of brain acetylcholine activity is desired. These include, Alzheimer's disease, tardive dyskinesia, Down's syndrome and Huntingdon's chorea. Physostigmine is also used to reverse the effects of overdose of anticholinergic agents, anti-Parkinson drugs, benzodiazepines and opiate analgesics.

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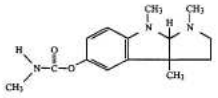

There is a need to provide new carbamate derivatives which show greater chemical stability than physostigmine.

Furthermore there is a need to provide new compounds which inhibit acetylcholinesterase in the brain for periods exceeding 3 hours but not more than 12 hours after a single administration.

There is also a need to provide new compounds which will be completely and reliably absorbed after oral administration.

There is also a need to provide new compounds which will be relatively less toxic than physostigmine. This means that the therapeutic ratio, defined as

$$\frac{\text{dose to produce therapeutic effect}}{\text{dose to produce mortality in 50\% of animals}}$$

should be significantly higher than those of physostigmine and that the incidence and severity of side effects should be less than those of physostigmine at therapeutic doses.

There is also a need to provide new compounds which can be given orally or parenterally to treat chronic conditions in which it is desired to raise cholinergic activity in the central nervous system. These include, Alzheimer's disease, Down's syndrome, Huntingdon's chorea, Friedrich's ataxia.

There is also a need to provide compounds that can be given parenterally at the end of operations, and anesthetic procedures, to restore wakefulness, respiration and cardiovascular parameters to normal, after the use of anticholinergic, opiates, benzodiazepines, neurolep-

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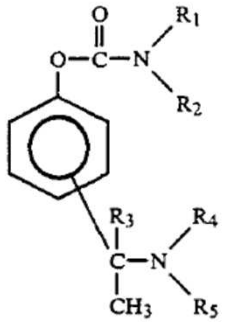
Thus according to the present invention there is now provided a pharmaceutical composition adapted to produce anticholinesterase activity in the central nervous system of mammals comprising a compound of the general formula I



I

wherein

R_1 is hydrogen, lower alkyl, cyclohexyl, allyl or benzyl,

R_2 is hydrogen, methyl, ethyl or propyl, or

R_1 and R_2 together with the nitrogen to which they are attached form a morpholino or piperidino radical,

R_3 is hydrogen or lower alkyl,

R_4 and R_5 are the same dr different and each is a lower alkyl, and the dialkylaminoalkyl group is in the meta, ortho or para position,

or a pharmacologically acceptable salt thereof and a physiologically acceptable carrier therefor. Hereinafter these compounds are called compounds of the invention.

Hereinafter these compounds are called compounds of the invention.

Rosin (Ex. 1008):

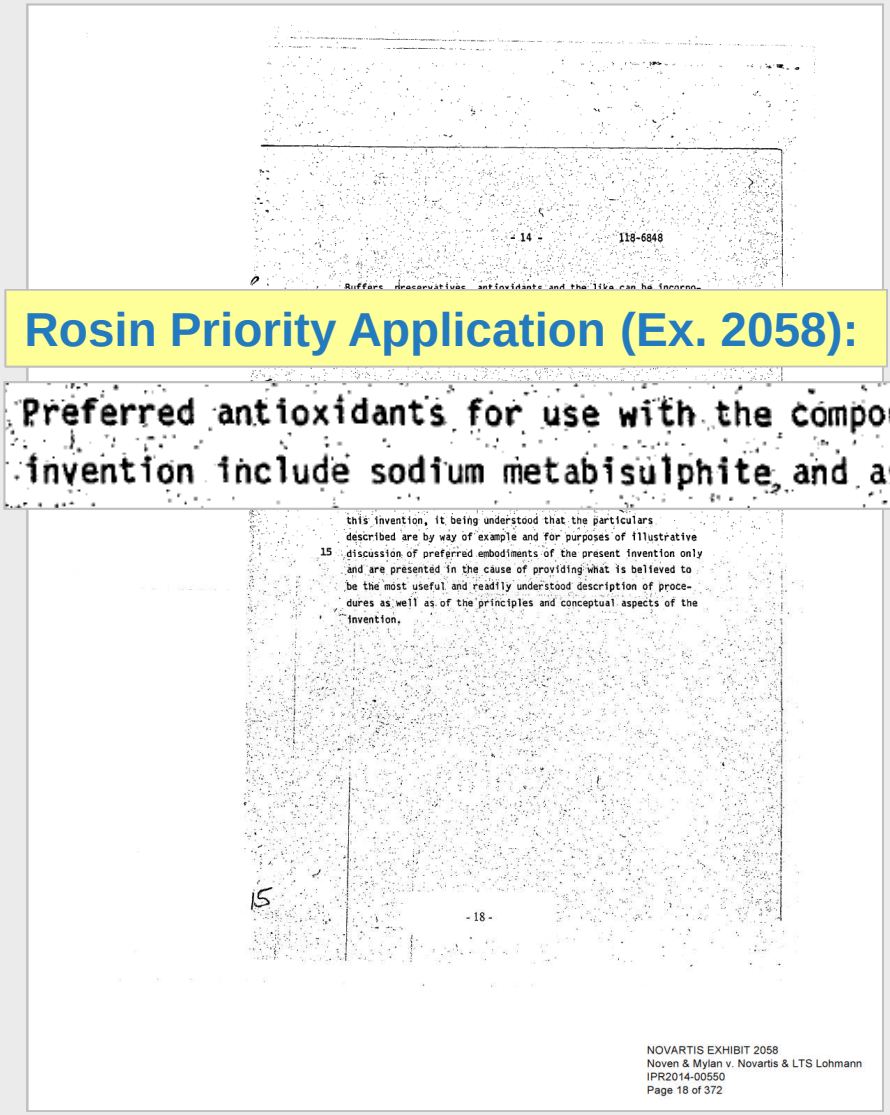
Ex. 1008 at 4:21-53; Ex. 2012 at ¶ 63

The "Compounds Of The Present Invention" Include The Large Class Of Eight Million-Plus Compounds

Paper 43 at 7-8; *see also* Paper 25 at 24-25 & n.4

Rosin Priority Application (Ex. 2058):

Preferred antioxidants for use with the compounds of the present invention include sodium metabisulphite and ascorbic acid.



- 14 - 118-6848

Buffers, preservatives, antioxidants and the like can be incorpo-

this invention, it being understood that the particulars described are by way of example and for purposes of illustrative discussion of preferred embodiments of the present invention only and are presented in the cause of providing what is believed to be the most useful and readily understood description of procedures as well as of the principles and conceptual aspects of the invention.

