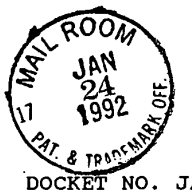


IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

DOCKET NO. JAB 775

ANTICIPATED CLASSIFICATION OF THIS APPLICATION:

CLASS_____SUBCLASS_____

PRIOR APPLICATION: JAB 600

EXAMINER: R. Travers

ART UNIT: 125

The Hon. Commissioner of Patents and Trademarks
Washington, D. C. 20231

Dear Sir:

This is a request for filing a

[X] Continuation

[ ] Divisional

application, under 37 CFR 1.60, of pending prior application Serial No. 325,181, filed on March 16, 1989, of Raymond Mathieu Xhonneux et al.
(Date) (Inventor)
for METHOD OF LOWERING THE BLOOD PRESSURE.
(Title of Invention)

1. [X] Enclosed is a copy of the prior application, including the Oath or Declaration as originally filed.

I hereby verify that the attached papers are a true copy of prior application Serial No. 325,181, as originally filed on March 16, 1989,

and further that this statement was made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

2. [X] The filing fee is calculated below:

Claims as filed in the prior application, including any claims added or canceled by amendment below

For--	No. Filed	No. Extra	Rate	Fee
Total Claims	8 - 20 =	0	x $20 =	$000.00
Independent Claims	2 - 3 =	0	x $72 =	$000.00
Basic fee (minimum amount required)				$690.00
Total Filing Fee				$690.00

3. [X] The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment, to Account No. 10-750/JAB 775/CJM. Three copies of this sheet are enclosed.

4. [ ] A check in the amount of $_____ is enclosed.

5. [X] Cancel in this application original Claims 2-17 of the prior application before calculating the filing fee. (At least one original independent claim must be retained for filing purposes.)

6. [X] Amend the specification by inserting before the first line the sentence: -- This is a [X] continuation, [ ] division, of application Serial No. 325,181, filed March 16, 1989. --

7. [ ] Transfer the drawings from the prior application to this application and abandon said prior application as of the filing date accorded this application. A duplicate copy of this sheet is enclosed for filing in the prior application file.

7a. [ ] New formal drawings are enclosed.

7b. [ ] Priority of application Serial No. _____, filed on _____ ___ in _____ (Country) is claimed under 35 U.S.C. 119.

7c. [ ] The certified copy of the priority application has been filed in prior application Serial No. _____, filed _____.

8. [X] The prior application is assigned to JANSSEN PHARMACEUTICA NV.

9. [X] The power of attorney in the prior application is to Robert L. Minier (Reg. #20,083), Audley A. Ciamporcero, Jr. (Reg. #26,051), Steven P. Berman (Reg. #24,772), Wayne R. Eberhardt (Reg. #22,804), Jason Lipow (Reg. #25,509), Donal B. Tobin (Reg. #25,711), and David J. Levy (Reg. #27,655), Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, New Jersey 08933-7003.

9a. [X] The power appears in the original papers in the prior application.

9b. [ ] Since the power does not appear in the original papers, a copy of the power in the prior application is enclosed.

9c. [X] Address all future communications to Robert L. Minier (Reg. #20,083), Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ 08933-7003.

10. [X] A Preliminary Amendment is enclosed.

January 24, 1992
(Date)

Charles J. Metz
Reg. No. 20,359

Address of Signer:
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933

908-524-2814

[ ] Inventor(s)
[ ] Assignee of complete interest
[ ] Attorney or agent of record
[X] Filed under Section 1.34(a)

07/825488

DOCKET NO. JAB-775

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Raymond Mathieu Xhonneux et al.

For : METHOD OF LOWERING THE BLOOD PRESSURE

Express Mail Certificate

"Express Mail" mailing number RB759706376

Date of Deposit January 24, 1992

I hereby certify that this request for filing a Continuation application under 37 CFR 1.60 of prior application Serial No. 325,181 (JAB-600), copy of prior application, Declaration (2) and Preliminary Amendment and Information Disclosure Statement and reference are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patent and Trademarks, Washington, D.C. 20231.

Charles J. Metz
(Typed or printed name of person mailing paper or fee)

Charles J. Metz
(Signature of person mailing paper or fee)

1303f

JAB 600

METHOD OF LOWERING THE BLOOD PRESSURE

Cross-reference to related applications

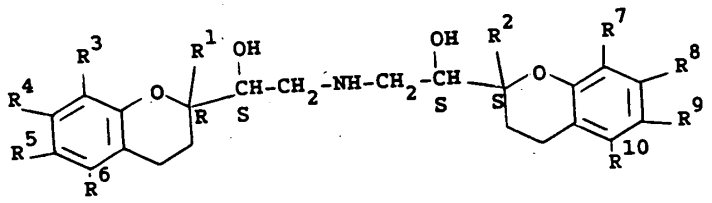
This is a continuation-in-part of our copending application 172,747 filed March 23, 1988.

Background of the Invention

In U.S. Pat. No. 4,654,362 there are described 2,2'-iminobisethanol derivatives having ß adrenergic blocking properties. It now has been found that a certain class of isomers of said bisethanol derivatives potentiate the activity of blood pressure reducing agents.

Description of the Invention

The present invention is concerned with a group of compounds capable of potentiating the effects of blood pressure reducing agents, said compounds being represented by the formula



(I),

or the pharmaceutically acceptable acid addition salts thereof, wherein

R^1 and R^2 each independently are hydrogen or C_{1-6}alkyl;

R^3, R^4, R^5, R^6, R^7, R^8, R^9 and R^{10} each independently are hydrogen, halo, C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxy, cyano, carboxy or C_{1-6}alkyloxycarbonyl;

or two vicinal radicals of R^3, R^4, R^5, R^6, R^7, R^8, R^9 and R^{10} taken together may form a -CH=CH-CH=CH- or $-(CH_2)_4-$ radical.

As used in the foregoing definitions the term halo is generic to fluoro, chloro, bromo and iodo; the term "C_{1-6}alkyl" defines straight and branch chained saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as, for example, methyl, ethyl, 1-methylethyl, 1,1-dimethylethyl, propyl, 2-methylpropyl, butyl, pentyl, hexyl and the like.

The descriptors R and S as used in the above formula (I) indicate the absolute configuration at the respective carbon atoms. The carbon atom bearing R^1 has the R configuration, whereas the carbon atoms bearing the hydroxy functions and the carbon atoms bearing R^2 have the S configuration.

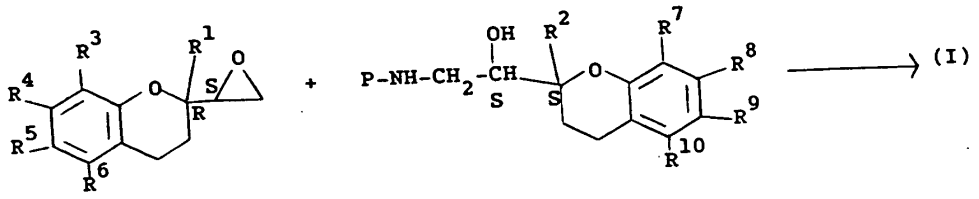
Preferred compounds of formula (I) are those wherein R^3, R^4, R^6, R^7, R^8, ~~R^9~~ and R^{10} are hydrogen.

Particularly preferred are those preferred compounds wherein R^5 and R^9 are hydrogen or halo, particularly fluoro.

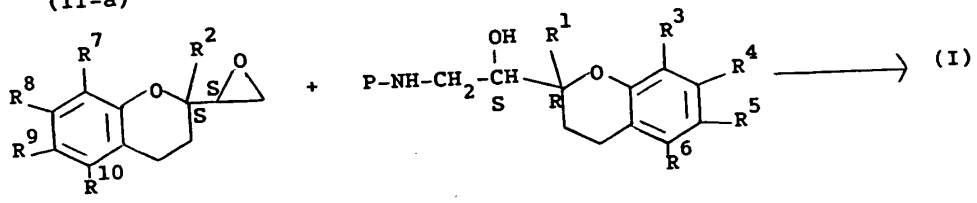
The most preferred compound is [2R,αS,2'S,α'S]-α,α'-[imino-bismethylene]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol] or a pharmaceutically acceptable acid addition salt thereof.

The compounds of formula (I) can be prepared following the procedures described in U.S. Pat. No. 4,654,362. Some particular ways of obtaining the compounds of formula (I) will be described hereinafter in some more detail.

The compounds of formula (I) can be prepared by reacting an oxirane of formula (II-a) or (II-b) with an amine of formula (III-a) or (III-b).



(II-a) (III-a) (I)



(II-b) (III-b) (I)

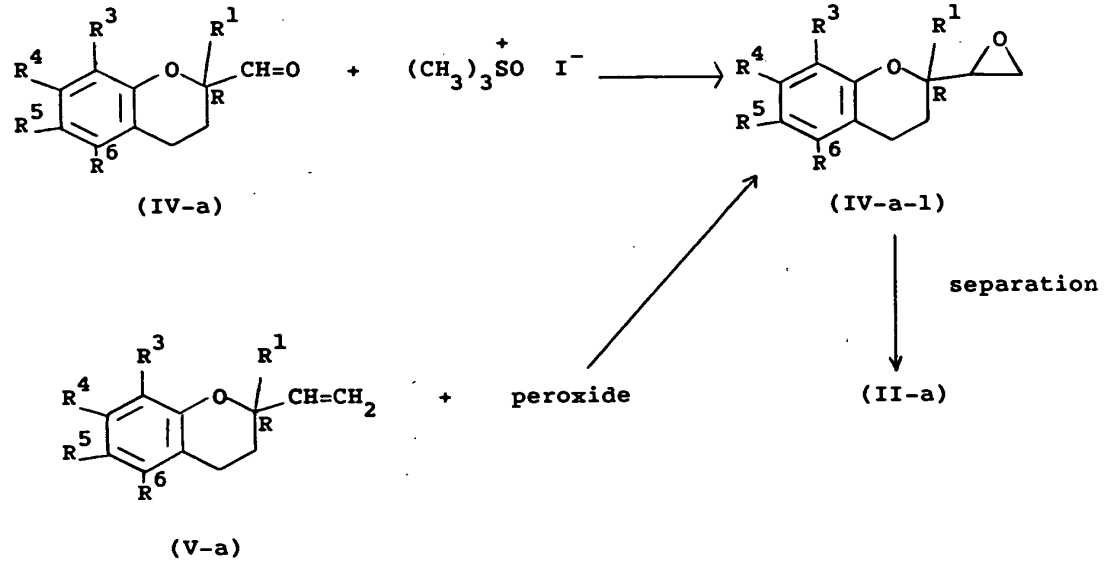
In (III-a) and (III-b), P is either hydrogen or an appropriate protecting group, for example an allyl group, or in particular P may be a benzyl group. Or, a reagent $P\text{-}NH_2$ may be reacted with (II-a) and (II-b) in a one-pot procedure. The above described reactions to prepare a compound of formula (I) may be conducted in a reaction-inert solvent such as, for example, an aromatic hydrocarbon, e.g. benzene or methylbenzene; an alkanol, e.g. methanol, ethanol, propanol; a ketone, e.g. 2-propanone, 4-methyl-2-pentanone; an ether, e.g. 1,4-dioxane, tetrahydrofuran, 1,1'-oxybisethane; a dipolar aprotic solvent, e.g. N,N-dimethylformamide or N,N-dimethylacetamide and the like solvents. In certain instances, in order to increase the reaction rate, it may be appropriate to heat the reaction mixture.

If in the above reactions P is other than hydrogen, the N-protected derivatives of formula (I) are obtained wherefrom the compounds of formula (I) themselves can be obtained by a deprotection reaction. For example, where P is allyl, by reaction with an appropriate noble metal compound such as $PdCl_2$ or $Rh[P(C_6H_5)_3]Cl$, or where P is benzyl, by a catalytic hydrogenation procedure, e.g. palladium or platinum on charcoal in a suitable solvent such as an ether, e.g. 1,4-dioxane, tetrahydrofuran, an alkanol, e.g. methanol, ethanol, an alkoxyalkanol, e.g. methoxyethanol and the like.

The intermediates of formula (III-a) or (III-b) are obtained by the

reaction of the amine P-NH_2 with (II-b) or (II-a) or, by reacting a reagent P_2NH, for example dibenzylamine, with (II-b) or (II-a) and subsequently selectively removing one of the P-groups, e.g. when P is benzyl by a catalytic hydrogenation procedure using one equivalent hydrogen. The afore described reactions to prepare (III-a) or (III-b) are conducted following the same procedures as described hereinabove for the preparation of the compounds (I).

The starting materials (II-a) are obtained by an oxiraneformation reaction from an aldehyde of formula (IV-a), e.g. by reaction of the latter with a trimethylsulfoxonium halide, or from an ethylene of formula (V-a) by reaction of the latter with a peroxide, e.g. a haloperbenzoic acid. In the same way, the intermediate (II-b) is obtained from the corresponding S-isomers (IV-b) or (V-b). The oxiranes of formula (IV-a-1) obtained in the aforementioned oxirane-formation reaction are separated in their stereoisomers, e.g. by HPLC or selective crystallization.



The compounds of formula (IV-a), (IV-b), (V-a) or (V-b) are obtained by a suitable separation procedure, i.e. by HPLC, or by a reduction

reaction of the corresponding optically active racemic acids whereas (IV-a) or (IV-b) can be converted to (V-a) or (V-b) by a Wittig reaction. The said corresponding optically active acids in turn can be obtained by conventional separation techniques, i.e. by salt or amide formation with an optically active reagent and a selective crystallization procedure or a HPLC separation.

The compounds of formula (I) have basic properties and, consequently, they may be converted to their therapeutically active non-toxic acid addition salt forms by treatment with appropriate acids, such as, for example, inorganic acids, such as hydrohalic acid, e.g. hydrochloric, hydrobromic and the like, and sulfuric acid, nitric acid, phosphoric acid and the like; or organic acids, such as, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids.

Conversely, the salt form can be converted by treatment with alkali into the free base form.

The compounds of formula (I) with the exception of (RSSS)-α,α'-[iminobis(methylene)bis(3,4-dihydro-2H-1-benzopyran-2-methanol] ethanedioate(1:1) are deemed to be novel compounds and constitute in an additional feature to the present invention.

The compounds of formula (I) and the pharmaceutically acceptable acid addition salts thereof potentiate the activity of blood pressure reducing agents. In particular they potentiate the reduction of the blood pressure and of the heart rate.

As blood pressure reducing agents of which the activity is potentiated there may be mentioned agents having adrenergic and/or vasodilating activity. In particular such agents may be the compounds mentioned in U.S. Pat. Nos. 3,663,607 and 3,836,671, in particular

atenolol; U.S. Pat. Nos. 3,337,628 and 3,520,919, in particular propranolol; U.S. Pat. No. 3,873,600, in particular metoprolol; U.S. Pat. No. 3,511,836, in particular prazosin; U.S.Pat. No. 2,484,029, in particular hydralazine; U.S. Pat. No. 2,928,829 in particular guanethidine; U.S. Pat. No. 2,503,059, in particular phentolamine; U.S. Pat. No. 3,261,859, in particular verapamil; U.S. Pat. No. 3,485,847 in particular nifedipine; U.S. Pat. No. 3,910,924, in particular carteolol; German Pat. Nos. 2,458,624 and 2,458,625, in particular celiprolol. A particular group of blood pressure reducing compounds are the compounds of U.S. Pat. No. 4,654,362 other than the compounds of formula (I) and in particular the enantiomers of the compounds of formula (I), i.e. the SRRR-isomers. A particular compound is [2S,αR,2'R,α'R]-α,α'-[iminobis-methylene]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol. These groups of active ingredients are listed with the purpose of providing representative examples but not with the purpose of restricting the scope of the present invention. The said SRRR isomers and the said particular compound can be prepared following the same procedures as previously described for the preparation of the compounds of formula (I), but starting from the enantiomers of the intermediates (II-a), (III-a), (II-b) and (III-b). The latter enantiomers in turn can be obtained as described hereinabove for the preparation of (II-a), (III-a), (II-b) and (III-b), but starting from the enantiomers of (IV-a) or (V-a) and isolating the appropriate stereoisomers in stereochemical separation procedures. The enantiomers of (IV-a) and (V-a) in the same way can be obtained as described for the preparation of (IV-a) and (V-a) starting from the appropriate enantiomeric starting materials and/or isolating the appropriate stereoisomers in stereochemical separations.

The compounds of formula (I) and the acid addition salts thereof may be administered before, during or after the administration of the blood pressure reducing agent provided that the time of the administration of the compounds of formula (I) in relation to the administration of the blood pressure reducing agent allows the compound of formula (I) to be effective in potentiating the effects of the blood pressure reducing agent. Preferably the compound of formula (I) and the blood pressure reducing agent are administered in the form of suitable compositions. Said compositions are meant to also comprise products containing a compound of formula (I) as defined hereinabove and a blood-pressure reducing agent as a combined preparation for simultaneous, separate or sequential use in blood-pressure reducing therapy. Such products may

for example comprise a kit comprising a container with a suitable composition containing a compound of formula (I) and another container containing a composition with a blood pressure reducing agent. Such product may have the advantage that the physician wishing to administer blood pressure reducing therapy can select, based on the diagnosis of the patient to be treated, the appropriate amounts of both components and the sequence of administration.

When administered during the administration of the blood pressure reducing agent, a composition containing both the blood pressure reducing agent and the active ingredient of formula (I) may particularly be convenient.