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- 18 -

NOVARTIS EXHIBIT 2058
Noven & Mylan v. Novartis & LTS Lohmann
IPR2014-00550
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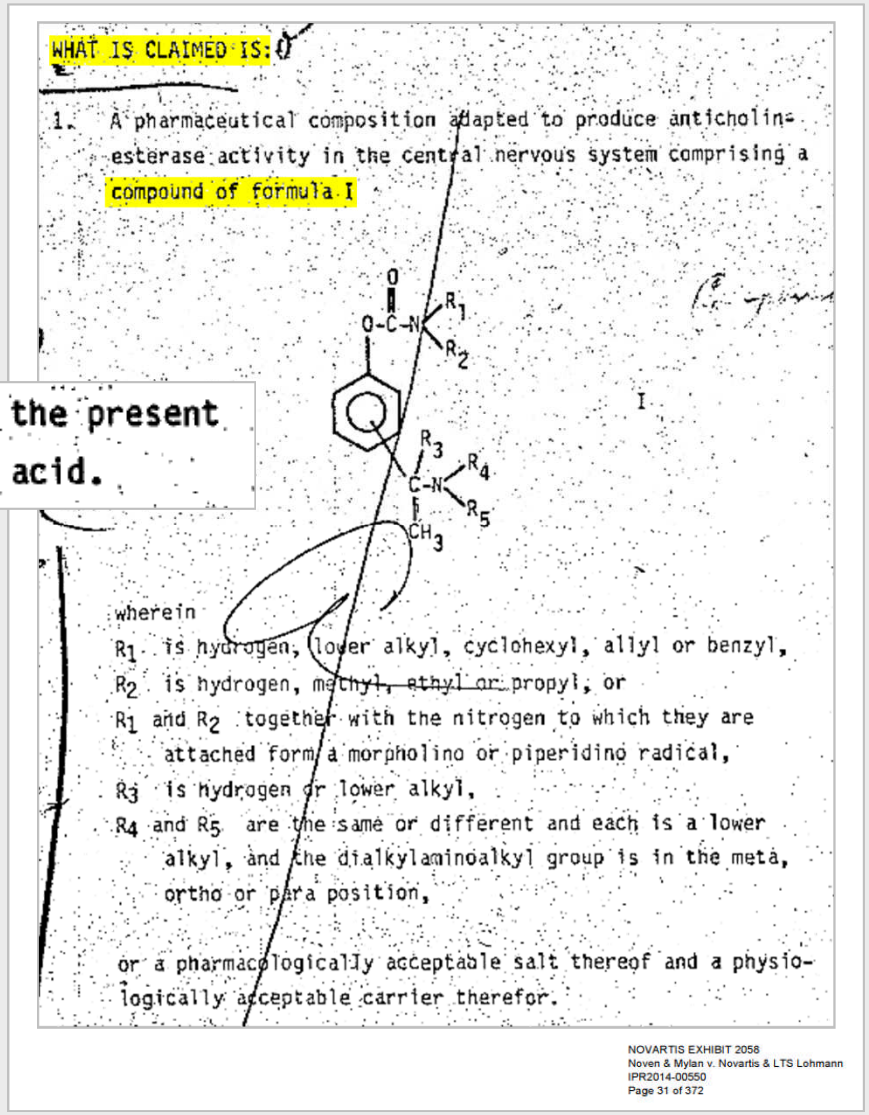

WHAT IS CLAIMED IS:

1. A pharmaceutical composition adapted to produce anticholinesterase activity in the central nervous system comprising a compound of formula I

I

wherein

R_1 is hydrogen, lower alkyl, cyclohexyl, allyl or benzyl,

R_2 is hydrogen, methyl, ethyl or propyl, or

R_1 and R_2 together with the nitrogen to which they are attached form a morpholino or piperidino radical,

R_3 is hydrogen or lower alkyl,

R_4 and R_5 are the same or different and each is a lower alkyl, and the dialkylaminoalkyl group is in the meta, ortho or para position,

or a pharmacologically acceptable salt thereof and a physiologically acceptable carrier therefor.

NOVARTIS EXHIBIT 2058
Noven & Mylan v. Novartis & LTS Lohmann
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Ex. 2058 at 18, 31; Ex. 1049 at 35:23-36:19, 37:16-39:5

Neither Rosin Nor Elmalem Discloses Transdermals

Paper 43 at 13; Paper 45 at 12-13; *see also* Paper 25 at 3-4, 27-28, 36

Dr. Kydonieus (Ex. 1026):

16 Q. Okay. It does not -- the '807 patent does
17 not discuss transdermal formulations; right?
18 A. No, it does not discuss.

17 Q. And Elmalem did not prepare any
18 transdermal formulations; right?
19 A. Right.

Ex. 1026 at 249:16-18, 257:17-19; *see also* Ex. 1026 at 186:6-10; Ex. 1049 at 39:15-25

Whether Rivastigmine Undergoes Oxidative Degradation Is Formulation-Specific

Paper 25 at 4, 13, 27, 36

Dr. Schöneich (Ex. 1026):

Q. And you agree with the general principle that the extent of degradation depends on the chemical environment in which a drug is formulated?

A. So if you have a drug which is susceptible to degradation, the extent to which it actually happens, that depends on the environment.

Ex. 1026 at 95:24-96:6; *see also* Ex. 2012 at ¶ 49

Whether Rivastigmine Undergoes Oxidative Degradation Is Formulation-Specific

Paper 25 at 4, 13, 27, 36

Dr. Kydonieus (Ex. 1026):

Q. So if you have oxidative degradation in a solution, you cannot conclude that it would also be a problem, for instance, in a transdermal patch; right?

A. I said that many times. That is formulation dependent.

Ex. 1026 at 258:8-13; *see also* Ex. 2012 at ¶ 49

Dosage Form Can Determine Whether An Antioxidant Is Required

Paper 45 at 12-13; *see also* Paper 25 at 13-14

Dr. Schöneich (Ex. 1048):

Q And it's your opinion that the dosage form is significant? That's what you say in the first line of 48; is that right?

A Yes.

Q And my question was whether or not the dosage form that is selected can determine whether or not an antioxidant is required.

MR. GLYNN: Objection to form.

Q It's your opinion that it could; correct?

MR. GLYNN: Objection to form. Also, compound question.

A The formulation, if you -- if you say the formulation is equivalent to the dosage form, it can make a difference, so, yes.

Q It can make a difference whether or not an antioxidant is required?

A Yes.

Ex. 1048 at 70:3-6, 70:21-71:12; *see also* Ex. 2012 at ¶ 49

Hydrolysis Of Carbamates Had Been Studied Experimentally Since The 1930s

Paper 25 at 31-32; Paper 45 at 13

Dr. Schöneich (Ex. 1048):

Q And you would agree with me that the hydrolysis of monomethyl carbamates has been studied experimentally since the 1930s?

A That's what Dr. Klibanov states.

Q And you don't dispute that, do you?

A I don't dispute it.

Q And you also don't dispute that the hydrolysis of dialkyl carbamates has been studied experimentally since the 1930s?

A Yes.

Ex. 1048 at 25:17-26:2; Ex. 2012 at ¶¶ 78, 81-82, 84-96

Mechanisms Of Hydrolysis Of Carbamates Had Been Experimentally Determined As Of 1998

Paper 25 at 31-32; Paper 45 at 13

Dr. Schöneich (Ex. 1048):

Q Okay. And you agree that the mechanism by which monomethyl carbamates undergo hydrolysis had been experimentally determined as of 1998?

A I think so.

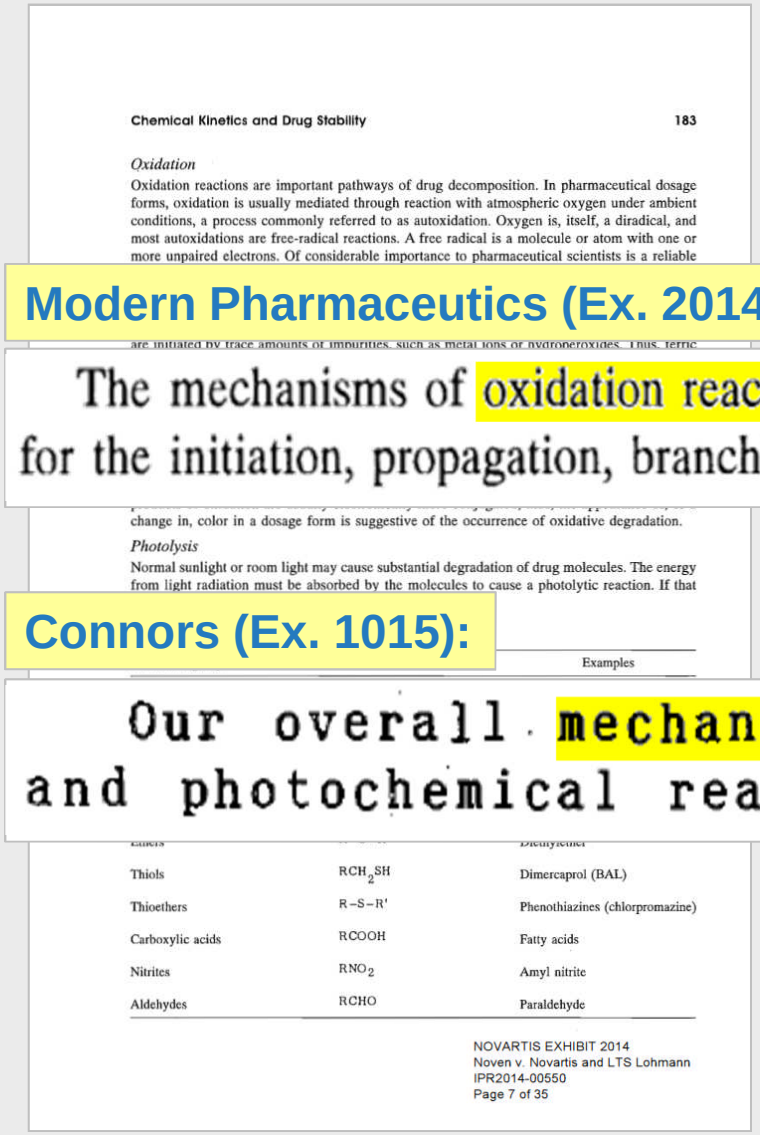
Q And you don't dispute that the mechanism by which dialkyl carbamates undergo hydrolysis had been experimentally determined by 1998?

A I don't dispute that.

Ex. 1048 at 26:11-20; Ex. 2012 at ¶¶ 78, 81-82, 84-96

Oxidative Mechanisms Were Poorly Understood As Of 1998

Paper 25 at 18-19



Chemical Kinetics and Drug Stability 183

Oxidation

Oxidation reactions are important pathways of drug decomposition. In pharmaceutical dosage forms, oxidation is usually mediated through reaction with atmospheric oxygen under ambient conditions, a process commonly referred to as autoxidation. Oxygen is, itself, a diradical, and most autoxidations are free-radical reactions. A free radical is a molecule or atom with one or more unpaired electrons. Of considerable importance to pharmaceutical scientists is a reliable

are initiated by trace amounts of impurities, such as metal ions or hydroperoxides. Thus, ferric

change in, color in a dosage form is suggestive of the occurrence of oxidative degradation.

Photolysis

Normal sunlight or room light may cause substantial degradation of drug molecules. The energy from light radiation must be absorbed by the molecules to cause a photolytic reaction. If that

Examples

Thiols	RCH_2SH	Dimercaprol (BAL)
Thioethers	R–S–R'	Phenothiazines (chlorpromazine)
Carboxylic acids	RCOOH	Fatty acids
Nitrites	RNO_2	Amyl nitrite
Aldehydes	RCHO	Paraldehyde

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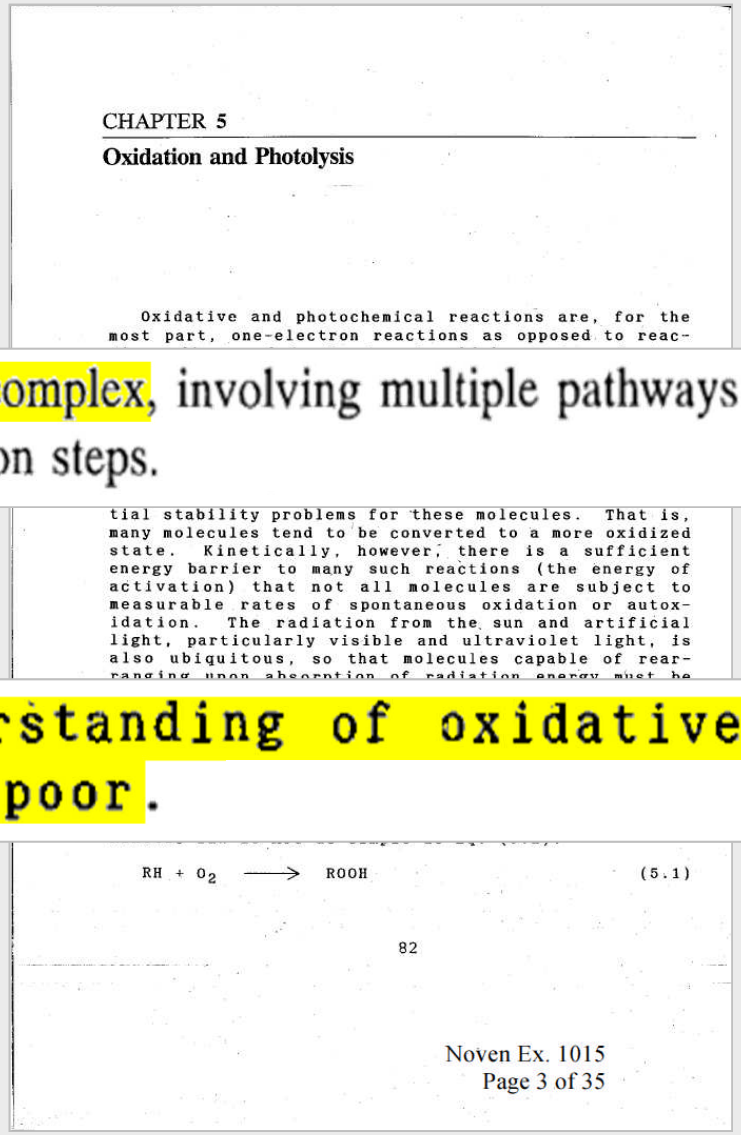