In a further aspect of the present invention there is provided a composition comprising an amount capable of potentiating the effects of blood pressure reducing agents of a compound of formula (I) as defined hereinabove and a blood pressure reducing agent. In the said composition, the molar ratio between the compound of formula (I) and the blood pressure reducing agent may be other than 1:1, but in particular may be 1:1. The amount of the active ingredient of formula (I) in such composition will be so that a potentiating effect on the effects of the blood-pressure reducing agent is obtained; the amount of the blood pressure reducing agent will be so that when potentiated, a blood pressure reducing effect is obtained upon administration. In particular, it is contemplated that the molar ratio of the compound of formula (I) to the blood pressure reducing compound may be situated between 50:1 and 1:50, in particular between 20:1 and 1:20, or between 10:1 and 1:10, or between 5:1 and 1:5, more particularly between 2:1 and 1:2. Particular such compositions are those wherein the blood pressure reducing agent is one of the agents pertaining to the patents cited hereinabove, and more particularly the agents specifically mentioned hereinabove.

The present invention also provides a composition comprising a pharmaceutically acceptable carrier and as active ingredient an amount capable of potentiating the effects of blood pressure reducing agents of a novel compound of formula (I) or a pharmaceutically acceptable acid-addition salt thereof, as defined hereinabove.

To prepare such pharmaceutical compositions, an effective amount of the particular compound or compounds, in base or acid-addition salt form, as the active ingredient or active ingredients is combined in intimate admixture with a pharmaceutically acceptable carrier, which

carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause a significant deletorious effect to the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment. Acid addition salts of (I) due to their increased water solubility over the corresponding base form, are obviously more suitable in the preparation of aqueous compositions.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical

carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

The present invention also concerns a method of potentiating the effects of blood pressure reducing agents in warm-blooded animals in need of blood pressure reducing medication, said method comprising administering to said warm-blooded animals of an effective amount of a blood pressure reducing agent and a compound of formula (I) as defined hereinabove.

Or alternatively, the present invention concerns a method of lowering the blood pressure in warm-blooded animals suffering therefrom, said method comprising administering to said warm-blooded animals of an effective amount of a blood pressure reducing agent and a compound of formula (I) as defined hereinabove.

Those of skill in treating subjects suffering from an increased blood pressure could easily determine the effective amount from the test results presented hereinafter. In general it is contemplated that an effective daily dose of the compounds of formula (I) or their pharmaceutically acceptable acid-addition salts would be from 0.01 mg/kg to 50 mg/kg body weight, in particular from 0.1 mg/kg to 10 mg/kg body weight and preferably from 0.1 mg/kg to 1 mg/kg body weight.

All above cited references are incorporated herein by reference.

The following examples are intended to illustrate and not to limit the scope of the present invention in all its aspects. Unless otherwise stated all parts therein are by weight.

Whenever used in the following examples "A" refers to the isomer which was first isolated and "B" to the one which was subsequently isolated.

EXPERIMENTAL PART

A. Preparation of the intermediates

Example 1

a) A mixture of 63.4 parts of 6-fluoro-4-oxo-4H-1-benzopyran-2-carboxylic acid and 400 parts of acetic acid was hydrogenated at normal pressure and at room temperature with 3 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was stirred in petroleumether. The product was filtered off and dried in vacuo at 70°C, yielding 49 parts (83%) of 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid (int. 1).

b) To a stirred solution of 9.75 parts of intermediate 1 in 90 parts of methylbenzene were added 16 parts of thionyl chloride. The mixture was stirred for 2 hours at 60°C. The reaction mixture was evaporated. The residue was taken up twice in 45 parts of methylbenzene and the latter was evaporated each time. The residue was taken up in 90 parts of methylbenzene. There were added first 10.5 parts of N,N-diethylethanamine and then a solution of 14.25 parts of (+)-1,2,3,4,4a,9,10,10a-octahydro-1,4a-dimethyl-7-(1-methylethyl)-1-phenanthrenemethanamine [(+)-dehydroabiethylamine] in 45 parts of methylbenzene. After stirring for 2 hours, the organic layer was washed successively with water, a sodium hydroxide solution 10%, a hydrochloric acid solution 10% and water, dried, filtered and evaporated. The residue was taken up in 120 parts of warm ethanol. The product was filtered off and crystallized from ethanol, yielding 6.6 parts (28.4%) of (A)-6-fluoro-3,4-dihydro-N-[dehydroabiethyl]-2H-1-benzopyran-2-carboxamide (int. 2).

c) A mixture of 6.8 parts of intermediate 2, 75 parts of acetic acid and 36 parts of concentrated hydrochloric acid was stirred for 24 hours at reflux temperature. After cooling, the reaction mixture was poured into water. The product was extracted with 1,1'-oxybisethane. The extract was washed twice with water, dried, filtered and evaporated. The residue was taken up in 1,1'-oxybisethane. 5 Parts of a sodium hydroxide solution were added. The product was filtered off, taken up in trichloromethane and treated with 50 parts of a hydrochloric acid solution 10%. The organic layer was dried, filtered and evaporated, yielding 1.1 parts of

(+)-(S)-6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid; mp. 99.7°C $[\alpha]_D^{25}$ =+14.88° (c= 1% in DMF) (int. 3).

d) To a stirred solution of 22.5 parts of intermediate 3 in 180 parts of tetrahydrofuran were added 18.7 parts of 1,1'-carbonylbis[1H-imidazole]. The whole was stirred for 1 hour at room temperature and cooled to -70°C. 136 Parts of a 25% solution of [bis(2-methylpropyl)]aluminum hydride in methylbenzene were added dropwise during a period of 20 minutes. Upon completion, stirring was continued for 20 minutes at -70°C. 40 Parts of methanol were added and the mixture was poured into water. The product was extracted with 1,1'-oxybisethane. The extract was washed successively with a hydrochloric acid solution 10%, water and a sodium hydrogen carbonate solution, dried, filtered and evaporated, yielding 12 parts (57.9%) of (+)-(S)-6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxaldehyde as an oily residue (int. 4).

e) 6.3 Parts of a sodium hydride dispersion 50% were washed twice with petroleum ether and then taken up in 250 parts of dimethyl sulfoxide. 29 Parts of trimethylsulfoxonium iodide were added during a period of 30 minutes and stirring was continued for 20 minutes. A solution of 12 parts of intermediate 4 in 10 parts of dimethyl sulfoxide was added dropwise and upon completion, the mixture was stirred for 30 minutes. The reaction mixture was poured into water and the product was extracted with 1,1'-oxybisethane. The extract was washed three times with water, dried, filtered and evaporated. The residue was purified by column chromatography (HPLC) over silica gel using a mixture of methylbenzene and ethyl acetate (90:10 by volume) as eluent. The pure fractions were collected and the eluent was evaporated, yielding 2.1 parts (9.8%) of (+)-[S(S)]-6-fluoro-3,4-dihydro-2-oxiranyl-2H-1-benzopyran as an oily residue (int. 5).

Example 2

a)In the procedure described hereinabove in example 1b) 6.1 parts (26.3%) of the compound (B)-6-fluoro-3,4-dihydro-N-[dehydroabiethyl]-2H-1-benzopyran-2-carboxamide (int. 6) was obtained as a residue.

b) A mixture of 6.1 parts of intermediate 6, 75 parts of acetic acid and 36 parts of concentrated hydrochloric acid was stirred for 24 hours at

reflux temperature. The reaction mixture was poured into water. The product was extracted with 1,1'-oxybisethane. The extract was washed twice with water, dried, filtered and evaporated in vacuo. The residue was crystallized from petroleum ether. The product was filtered off and dried, yielding 0.9 parts of (-)-(R)-6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid; mp. 102.5°C $[\alpha]_D^{25}$ = -13.39° (c= 1% in DMF) (int. 7).

c) To a stirred and refluxed solution of 36 parts of intermediate 7 in 400 parts of methanol were added 1.8 parts of sulfuric acid. The mixture was further and refluxed for 4 hours. After cooling, the reaction mixture was evaporated. The residue was taken up in 1,1'-oxybisethane. The mixture was washed successivily twice with a sodium hydrogen carbonate solution and once with water, dried, filtered and evaporated, yielding 33 parts (82.6%) of (-)-(R)-methyl 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxylate as an oily residue (int. 8).

d) To a stirred and cooled (-80°C) solution of 33 parts of intermediate 8 in 450 parts of methylbenzene were added dropwise 255 parts of a solution of [bis(2-methylpropyl)]aluminium hydride in methylbenzene under nitrogen atmosphere. Stirring was continued for 30 minutes at -80°C. 16 Parts of methanol were added and the reaction mixture was poured into water. The mixture was acidified with hydrochloric acid and the two layers were separated. The organic phase was dried, filtered and evaporated, yielding an oily residue of 32 parts (the residue was set aside). 9.6 Parts of a sodium hydride dispersion 50% were washed first three times with petroleumether and then taken up in 500 parts of dimethyl sulfoxide. 44 parts of trimethylsulfoxonium iodide were added portionwise and after complete addition, the whole was stirred for 20 minutes at room temperature. To the thus obtained mixture was added dropwise a solution of 32 parts of the oily residue, which was set aside (see above), in 20 parts of dimethyl sulfoxide. Upon completion, stirring was continued for 20 minutes at room temperature. The whole was poured into water and the product was extracted with 2,2'-oxybispropane. The extract was dried, filtered and evaporated. The residue was separated by column chromatography (HPLC) over silica gel using a mixture of hexane and ethyl acetate (80:20 by volume) as eluent. The desired fractions

were collected and the eluent was evaporated, yielding 8.2 parts (24.8%) of (-)-[R(S)]-6-fluoro-3,4-dihydro-2-oxiranyl-2H-1-benzopyran as a residue (int. 9).

e) A solution of 8.2 parts of intermediate 9 and 20 parts of benzenemethanamine in 80 parts of methanol was stirred overnight at room temperature. The reaction mixture was evaporated and the residue was taken up in 2,2'-oxybispropane. The precipitated product was filtered off and crystallized from acetonitrile. The product was filtered off and dried, yielding 4.6 parts (38.1%) of (-)-[R(S)]-6-fluoro-3,4-dihydro-α-[[(phenylmethyl)amino]methyl]-2H-1-benzopyran-2-methanol (int. 10).