CHAPTER 5

Oxidation and Photolysis

Oxidative and photochemical reactions are, for the most part, one-electron reactions as opposed to reac-

tial stability problems for these molecules. That is, many molecules tend to be converted to a more oxidized state. Kinetically, however, there is a sufficient energy barrier to many such reactions (the energy of activation) that not all molecules are subject to measurable rates of spontaneous oxidation or autox-idation. The radiation from the sun and artificial light, particularly visible and ultraviolet light, is also ubiquitous, so that molecules capable of rear-ranging upon absorption of radiation energy must be

$$RH + O_2 \longrightarrow ROOH \qquad (5.1)$$

82

Noven Ex. 1015
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Modern Pharmaceutics (Ex. 2014):

The mechanisms of oxidation reactions are usually complex, involving multiple pathways for the initiation, propagation, branching, and termination steps.

Connors (Ex. 1015):

Our overall mechanistic understanding of oxidative and photochemical reactions is poor.

Ex. 2014 at 7; Ex. 1015 at 3; Ex. 2012 at ¶ 121

Testing Was Required To Determine Intrinsic Stability

Paper 25 at 19

Dr. Kydonieus (Ex. 1010):

> Indeed, regulatory guidelines in effect as of January 1998 recommended that applicants perform stability tests on the drug substance and drug product. This included stress testing on the drug substance to determine its intrinsic stability and degradation pathways, as well as formal studies on the drug substance to show that it will remain within specification during the re-test period if stored under the recommended storage conditions. (*See* ICH Topic Q 1 A, Stability Testing Guidelines: Stability Testing of New Drug Substances and Products (CPMP/ICH/380/95) (Ex. 1014).)

Ex. 1010 at ¶ 25; Ex. 1014 at 2; Ex. 2012 at ¶ 35

Bond Strengths Do Not Indicate The Conditions Under Which A Radical Will Form

Paper 45 at 1; *see also* Paper 25 at 16-17

Dr. Schöneich (Ex. 1048):

Q And if you turn back to paragraph nine.

A Yes.

Q And you also discuss there relative radical stabilities; correct?

MR. GLYNN: Objection to form.

A What we see in this table, which is on page five, paragraph nine, first of all, on the right-hand column, absolute values, these are bond dissociation energies which are measured, and just for comparison, in the middle column, they are radical -- relative radical stabilities.

Q So, you are saying that methane is relatively less stable than the C-H bond to a tertiary carbon (CH3)3CH?

A So, the carbon-hydrogen bond in methane is stronger than the carbon-hydrogen bond in the tertiary -- in the tertiary carbon-hydrogen --

Q And that is a relative assessment; correct?

MR. GLYNN: Objection to form.

A It's a relative assessment within this group of compounds. But there are certainly absolute numbers to support that.

Q And those numbers don't tell us under what conditions the radicals were formed, do they?

A These numbers are absolute values of bond dissociation energies, so, they should be independent of the measurement. These are absolute numbers.

Q But they don't tell me under what conditions the radical will form, do they?

MR. GLYNN: Objection to form.

A The bond dissociation energy is just by its mere fact a bond dissociation energy. It does not tell you under which conditions you form radicals in any chemical reaction.

Ex. 1048 at 22:6-23:22

Testing Is Required To Determine Whether Rivastigmine Oxidative Degrades Under Pharmaceutically Relevant Conditions

Paper 25 at 2-3, 13-14, 16, 20, 22, 23, 27, 36, 42

Dr. Schöneich (Ex. 1026):

Q. So whether rivastigmine oxidatively degrades in a specific formulation is something that has to be shown?

A. Well, whether rivastigmine is susceptible to degradation that can be deduced from the structure, whether it actually happens, that needs to be shown experimentally and the extent to what it happens needs to be shown experimentally.

Ex. 1026 at 96:10-18

Testing Is Required To Determine Whether Rivastigmine Oxidative Degrades Under Pharmaceutically Relevant Conditions

Paper 25 at 2-3, 13-14, 22, 23, 27, 36, 42

Dr. Kydonieus (Ex. 1026):

Q. So let me go back to my question. Just knowing that a compound as you put it is susceptible to oxidation doesn't tell you how much oxidative degradation will occur over any particular time; right?

A. Over any particular time? It doesn't tell you how much degradation you will get period depending on that formulation.

Ex. 1026 at 232:6-13

Dextromethorphan Is "Especially Susceptible" To Oxidative Degradation But "Very Stable"

Paper 25 at 17; Paper 45 at 2-4

Carey & Sundberg (Ex. 1018):

- Benzylic positions are "**especially susceptible**" to oxidation

Dr. Schöneich's opinion (Exs. 1011, 1032):

- "Dextromethorphan Was **Known To Be Susceptible** To Oxidation"
- Dextromethorphan was "**prone to oxidation**"

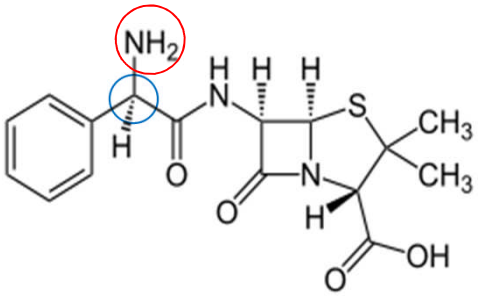
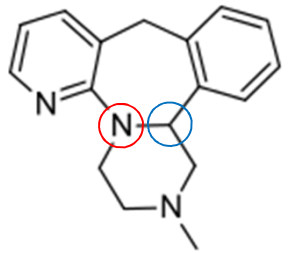
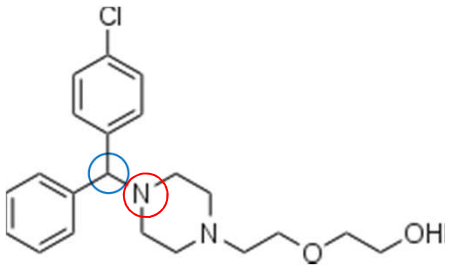
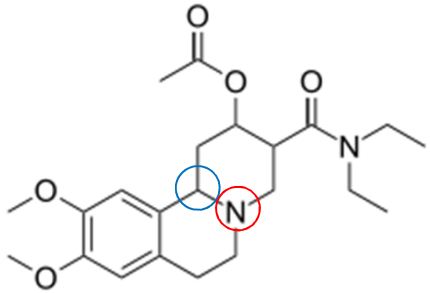
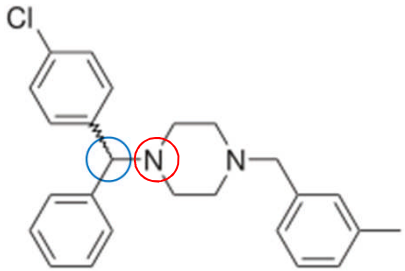
The prior art teaches (Exs. 2050, 2051):

- Dextromethorphan is "**very stable**"
- Dextromethorphan is "**stable** under **all normal conditions** of storage"
- Dextromethorphan has "**excellent stability**" under pharmaceutically relevant conditions

Ex. 1018 at 45; Ex. 1011 at ¶ 47; Ex. 1032 at ¶¶ 11, 60; Ex. 2050 at 6; Ex. 2051 at 4-5; Ex. 2012 at ¶¶ 140-41

Drugs With Structural Features Of Rivastigmine Were Not Reported To Undergo Oxidation

Paper 25 at 18

Ampicillin		Mirtazapine	
Hydroxyzine		Benzquinamide	
Meclizine			

Dr. Schöneich Provided No Evidence To Show Dr. Klibanov's Real-World Pharmaceuticals Were Unstable

Paper 45 at 5-6; *see also* Paper 25 at 18

Dr. Schöneich (Ex. 1048):

13 Q That wasn't my question. I was
14 asking you about whether you had done any
15 literature searches relating to any of the
16 five compounds, real world examples, that
17 Dr. Klibanov relied on saying that they
18 undergo oxidative degradation in any
19 formulation.
20 MR. GLYNN: Objection to form.
21 A I have not done literature research
22 to that respect.

Ex. 1048 at 49:13-22

Dr. Schöneich Provided No Evidence To Show Dr. Klibanov's Real-World Pharmaceuticals Were Unstable

Paper 45 at 5-6; *see also* Paper 25 at 18

Dr. Schöneich (Ex. 1048):

Q Okay. And you have a testing lab at Kansas, don't you?

A I have a laboratory, yes.

Q Okay. And that lab could have run some tests on any one of these drugs to determine whether or not they undergo oxidative degradation under a certain set of conditions; correct?

A Well, certainly we have the capacity, but we haven't done it.

Q You chose not to do that; correct?

A We chose not to do that.

Ex. 1048 at 50:5-16; *see also* Ex. 2012 at ¶¶ 132-34

PDR Reports Chemical Instability Of Nicotine

Paper 45 at 8; *see also* Paper 25 at 17-18

Physicians' Desk Reference (Ex. 2022):

Nicotine has a characteristic pungent odor and turns brown on exposure to air or light.

Dr. Schöneich (Ex. 1048):

13 Q And "turns brown on exposure to
14 air" is a reference to the oxidation of
15 nicotine?
16 A It implies oxidation.

12 Q So, but a person of ordinary skill
13 in the art would understand that to be a
14 reference to oxidative instability of
15 nicotine; correct?
16 A A POSA would certainly see this as
17 a warning that nicotine would undergo
18 oxidation.

There Are Reasons Other Than Oxidative Instability To Select A Dry Dosage Form

Paper 45 at 11; *see also* Paper 25 at 18

Dr. Schöneich (Ex. 1048):

Q Well, just generally speaking, there are reasons to select a dry dosage form other than chemical instability?

A Well, the mode of application. If you want to give a tablet, it's a dry dosage form, yeah.

Q Yes. So there are other reasons.

A Okay.

Q Do you agree?

A But that doesn't exclude the oxidation sensitivity as a problem.

Q I understand that, but just taking this one step at a time. Okay. There are reasons other than chemical stability for selecting a dry dosage form; correct?

A Let me think a moment.

I would say predominantly dry dosage forms are selected if you have chemically unstable molecules, but, okay, there could be some other reasons.

Q Well, how about convenience to the patient of taking a dry dosage form, such as a tablet?

A Yeah, that could be. I said that, yeah.

Q And what about reasons other than oxidative instability? There are reasons -- strike that.

There are reasons other than oxidative instability for selecting a dry dosage form; correct?

A Yes.

Q And one of those would be, for example, avoiding hydrolysis?

A For example.

Ex. 1048 at 71:21-73:7; *see also* Ex. 2012 at ¶ 134

The Salt Form Of A Drug May Undergo Oxidative Degradation

Paper 43 at 4-5; *see also* Paper 25 at 18

Dr. Kydonieus (Ex. 1049):

Q. And it's your opinion that the salt of morphine needed to be mixed with an antioxidant prior to use to prevent oxidative degradation, correct?

A. Yes, there's saline -- first of all, what that statement basically says that you have to dissolve it. I mean, you cannot inject a crystal into a person or an animal. You can cause thrombosis and whatever else, so you have to dissolve it, and you dissolve it and you know that morphine is susceptible to oxidation. You would use saline plus an antioxidant.

Q. So even though it's a salt, you would still use an antioxidant, correct?

MR. COULSON: Objection.

A. Okay, I will give you my opinion, my extensive opinion -- my extensive experience. Salts are always better than the bases. Not always. Again, never always. 95 percent of the time, as far as oxidation is concerned, are better than the base. But that does not mean, necessarily, that the salt does not degrade. It degrades to a lesser extent most of the time, but it doesn't mean that it will not degrade.

Ex. 1049 at 93:6-94:5; *see also* Ex. 2012 at ¶ 134

Formulation In A Dry Dosage Form Does Not Indicate The Real-World Pharmaceuticals Are Susceptible To Oxidation

Paper 45 at 11; *see also* Paper 25 at 18

Petitioners' Response (Paper 52):

Response to p. 11 ¶¶ 1-2: Patent Owners mischaracterize Dr. Schöneich's testimony. Patent Owners incorrectly assert that Dr. Schöneich testified that formulation of a compound in a dry dosage form establishes that is susceptible to oxidation or that measures were taken to avoid oxidation. Dr. Schöneich testified that the so-called "real world examples" selected by Dr. Klibanov from the PDR were formulated as a dry dosage form, as a salt, or both. (Ex. 1032 ¶ 47.)

Paper 52 at 10-11; *see also* Ex. 2012 at ¶ 134

Whether Rivastigmine Would Degrade In An Acrylic Adhesive Could Not Be Reasonably Predicted From Its Structure

Paper 25 at 42

Dr. Kydonieus (Ex. 1026):

Q. Could you turn to your deposition, Page 89?

Let's put it on the screen. It will be easier. Page 89, and 18, Line 18. And you were asked the question: "So am I right that it's your opinion that when rivastigmine's in an acrylic adhesive, it will not necessarily undergo oxidative degradation?