B. Preparation of the final compounds

Example 3

a) A solution of 1.8 parts of intermediate 5 and 2 parts of intermediate 10 in 40 parts of ethanol was stirred for 4 hours at reflux temperature. The reaction mixture was evaporated, yielding 3.5 parts (100%) of [2R,αS,2'S,α'S]-α,α'-[[(phenylmethyl)imino]bismethylene]bis-[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol] as a residue (int. 11).

b) A mixture of 3.5 parts of intermediate 11 and 250 parts of 2-methoxyethanol was hydrogenated at normal pressure and at room temperature with 2 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was taken up in trichloromethane and purified by column chromatography over silica gel using trichloromethane as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized twice from acetonitrile. The product was filtered off and dried, yielding 1.2 parts (42%) of [2R,αS,2'S,α'S]-α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol]; mp. 142.7°C (compound 1).

Example 4

A mixture of 19.4 parts of (RS,SS)-α,α'-[[(phenylmethyl)imino]bis-(methylene)bis[3,4-dihydro-2H-1-benzopyran-2-methanol], prepared as described in US-4,654,362 (see compound 16 in the experimental part of the latter; the designation "A^-B^+ referring to the RSSS isomer) and

243 parts of 2-methoxyethanol was hydrogenated at normal pressure and at room temperature with 2 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the reaction mixture was filtered over diatomaceous earth and evaporated. The residue was crystallized twice from acetonitrile, yielding 6.8 parts (43.8%) of (RS,SS)-α,α'-[iminobis(methylene)]]bis[3,4-dihydro-2H-1-benzopyran-2-methanol]; mp. 136.1°C (compound 2).

Example 5

A mixture of 6 parts of intermediate 10, 5 parts of (SS)-3,4-dihydro-2-oxiranyl-2H-1-benzopyran, prepared as described in example 17 of US-4,654,362 (intermediate 53, the designation "B^+" referring to the SS-isomer) and 119 parts of ethanol was refluxed for 18 hours. The reaction mixture was evaporated and the residue was added to 275 parts of 2-methoxyethanol and hydrogenated at normal pressure and at room temperature with 2 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was crystallized from acetonitrile, yielding 3.8 parts (49.3%) of (RSSS)-α-[[[2-(3,4-dihydro-2H-1-benzopyran-2-yl)-2-hydroxyethyl]amino]methyl]-6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol; mp. 154.2°C (compound 3).

Example 6

Following the same procedures as described in example 5 and starting from (SS)-6-fluoro-3,4-dihydro-α-[[(phenylmethyl)amino]methyl]-2H-1-benzopyran-2-methanol (obtained from the reaction of intermediate 5 with benzenemethanamine) and (SR)-3,4-dihydro-2-oxiranyl-2H-1-benzopyran (obtained as described in example 17, compound 52 of US-4,654,362; the designation "A^-" referring to the SR isomer) there was also prepared (SSSR)-α-[[[2-(3,4-dihydro-2H-1-benzopyran-2-yl)-2-hydroxyethyl]amino]-methyl]-6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol; mp. 140.7°C (compound 4).

C. Pharmacological examples

Adult spontaneous hypertensive rats (6 months of age) were

anesthetized by ether inhalation. The femoral artery was dissected and cannulated, and the catheter was connected to a strain-gauge blood pressure transducer. When the animals were fully awake, they were restrained and the systolic and diastolic arterial blood pressure were continuously recorded. An observation period of at least 30 min preceded the administration of the test compound. All test compounds were dissolved in 20% polypropylene glycol and injected intraperitoneally. After administration of the test drug the systolic and diastolic arterial blood pressure and the heart rate were recorded during a period of 120 minutes. The average blood pressure and heart rate was calculated from the results obtained at various time intervals after administration of the test drug. The following table illustrates the difference between treated and untreated animals expressed as a percentage (Δ%) in the systolic and diastolic blood pressure and the heart rate.

Δ% Changes (average 120 min) in systolic and diastolic (SBP, DBP) and in heart rate (HR) in spontaneous hypertensive rats

	* 1.25 mpk	Hydralazine 0.63 mpk	Guanethidine 2.5 mpk	Phentolamine 0.63 mpk
SBP	0	-7.5	-9.3	-9.85
DBP	+2.1	-9.9	-6.2	-13.1
HR	0.5	-1.45	-7.9	+5.1
		Hydralazine 0.63 mpk + * 1.25	Guanethidine 2.5 mpk + * 1.25	Phentolamine 0.63 mpk + * 1.25
SBP		-20.9	-15.7	-16.7
DBP		-28	-16.7	-21.2
HR		-3.6	-17.6	+0.9

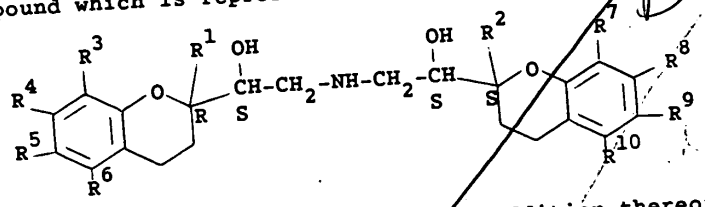
TD160

	* 2.5 mpk	Atenolol 10 mpk	Propranolol 5 mpk	Metoprolol 10 mpk	Prazosin 0.01 mpk
SBP	-7	-3.7	-2	-1.2	-10.9
DBP	0	+5.9	+12.4	+12.8	-11.3
HR	0	-28.1	-20.7	-16.6	+1.6
		Atenolol 10 mpk + * 2.5	Propranolol 5 mpk + * 2.5	Metoprolol 10 mpk + * 2.5	Prazosin 0.01 mpk + * 2.5
SBP		-21	-9.6	-12.7	-27.6
DBP		-21	+3.2	-4	-28.7
HR		-32	-33.1	-28.25	-6.8

* = [2R,αS,2'S,α'S]-α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol]. (compound 1).

What is claimed is :

1. A method of potentiating the effects of blood pressure reducing agents in warm-blooded animals in need of blood pressure reducing medication, said method comprising administering to said warm-blooded animals of an effective amount of a blood pressure reducing agent and a compound which is represented by the formula



(I),

or a pharmaceutically acceptable acid addition thereof, wherein

R^1 and R^2 each independently are hydrogen or C_{1-6}alkyl;

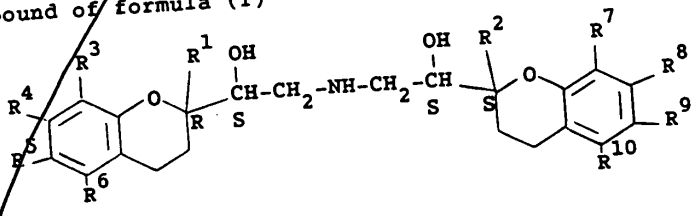
R^3, R^4, R^5, R^6, R^7, R^8, R^9 and R^{10} each independently are hydrogen, halo, C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxy, cyano, carboxy or C_{1-6}alkyloxycarbonyl;

or two vicinal radicals of R^3, R^4, R^5, R^6, R^7, R^8, R^9 and R^{10} taken together may form a -CH=CH-CH=CH- or $-(CH_2)_4-$ radical.

2. A method according to claim 1 wherein R^3, R^4, R^6, R^7, R^8, R^9 and R^{10} are hydrogen.

3. A method according to claim 1 wherein the compound is [2R,αS,-2'S,α'S]-α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol].

4. A pharmaceutical composition comprising an amount, capable of potentiating the effects of blood pressure reducing agents, of a compound of formula (I)



(I),

or a pharmaceutically acceptable acid addition thereof, wherein R^1 and R^2 each independently are hydrogen or C_{1-6}alkyl; R^3, R^4, R^5, R^6, R^7, R^8, R^9 and R^{10} each independently are hydrogen, halo, C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxy, cyano, carboxy or C_{1-6}alkyloxycarbonyl; or two vicinal radicals of R^3, R^4, R^5, R^6, R^7, R^8, R^9 and R^{10} taken together may form a -CH=CH-CH=CH- or $-(CH_2)_4-$ radical, and an effective amount of a blood pressure reducing agent.

5. A composition according to claim 4 wherein R^3, R^4, R^6, R^7, R^8, R^9 and R^{10} are hydrogen.

6. A composition according to claim 4 wherein the compound of formula (I) is [2R,αS,2'S,α'S]-α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol].