"Answer: I don't know the answer."

A. Absolutely correct. Yes.

Q. Now, Dr. Kydonieus --

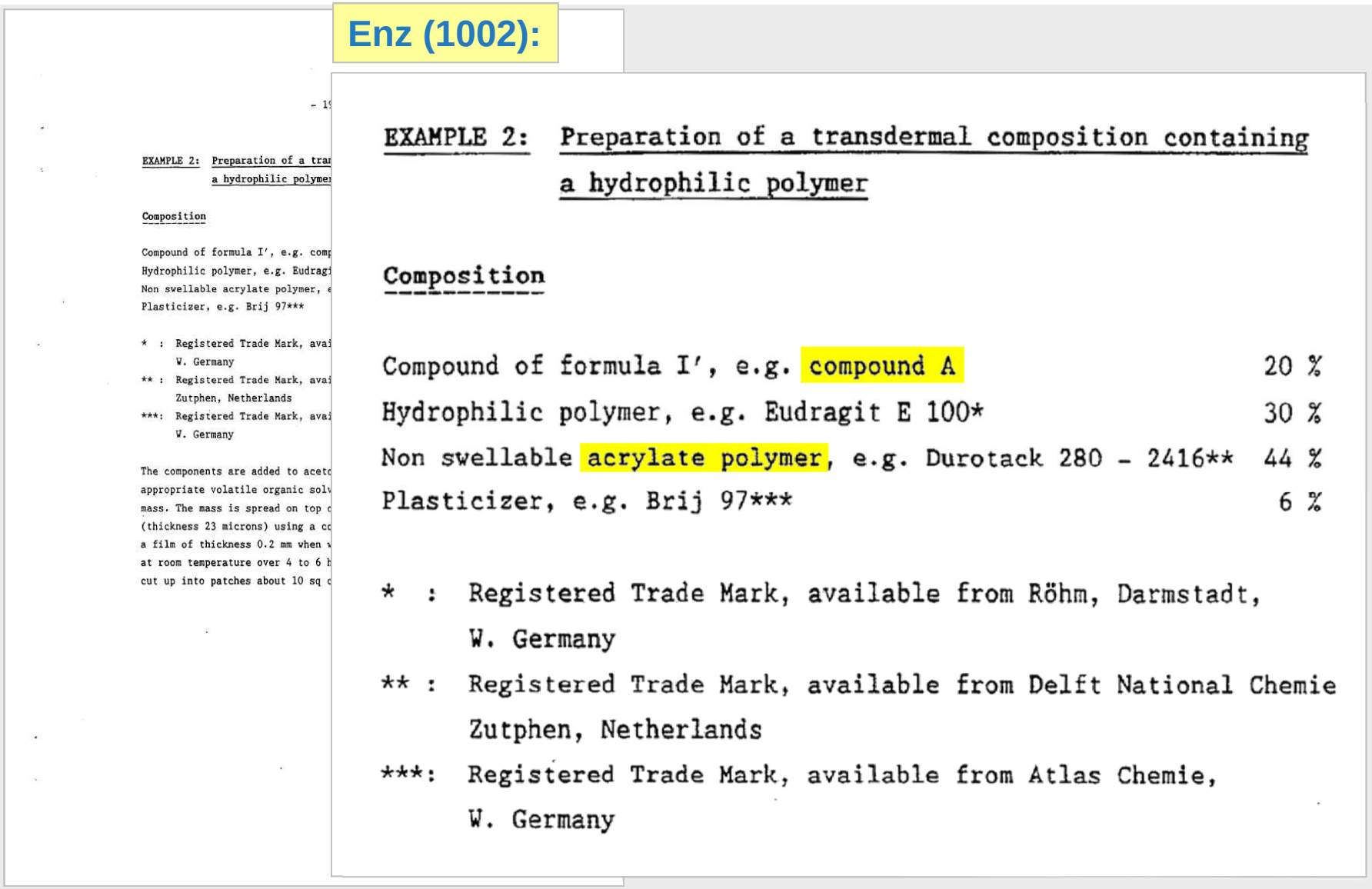
A. May I finish. It is formulation dependent.

Ex. 1026 at 283:12-24; *see also* Ex. 2012 at ¶ 156 & n.17

Enz Discloses Rivastigmine In An Acrylic Adhesive Without Requiring An Antioxidant

Paper 25 at 43-44

Enz (1002):



EXAMPLE 2: Preparation of a transdermal composition containing a hydrophilic polymer

Composition

Compound of formula I', e.g. compound A	20 %
Hydrophilic polymer, e.g. Eudragit E 100*	30 %
Non swellable acrylate polymer, e.g. Durotack 280 - 2416**	44 %
Plasticizer, e.g. Brij 97***	6 %

* : Registered Trade Mark, available from Röhm, Darmstadt, W. Germany

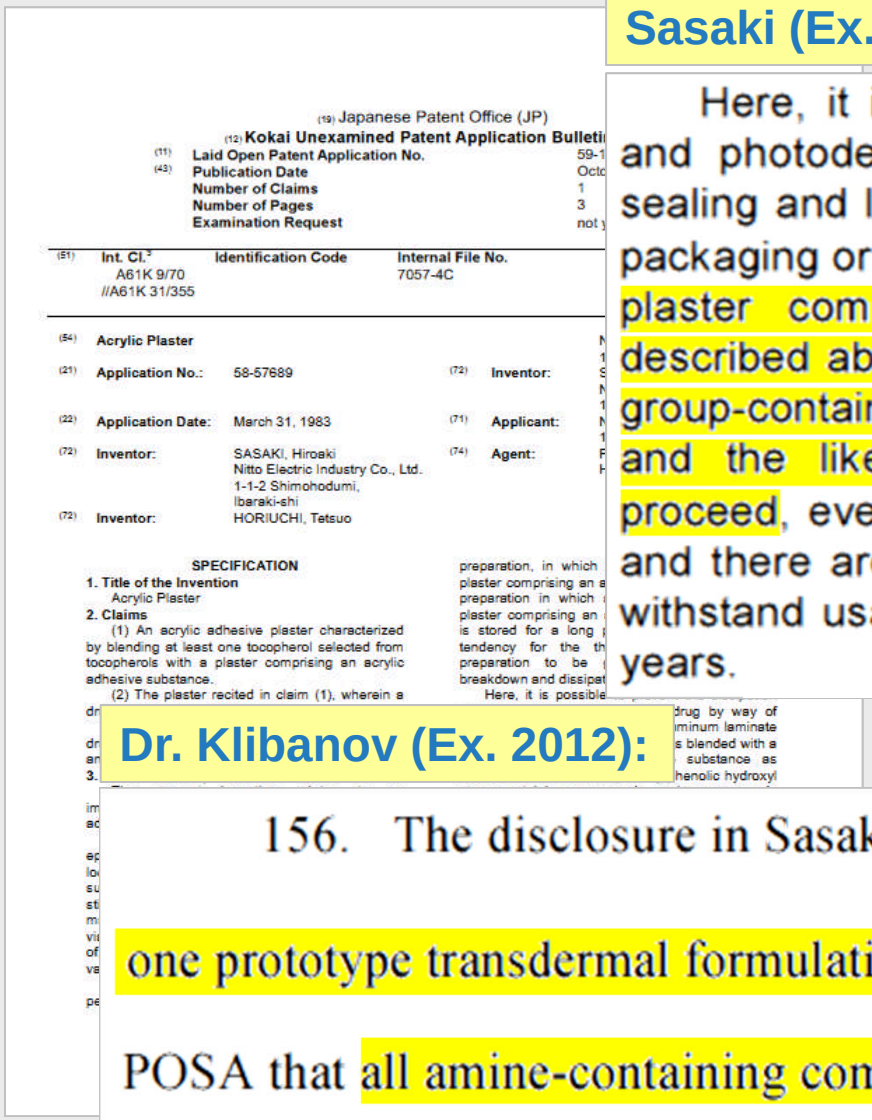
** : Registered Trade Mark, available from Delft National Chemie Zutphen, Netherlands

***: Registered Trade Mark, available from Atlas Chemie, W. Germany

Ex. 1002 at 19; Ex. 2012 at ¶ 158

A POSA Would Not Believe That All Amines Break Down In Acrylic Adhesives Based On Two Amines In Sasaki

Paper 25 at 42



(19) Japanese Patent Office (JP)

(12) Kokai Unexamined Patent Application Bulleti

(11) Laid Open Patent Application No. 59-1

(43) Publication Date Octo

Number of Claims 1

Number of Pages 3

Examination Request not

(51) Int. Cl.³ A61K 9/70 //A61K 31/355 — Identification Code — Internal File No. 7057-4C

(54) Acrylic Plaster

(21) Application No.: 58-57689

(22) Application Date: March 31, 1983

(72) Inventor: SASAKI, Hiroaki, Nitto Electric Industry Co., Ltd. 1-1-2 Shimohodumi, Ibaraki-shi

(72) Inventor: HORIUCHI, Tetsuo

(72) Inventor:

(71) Applicant:

(74) Agent:

SPECIFICATION

1. Title of the Invention
Acrylic Plaster

2. Claims
(1) An acrylic adhesive plaster characterized by blending at least one tocopherol selected from tocopherols with a plaster comprising an acrylic adhesive substance.
(2) The plaster recited in claim (1), wherein a

preparation, in which
plaster comprising an a
preparation in which
plaster comprising an
is stored for a long
tendency for the th
preparation to be
breakdown and dissipat
Here, it is possible

drug by way of
minum laminate
s blended with a
substance as
henolic hydroxyl

Sasaki (Ex. 1005):

> Here, it is possible to prevent the dissipation and photodecomposition of the drug by way of sealing and light shielding with aluminum laminate packaging or the like, but with drugs blended with a plaster comprising an adhesive substance as described above, and especially phenolic hydroxyl group-containing compounds, amine compounds and the like, breakdown of the drug will still proceed, even with aluminum laminate packaging, and there are more than a few drugs that cannot withstand usage involving storage for two to three years.

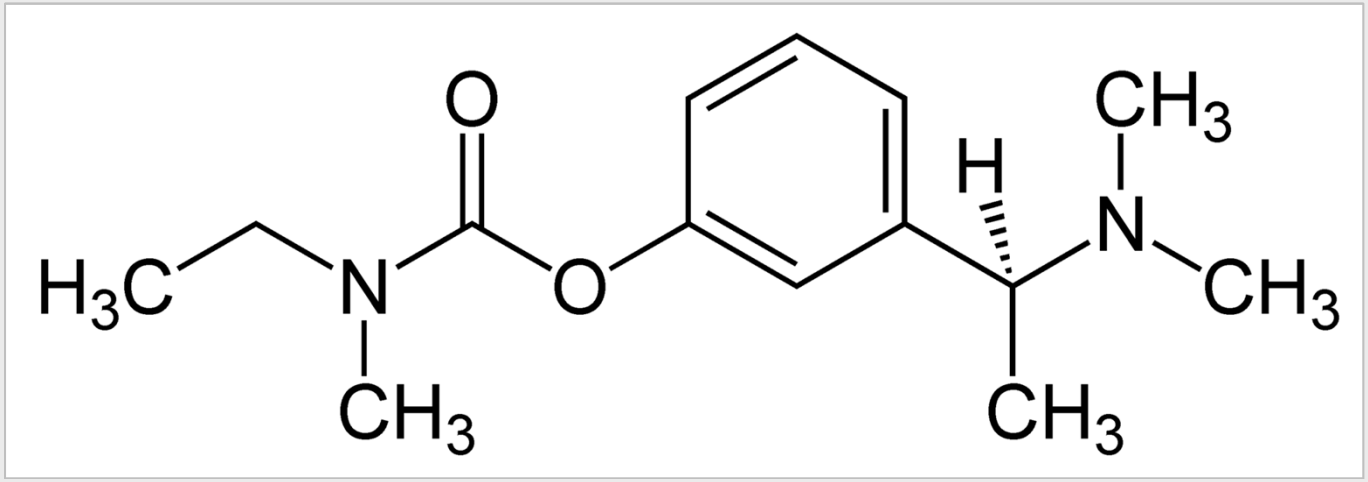
Dr. Klibanov (Ex. 2012):

> 156. The disclosure in Sasaki of just two amine-containing compounds in one prototype transdermal formulation would not have taught or suggested to a POSA that all amine-containing compounds break down in any acrylic adhesive.[17]