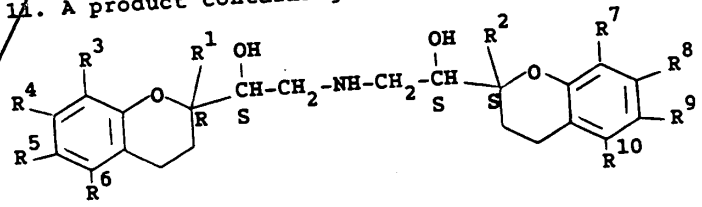
7. A composition according to claim 4 wherein the blood pressure reducing agent is selected from atenolol, propranolol, metoprolol, prazosin, hydralazine, guanethidine, phentolamine, verapamil, nifedipine, carteolol, celiprolol.

8. A composition according to claim 4 wherein the blood pressure reducing agent is [2S,αR,2'R,α'R)-α,α'-[iminobismethylene]bis-[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol].

9. A composition according to claim 8 wherein the molar ratio of both active ingredients is 1:1.

10. A composition according to claim 8 wherein the molar ratio of both active ingredients is other than 1:1.

11. A product containing a chemical compound of formula



(I),

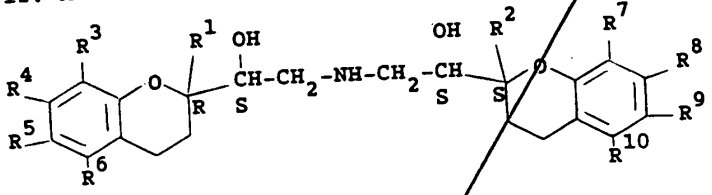
or a pharmaceutically acceptable acid addition thereof, wherein

R^1 and R^2 each independently are hydrogen or C_{1-6}alkyl;

R^3, R^4, R^5, R^6, R^7, R^8, R^9 and R^{10} each independently are hydrogen, halo, C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxy, cyano, carboxy or C_{1-6}alkyloxycarbonyl;

or two vicinal radicals of R^3, R^4, R^5, R^6, R^7, R^8, R^9 and R^{10} taken together may form a -CH=CH-CH=CH- or $-(CH_2)_4-$ radical, and a blood pressure reducing agent, as a combined preparation for simultaneous, separate or sequential use in blood pressure reducing therapy.

12. A chemical compound of formula



(I),

or a pharmaceutically acceptable acid addition thereof, wherein

R^1 and R^2 each independently are hydrogen or C_{1-6}alkyl;

R^3, R^4, R^5, R^6, R^7, R^8, R^9 and R^{10} each independently are hydrogen, halo, C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxy, cyano, carboxy or C_{1-6}alkyloxycarbonyl;

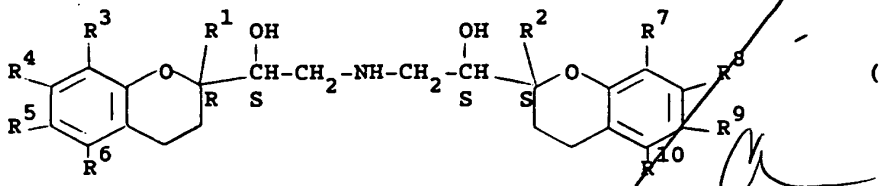
or two vicinal radicals of R^3, R^4, R^5, R^6, R^7, R^8, R^9 and R^{10} taken together may form a -CH=CH-CH=CH- or $-(CH_2)_4-$ radical, the compound (RSSS)-α,α'-[iminobis(methylene)bis(3,4-dihydro-2H-1-benzopyran-2-methanol] ethanedioate(1:1) being excluded.

13. A compound according to claim 12 wherein R^3, R^4, R^6, R^7, R^8, R^9 and R^{10} are hydrogen.

14. A compound according to claim 12 wherein the compound is [2R,αS,2'S,α'S]-α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol].

15. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredient an amount capable of

potentiating the effects of blood pressure reducing agents of a compound of formula (I)



(I),

or a pharmaceutically acceptable acid addition thereof, wherein

R^1 and R^2 each independently are hydrogen or C_{1-6}alkyl;

R^3, R^4, R^5, R^6, R^7, R^8, R^9 and R^{10} each independently are hydrogen, halo, C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxy, cyano, carboxy or C_{1-6}alkyloxycarbonyl;

or two vicinal radicals of R^3, R^4, R^5, R^6, R^7, R^8, R^9 and R^{10} taken together may form a -CH=CH-CH=CH- or $-(CH_2)_4-$ radical, the compound (RSSS)-α,α'-[iminobis(methylene)bis(3,4-dihydro-2H-1-benzopyran-2-methanol] ethanedioate(1:1) being excluded.

16. composition according to claim 15 wherein R^3, R^4, R^6, R^7, R^8 and R^{10} are hydrogen.

17. A composition according to claim 15 wherein the compound of formula (I) is [2R,αS,2'S,α'S]-α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol].

ABSTACT

METHOD OF LOWERING THE BLOOD PRESSURE

A method of potentiating the effects of blood pressure reducing agents in warm-blooded animals, said method comprising administering to said warm-blooded animals of an effective amount of a blood pressure reducing agent and a 2,2'-iminobisethanol derivative.

07/825488

JAB 775

#31B 4pm 2/28/92

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Raymond Mathieu Xhonneux et al.

Serial No.: Rule 60 Continuation of Serial No. 07/325,181 Filed March 16, 1989 — Art Unit: 125 — Examiner: R. Travers

For : METHOD OF LOWERING THE BLOOD PRESSURE

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

PRELIMINARY AMENDMENT AND
INFORMATION DISCLOSURE STATEMENT

Prior to examination, please amend the above-identified application as follows:

In The Specification

Page 1, cancel lines 14-15 and insert therefor the following paragraph:

--- This application is a continuation of our copending application Serial No. 07/325,181, filed on March 16, 1989, (now abandoned) which in turn was a continuation-in-part of application Serial No. 07/172,747, filed on March 23, 1988. (now abd) ---

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Page 2, line 22, delete R^9.

In The Claims

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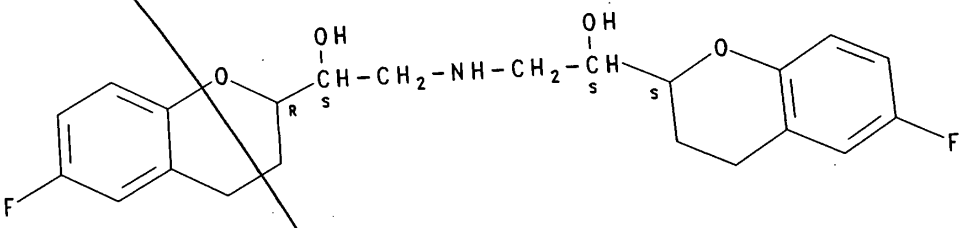
Cancel Claim 1 and add the following claims:

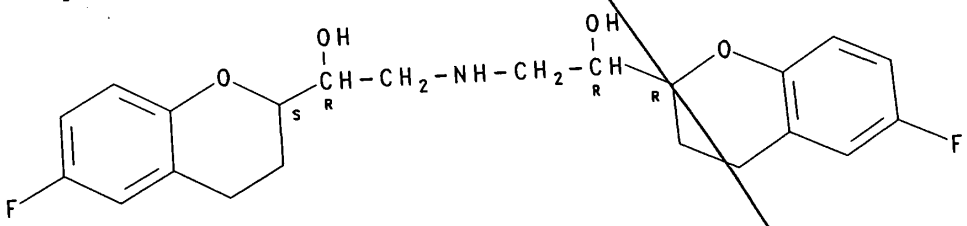
18. The compound [2R,αS,2'S,α'S]-α,α'-[iminobismethylene]-bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol] having the formula:



or a pharmaceutically acceptable acid addition salt thereof.

19. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredients, the compounds:

(a) the blood pressure reducing compound [2S,αR,2'R,α'R]-α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol] having the formula:



or a pharmaceutically acceptable acid addition salt thereof; and

(b) the compound of claim 18 in an amount capable of potentiating the blood pressure lowering effect of compound (a), above.

20. A composition according to Claim ~~19~~ 26 wherein the molar ratio of the compounds (a) and (b) is within the range of from about 5:1 to about 1:5.

21. A composition according to Claim ~~19~~ 26 wherein the molar ratio of the compounds (a) and (b) is about 1:1.

22. A method of treating hypertension in warm blooded animals in need of such treatment which comprises administering to said warm blooded animals an effective amount of the pharmaceutical composition of Claim ~~19~~ 26.

23. A method of treating hypertension in warm blooded animals in need of such treatment which comprises administering to said warm blooded animals an effective amount of the pharmaceutical composition of Claim 20.

24. A method of treating hypertension in warm blooded animals in need of such treatment which comprises administering to said warm blooded animals an effective amount of the pharmaceutical composition of Claim 21.

REMARKS

In the specification, the status of the parent applications has been brought up to date, and an error on page 2, line 22, has been corrected.

Applicants intend to expressly abandon the immediate parent application, Serial No. 07/325,181, as soon as Applicants receive the filing receipt for the present application.

The claimed invention relates to a particular stereoisomeric form of the base compound α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol], to a pharmaceutical composition containing this compound plus a particular blood pressure reducing agent (the mirror image stereoisomer of the subject claimed compound), and to a method of treating hypertension in warm blooded animals which comprises administering to warm blooded animals in need of such treatment an effective amount of said pharmaceutical composition.

The base compound α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol] is a compound having the structure:

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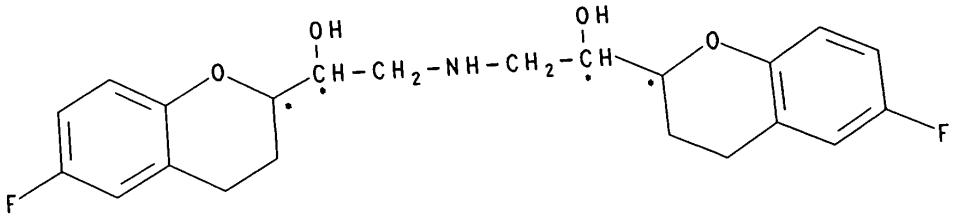

This compound has four asymmetric centers, which are indicated in the formula with asterisks ("*"). Each asymmetric center can have either of two absolute spatial configurations, designated by convention as "R" or "S". Theoretically, a compound having 4 asymmetric centers, each of which can have 2 absolute spatial configurations, would have sixteen [i.e., 2^4] possible specific stereoisomers or diastereomers. The present base compound, however, has only ten diastereomers. The enumeration and description of the ten possible diastereomers can be explained by reference to the system that is used to refer to the possible diastereomers in the prior art patent that discloses the base compound.

The base compound, unresolved into specific diastereomers, is known from Van Lommen et al., U.S. Patent No. 4,654,362 (see compound Nos. 84 and 87, shown in the table in Col. 21 of the patent). Compound Nos. 84 and 87 of Van Lommen et al. are designated as "AB" and "AA" diastereomers of the base compound. It is pointed out at Col. 5, lines 1-4 of Van Lommen et al., that the "A" designation denotes the RS or the SR configuration (which one is not specified - thus, the designation "A" can be taken to denote a mixture of both the RS and the SR diastereomers) and the "B"

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designation denotes the RR or the SS configuration (which one is not specified - thus, the designation "B" can be taken to denote a mixture of both the SS and the RR diastereomers). Since "A" or "B" refers to one half of the molecule, it is seen that, using the system Van Lommen et al. used, the possible stereoisomeric designations for the final molecules are "AA", "AB", "BA", or "BB". The possible absolute configurations are therefore the following:

From the AA designation:

Since A = RS + SR, then AA = (RS + SR) · (RS + SR);

(RS + SR) · (RS + SR) = RSRS + RSSR + SRRS.

Thus there are three possible absolute stereoisomeric configurations with the AA designation. [The SRSR configuration, which is formed by addition of SR + SR, is equivalent to the RSRS configuration because both right and left halves of the molecule (as one views the formula shown above) are identical, but just "written" either forwards or backwards, say, like HAT or TAH.]

From the BB designation:

Since B = RR + SS, then BB = (RR + SS) · (RR + SS);

(RR + SS) · (RR + SS) = RRRR + RRSS + SSSS.

There are therefore three possible absolute configurations with the BB designation. (The SSRR configuration, which is formed by addition of SS + RR, is identical to the RRSS configuration.)

From the AB designation:

A = RS + SR and B = RR + SS; AB = (RS + SR) · (RR + SS);

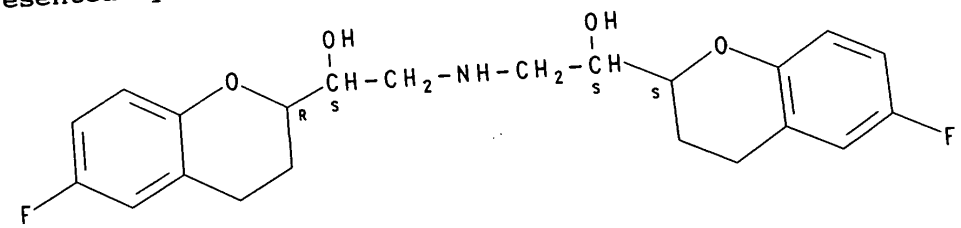
(RS + SR) · (RR + SS) = RSRR + RSSS + SRRR + SRSS.

Thus, four possible diastereomers are possible from the AB designation.

All possible diastereomers formed from the BA designation would be identical to those formed from the AB designation.

From the above discussion, it is seen that there are a total of ten possible diastereomers of the base compound. The present invention is based on the discovery that one of these ten possible diastereomers possesses unexpected properties, as is discussed more fully below.

The specific stereoisomeric compound of the invention is represented by the formula:



It will be seen that the four asymmetric centers, reading from left to right in the formula, have, respectively, the R, S, S, and

S absolute configurations. For brevity, this compound will be referred to herein as the "RSSS compound". The RSSS compound is the preferred compound disclosed in the subject specification, as is disclosed on page 2, lines 25-27.

The mirror image of the RSSS compound will be referred herein to as the "SRRR compound". As is disclosed in the specification at page 6, lines 12-13, the SRRR compound is a preferred blood pressure reducing agent to be used in combination with the RSSS compound.

The subject RSSS compound has an unexpected and valuable potentiating effect on blood pressure reducing compounds, and in particular, on its mirror image diastereomer, the SRRR compound. This unexpected potentiating effect will be demonstrated below.

The Examiner's attention is now specifically directed to the accompanying Rule 132 Declarations, one by Applicant Xhonneux and one by Petrus J. Pauwels. Please refer first to Mr. Xhonneux' Declaration, in which biological data demonstrating the potentiating effect of the subject RSSS compound is presented. Table 1 presents data showing the effect of various dosages of the subject RSSS compound alone on spontaneously hypertensive rats "SHR". It is seen that (i) at dosages of up to 5 mg/kg, there is no significant effect on diastolic blood pressure, (ii) at a dosage of 2.5 mg/kg, there is only a slight effect on systolic blood pressure, and (iii) at a dosage of 5 mg/kg there is only a slight effect on heart rate. Thus, it is clear that the subject RSSS

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compound only minimally affects blood pressure and heart rate when given alone.

The Examiner's attention is now respectfully invited to Tables 2 and 3. Table 2 presents data in which SHR were given the mirror image SRRR compound alone at varying dosages. Table 2 shows that a significant systolic blood pressure reduction is obtained at a dosage of 0.63 mg/kg of the SRRR compound and a significant diastolic blood pressure reduction is obtained at a dosage of 1.25 mg/kg of the SRRR compound.

Table 3 presents data in which SHR were given a dosage of 1.25 mg/kg of the SRRR compound, and varying dosages of the subject RSSS compound, from 0 up to 5 mg/kg. As can be seen from the data in which no RSSS compound is added to the SRRR compound (and also from the data presented in Table 2), the SRRR compound is a potent blood pressure reducing agent when used by itself. However, please note that a significant reduction in systolic blood pressure is seen when 0.16 mg/kg of the subject RSSS compound is added to the 1.25 mg/kg of the SRRR compound; a significant reduction is diastolic blood pressure is seen when 0.31 mg/kg of the subject RSSS compound is added to the 1.25 mg/kg of the SRRR compound; and significant additional heart rate reduction is seen when a dosage of 2.5 mg/kg of the subject RSSS compound is added to the 1.25 mg/kg of the SRRR compound. As this data demonstrates, at dosages in which the subject RSSS compound has little or no effect when used alone, when it is combined with the SRRR compound, significant additional blood pressure reducing effect is obtained. Also, please compare, for

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instance, the data from Table 3 wherein 1.25 mg/kg of each compound was administered (i.e., a total dosage of the base compound of 2.5 mg/kg) with the results shown in Table 2 wherein 2.5 mg/kg of the SRRR compound was used (again, a dosage of the base compound of 2.5 mg/kg). It is seen that when the mixture of the two compounds is used, a significantly greater decrease in blood pressure is obtained than when the SRRR compound is used alone in an equimolar amount.

The experimental results presented in the Xhonneux Declaration are shown graphically on page 264 of the Xhonneux et al. article that is appended to the Xhonneux Declaration. It is believed that the data presented in the Xhonneux Declaration and shown in the said article illustrates a classic case of synergistic results wherein the benefits of the two materials when used in combination far exceeds the additive effects what would have been expected from their properties that are observed when each is used alone.