Ex. 1005 at 1; Ex. 2012 at ¶ 156

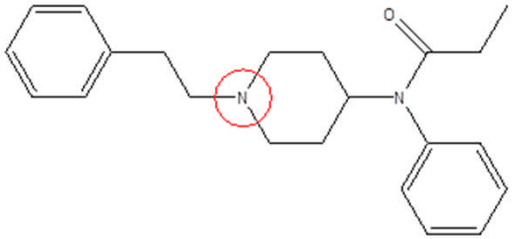
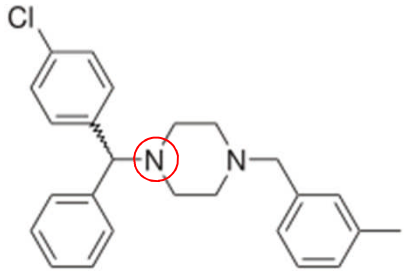
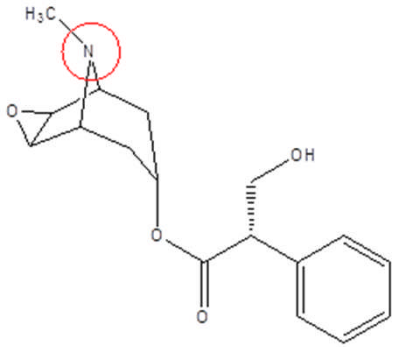
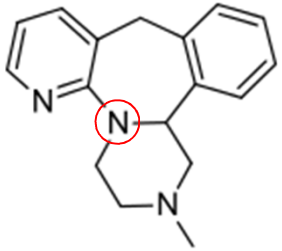
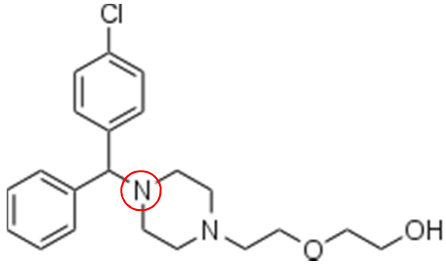
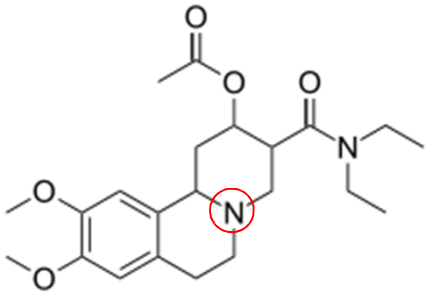
Rivastigmine

Paper 25 at 17-18



Amine-Containing Drugs Were Not Reported To Contain Antioxidants In Commercial Formulations

Paper 25 at 42-43

Fentanyl		Meclizine	
Scopolamine		Mirtazapine	
Hydroxyzine		Benzquinamide	

Amine Or Phenolic Hydroxyl Compounds In An Acrylic Adhesive Were Not Reported To Contain An Antioxidant

Paper 25 at 42-43 & n.11

Physicians' Desk Reference (Ex. 2022):

The Climara® system comprises two layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent polyethylene film, and (2) an acrylate adhesive matrix containing estradiol USP.

The Vivelle system comprises three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent flexible film consisting of an ethylene vinyl alcohol copolymer film, a polyurethane film, urethane polymer and epoxy resin, (2) an adhesive formulation containing estradiol, acrylic adhesive, polyisobutylene, ethylene vinyl acetate copolymer, 1,3 butylene glycol,

Habitrol systems are round, flat, 0.6-mm-thick multi-layer units containing nicotine as the active agent. Proceeding from the visible surface toward the surface attached to the skin are: (1) a tan-colored aluminized backing film; (2) a pressure-sensitive acrylate adhesive; (3) a layer containing a methacrylic acid copolymer solution of nicotine dispersed in a pad of nonwoven viscose and cotton;

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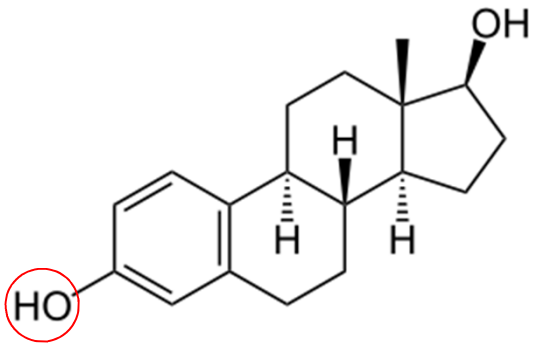
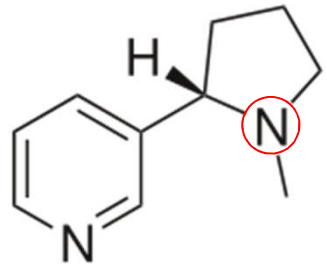
Estradiol



Nicotine



Ex. 2022 at 6, 23, 27; Ex. 2012 at ¶¶ 157 & n.18

"Susceptibility" Does Not Indicate Whether Rivastigmine Will Undergo Any Oxidative Degradation

Paper 43 at 4; *see also* Paper 25 at 13-14, 16-17

Dr. Kydonieus (Ex. 1031):

10. Of course, whether rivastigmine would actually undergo oxidative degradation in a particular pharmaceutical formulation depends on the specific formulation. This is why, for a particular formulation, a POSA would conduct testing to confirm to what extent, if any, the drug in the formulation oxidatively degrades.

Ex. 1031 at ¶ 10; Ex. 1026 at 96:10-18

Ebert Discloses An Unconventional Method

Paper 25 at 37-38

Dr. Klibanov (Ex. 2012):

169. Ebert discloses a ***non-conventional*** method for manufacturing transdermal devices containing "volatile or heat-sensitive drugs, enhancers or other components cannot be subjected to drying or heating, such as would occur in an oven." (Ex. 1006, Ebert at 5, ll. 16-21.)

171. To address such nicotine-specific problems, Ebert discloses a method of manufacturing transdermal devices wherein an "active gel" of nicotine, BHT (thus notably in contradiction to Sasaki), and hydroxypropyl cellulose (HPC) is prepared by stirring for an "extended period of time." (*Id.* at 19, l. 34-20, l. 3.) In Example 1, nicotine was mixed with HPC for 26.5 hours in air, thereby amply exposing nicotine to air. (*Id.* at 20, ll. 10-12.) The active gel is then extruded onto an adhesive layer. (*Id.* at 1, ll. 13-20.)

Ex. 2012 at ¶¶ 169, 171; Ex. 1006 at 1:13-20, 5:16-21, 19:34-20:12

Rivastigmine Transdermal Can Be Prepared Using Conventional Methods

Paper 25 at 37-38

Enz (Ex. 1002):

tion (19) GB (11) 2 203 040 (13) A

(43) Application published 12 Oct 1988

The present invention furthermore provides a pharmaceutical composition comprising a compound according to the invention in association with at least one pharmaceutical carrier or diluent. Such compositions may be manufactured in conventional manner.

The active agents may be administered in any conventional liquid or solid transdermal pharmaceutical composition

mass. The mass is spread on top of an aluminised polyester foil (thickness 23 microns) using a conventional apparatus, to produce a film of thickness 0.2 mm when wet.

Ex. 1002 at 11, 17, 20; Ex. 2012 at ¶ 169

Respectfully submitted,

Dated: May 26, 2015

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CERTIFICATE OF SERVICE

I certify that a copy of the foregoing PATENT OWNERS' DEMONSTRATIVE EXHIBITS PURSUANT TO 37 C.F.R. § 42.70(b) were served on May 26, 2015 by causing them to be sent by email to counsel for Petitioners at the following email addresses:

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