The Examiner's attention is now respectfully directed to the Pauwels Declaration and the Pauwels et al. article that is appended thereto. This article relates to the receptor binding profile of the enantiomers of the compound α,α'-[iminobis(methylene)]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol], the base compound of the subject claimed RSSS compound, and the SRRR compound. In the article, the RSSS isomer is identified as R 67,145 and the SRRR compound is identified as R 67,138. First, please refer to page 848, right hand column, at lines 2-6. As disclosed here in the article, the 1:1 mixture of these two enantiomers, identified by

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the generic name "nebivolol", is found to be a potent β_1-adrenergic blocker as tested by binding studies on receptors in rabbit lung, the SRRR compound (R 67,138) is equally potent (and therefore is a conventional β-adrenergic blocking agent), whereas the RSSS isomer (R 67,145) is 175-fold less potent. Thus, while the RSSS isomer of this invention does have β-adrenergic blocking activity, it is considerably less potent than conventional β-blockers. Therefore, it is surprising that when it is mixed with a conventional β-blocker, the said β-blocker is potentiated by a significant degree.

The Examiner's attention is now respectfully directed to page 849 of the Pauwels et al. article. Please note the discussion beginning in the middle of the right hand column. The following quotation is significant:

> **Mode of action of nebivolol as antihypertensive agent.** Clinical and *in vivo* pharmacological studies with nebivolol revealed an interesting hemodynamic profile, different from that of classical β-adrenergic blockers (see introduction). Observed reductions in heart rate can probably be attributed to β_1-adrenergic receptor blockade. However, improved left ventricular function, reduction in systemic vascular resistance, and related cardiac output seen with nebivolol are not properties of classical β-adrenergic blockers. Also, the immediate reduction in blood pressure, obtained after administration of nebivolol to conscious spontaneous hypertensive rats, has not been observed with known β-adrenergic blockers. Recent observations have revealed that the particular hemodynamic profile is specifically obtained with nebivolol, whereas the β_1-adrenergic active enantiomer R 67,138 (S,R,R,R) showed the activities of a typical β-adrenergic blocker. Hence the properties of nebivolol apparently resulted from the combined activities of the two enantiomers. (Underscoring added.)

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The underscored matter in this quotation speaks for itself. However, it is clear that the combination of the two enantiomers, i.e., the SRRR and the RSSS enantiomers, do not behave like the heretofore known β-blockers. This is entirely unexpected and could not have been predicted from the prior art.

For all of the reasons that are set forth above, and for the reasons that are presented in the accompanying Declarations by Messrs. Pauwels and Xhonneux, it is urged that the presently claimed invention is patentable over the Van Lommen et al. patent, U.S. Patent No. 4,654,362. A copy of this patent is included herewith along with a filled out form PTO 1449.

Early favorable action is respectfully requested.

Respectfully submitted,

Charles J. Metz

Charles J. Metz
Attorney for Applicant(s)
Registration #20,359

Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933

(908) 524-2814

January 24, 1992

B

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

ONLINE SEARCH REQUEST FORM

USER R T Travers SERIAL NUMBER 07,325,481

ART UNIT 125 PHONE 9580 DATE 2-26-90

Please give a detailed statement of requirements. Describe as specifically as possible the subject matter to be searched. Define any terms that may have special meaning. Give examples or relevant citations, authors, or keywords, if known.

You may include a copy of the broadest and or relevant claim(s).

Blood Pressure Reducing agents -

2R, 4S) - 2'S, 4'S - [iminobis methylene] bis [6 fluoro - 3,4 - dihydro - 2H - 1 - benzopyran - 2 - methanol]

and atenolol - used together to lower blood pressure

Sheet of Claims Attached

8A

8C 11

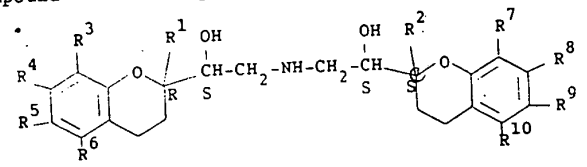
STAFF USE ONLY

COMPLETED Feb 28, 1990
SEARCHER Sheppard
ONLINE TIME 20" TOTAL TIME 30"
(in minutes)
NO. OF DATABASES 3

SYSTEMS
✓ CAS ONLINE
___ DARC/QUESTEL
___ DIALOG
___ SDC
___ OTHER

Petitioner
Exhibit 1002 - 037

1. A me ntiating the effects of blood pressure reducing agents in wa. -blooded animals in need of blo. pressure reducing medication, said method comprising administering to said warm-blooded animals of an effective amount of a blood pressure reducing agent and a compound which is represented by the formula



(I),

or a pharmaceutically acceptable acid addition thereof, wherein

R^1 and R^2 each independently are hydrogen or C_{1-6}alkyl;

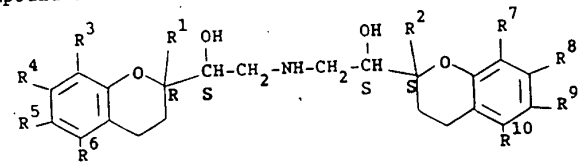
R^3, R^4, R^5, R^6, R^7, R^8, R^9 and R^{10} each independently are hydrogen, halo, C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxy, cyano, carboxy or C_{1-6}alkyloxycarbonyl;

or two vicinal radicals of R^3, R^4, R^5, R^6, R^7, R^8, R^9 and R^{10} taken together may form a -CH=CH-CH=CH- or $-(CH_2)_4-$ radical.

2. A method according to claim 1 wherein R^3, R^4, R^6, R^7, R^8, R^9 and R^{10} are hydrogen.

3. A method according to claim 1 wherein the compound is [2R,αS,-2'S,α'S]-α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol].

4. A pharmaceutical composition comprising an amount, capable of potentiating the effects of blood pressure reducing agents, of a compound of formula (I)



(I),

Barrett
A.I + AJ

US JAB 775

#4 mmb 2/28/92

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of
Xhonneux Raymond Mathieu et al.
Rule 60 Continuation of Serial No. 07/325,181
filed March 16, 1989
for METHOD OF LOWERING THE BLOOD PRESSURE

Examiner Russell Travers

Group 120-Art Unit 125

DECLARATION

I, Pauwels, Petrus Johan Antoon, a citizen of Belgium residing at Renier Sniederspad 21, 2350 Vosselaar, Belgium, make the following declaration :

1. I am biologist which degree I obtained from the State University of Ghent in 1984. Since 1984 I am employed at JANSSEN PHARMACEUTICA , N.V., having its principal place of business at Turnhoutseweg 30, B-2340-Beerse, Belgium, as Senior Scientist in the Department of Biochemical Pharmacology.

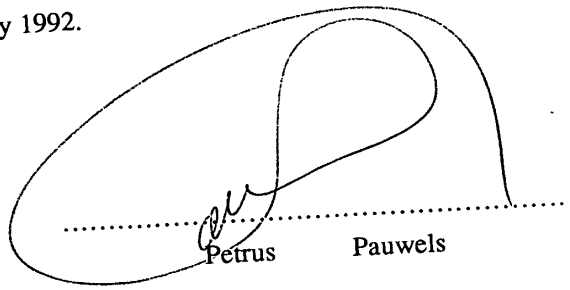
2. I am the author or co-author of many publications in the biochemical-pharmacological field and I am well acquainted with the techniques employed to evaluate the interaction of cardiovascular drugs with neurotransmitter receptors.

3. I am the author of the attached article which is entitled "The Receptor Binding Profile of the New Antihypertensive Agent Nebivolol and its stereoisomers Compared with Various β-adrenergic Blockers" and which was published in Molecular Pharmacology, 34, 843-851 (1988). The tests presented in this article were conducted in our department and the results obtained therein are those reported in the article. The article is primarily concerned with a number of detailed receptor-binding studies on the various stereochemical forms of the antihypertensive drug nebivolol. One salient finding of the reported test results

is mentioned on page 845, column 2, line 11-20 and relates to the fact that nebivolol and its d-enantiomer (SRRR) have about similar binding affinity for β-adrenergic receptors whereas its l-enantiomer (RSSS) has about 100 times less binding affinity for said receptors. Consequently, the β-adrenergic blocking properties of nebivolol are predominantly due to the d-enantiomer. However, as is mentioned on page 849, second column in the paragraph entitled "Mode of action of nebivolol as antihypertensive agent" : "*Recent observations have revealed that the particular hemodynamic profile is specifically obtained with nebivolol, whereas the β1-adrenergic active enantiomer R 67 138 (S,R,R,R) showed the activities of a typical β-adrenergic blocker. Hence, the properties of nebivolol apparently resulted from the combined activities of the two enantiomers* ". Indeed, research results not reported in the present article show that the unusual pharmacological profile of nebivolol which differs from other classical β-adrenergic blockers, cannot be attributed to the d-enantiomer (SRRR) alone. The peculiar, advantageous properties of nebivolol such as improved left ventricular function, reduction in systemic vascular resistance, and related increased cardiac output (i.e. positive inotropy) and the immediate reduction in blood pressure which are obtained after administration of nebivolol are mediated by the l-enantiomer.

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

Signed, this ١٢ day of January 1992.



Petrus Pauwels

07/825488

#4
ynlt
01/28/92

US JAB 775

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of
Xhonneux Raymond Mathieu et al.
Rule 60 Continuation of Serial No. 07/325,181
filed March 16, 1989
for METHOD OF LOWERING THE BLOOD PRESSURE

Examiner Russell Travers

Group 120-Art Unit 125

DECLARATION

I, Raymond M. Xhonneux, a citizen of Belgium residing at Hei-ende 58, B-2340-Beerse, Belgium, make the following declaration :

1. I am Pharmacologist which degree I obtained from the Institute for Tropical Medicine Antwerp (Belgium). Since 1960 I am employed at JANSSEN PHARMACEUTICA , N.V., having its principal place of business at Turnhoutseweg 30, B-2340-Beerse, Belgium, as head of the Cardiovascular Department.

2. I am the author or co-author of many publications in the pharmacological field and I am well acquainted with the techniques employed to evaluate cardiovascular drugs.

3. The attached article entitled 'The l-enantiomer of nebivolol potentiates the blood pressure lowering effect of the d-enantiomer' which was published in the European Journal of Pharmacology, 181, p. 261-265, 1990, was authored by colleagues of mine and me. I acknowledge that a printing error has occured therein on page 261, second column, lines 10 to 11 where both the d- and l-enantiomers are wrongly assigned the same absolute stereochemical configuration (RSSS). The absolute stereochemical configuration of d-nebivolol is (SRRR) and not (RSSS), the

designation of l-nebivolol is correct. The tests presented in this article were conducted under my direct supervision and the results obtained therein are those reported in the article.
The results shown graphically in Figures 3A and C on page 264, are represented numerically (median values and 95% confidence limits) in paragraph 4 hereinbelow together with a description of the test-setup.

4. The following experiments with adult (6 months old) spontaneous hypertensive rats (SHR) were conducted under my direct supervision. The animals were anaesthetized with ether and a femoral artery was dissected and canulated with a polyethylene catheter connected to a strain gauge blood pressure transducer. When the animals were fully awake, they were restrained in Bollman cages, and lidocaine (20%) was administered to the wound around the femoral canula. Systolic and diastolic arterial blood pressure and heart rate were continuously recorded. An observation period of at least 30 min preceded the intraperitoneal administration of the test compounds.

As potentiator of blood pressure reducing agents there was used in this test (RSSS)-α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol], which is compound 1 of U.S. Ser. No 325,181 and which is denoted "(RSSS)-compound" hereinafter. As blood pressure reducing agent there was used in this test (SRRR)-α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol],which is the enantiomer of the potentiating compound 1 and which is disclosed on page 6, lines 12-13 of U.S. Ser. No. 325,181. Said blood pressure reducing agent is denoted "(SRRR)-compound" hereinafter. The test compounds were dissolved in 20% polypropylene glycol at a concentration of 1 $mg.ml^{-1}$.
In a first series of experiments the potentiating (RSSS)-compound was injected in doses of 0.63, 1.25, 2.5 and 5 $mg.kg^{-1}$ (n= 18 per dose). In a second series of experiments the blood pressure reducing (SRRR)-compound was injected in doses of 0.63, 1.25, 2.5 and 5 $mg.kg^{-1}$ (n = 18 per dose). A group of 24 SHR receiving placebo served as control. In another series of experiments, seven groups of SHR (n= 12 per group) were given the blood pressure reducing (SRRR)-compound, at a dose of 1.25 $mg.kg^{-1}$ i.p., either alone or combined with the following doses of potentiating (RSSS)-compound : 0.16, 0.31, 0.63, 1.25, 2.5 and 5 $mg.kg^{-1}$. In these experiments the changes recorded after administration of (SRRR)-compound alone were taken as controls.

The effect of the compounds or placebo on systolic and diastolic blood pressure, and on heart rate was assessed by averaging the % changes in these variables over a period of 120 min. The tables 1, 2 and 3 show the median percentage changes and 95 % confidence limits in systolic (SBP) and diastolic (DBP) blood pressure and heart rate (HR) in SHR, following i.p. administration.
The statistical significance of the different effects compared to controls was assessed with the Mann-Whitney U-test. Two-tailed probabilities ≤0.05 were considered to be significant (*).

Table 1

(RSSS)-compound (mg/kg) i.p.	n	median % changes (95% confidence limits)		
		SBP	DBP	HR
0	24	3.8 (1.24; 6.26)	4.13 (3.18; 7.59)	1.79 (0.25; 5.4)
0.63	18	4.21 (2.98; 8.27)	4.91 (4.46;8.76)	4.66 (1.5; 6.5)
1.25	18	2.87 (2.71; 5.63)	4.84 (3.6; 8.4)	3.63 (1.1; 5.9)
2.5	18	-1.93 (-3.24; -0.78)*	1.07 (0.42; 2.37)	0.59 (-0.4; 3.5)
5	18	-0.012 (-5.8; +1.5)*	4.17 (2.65; 8.31)	-6.36 (0.6; -9.6)*

Table 2

(SRRR)-compound (mg/kg) i.p.	n	median % changes (95% confidence limits)		
		SBP	DBP	HR
0	24	3.8 (1.24; 6.26)	4.13 (3.18; 7.59)	1.79 (0.25; 5.4)
0.63	18	-0.47 (0.85; -1.91)*	4.13 (1.62; 5.90)	-13.67 (-16.24; -10.40)*
1.25	18	-4.98 (-1.98; -5.39)*	2.06 (-0.65; 3.14)*	-18.91 (-20.20; -14.12)*
2.5	18	-7.36 (-6.0; -9.71)*	1.23 (-1.95; 2.5)*	-25.31 (-27.62; -19.43)*
5	18	-9.26 (-8.40; -12.98)*	-1.03 (-4.22; 0.45)*	-31.13 (-34.82; -25.00)*

Table 3

1.25 mg/kg (SRRR)-compound + (RSSS)-compound (mg/kg) i.p.	n	median % changes (95% confidence limits)		
		SBP	DBP	HR
0	18	-4.98 (-1.98;-5.39)	2.06 (0.65; 3.14)	-18.91 (-20.20; -14.12)
0.16	12	-6.78 (-5.21; -9.24)*	1.36 (2.82; -1.12)	-21.75 (-17.42; -23.26)
0.31	12	-10.39 (-8.23; -13.12)*	-4.08 (-1.44; -6.0)*	-22.62 (-15.30; -23.46)
0.63	12	-9.49 (-6.02; -11.32)*	-4.08 (-1.98; -5.54)*	-22.91 (-16.18; -25.32)
1.25	12	-12.29 (-10.68; -15.27)*	-4.76 (-3.21; -7.0)*	-24.65 (-18.24; -26.36)
2.5	12	-16.04 (-11.20; -18.02)*	-10.2 (-6.24; -10.98)*	-30.16 (-25.64; -31.70)*
5	12	-19.43 (-14.26; -21.0)*	-11.56 (-8.98; -13.82)*	-32.48 (-27.32; -34.46)*

Conclusion

From the findings in the above study, I draw the following conclusions :

(a) The potentiating (RSSS)-compound only minimally affects blood pressure when administered alone (Table 1);

(b) The blood pressure reducing (SRRR)-compound is a potent blood pressure reducing agent when administered alone (Table 2); and

(c) The blood pressure reducing effect of the (SRRR)-compound administered at a dose of 1.25 mg/kg i.p. is potentiated significantly when the potentiating (RSSS)-compound is administered concommittantly at a dose ranging from 0.16 to 5 mg/kg i.p.

(d) At 1.25 $mg.kg^{-1}$, the (SRRR)-compound significantly reduces heart rate, an effect which is not potentiated by the (RSSS)-compound in doses up to 1.25 $mg.kg^{-1}$.

All these findings indicate that the (RSSS)-compound potentiates the antihypertensive effects of the (SRRR)-compound, but not the bradycardiac affects of the (SRRR)-compound.

5. I finally declare that all statements herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the

like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed, this 16 day of January 1992.

Raymond M. Xhonneux

SC

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address : COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/825,488	01/24/92	XHONNEUX R	JAB-775

EXAMINER
TRAVERS, R

ART UNIT	PAPER NUMBER
1205	6

ROBERT L. MINIER
JOHNSON & JOHNSON
ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, NJ 08933-7003

DATE MAILED: 05/29/92

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 1/24/92 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449. ✓
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 18-24 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 18-24 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

PTO-326 (Rev. 9-89)

The preliminary amendment and the information disclosure statement filed January 24, 1992 has been received and entered into the file.

Claims 18-24 are presented for examination.

35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 18-24 are rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 1-12 of prior U.S. Patent No. 4,654,362. This is a double patenting rejection.

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

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 18-24 are rejected under 35 U.S.C. § 102(a) as being anticipated by Xhonneux et al.

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

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

Claims 18-24 are rejected under 35 U.S.C. § 102(b) as being anticipated by Xhonneux et al.

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

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 18-24 are rejected under 35 U.S.C. § 103 as being unpatentable over Xhonneux et al.

Xhonneux et al teach the claim designated compounds as old, well known and in combination with various carriers and excipients as useful for the claimed utility. This teaching includes all position isomers inherent in the claimed compound. The skilled artisan would have known that various isomers would exhibit biological activity at various levels. Absent information to the contrary, the skilled artisan would have seen optical isomer separation as a routine procedure leading to the compounds claimed herein. Biological testing for the claimed compounds would have been well within the skill of the artisan, and such artisan would have expected the various biological activity levels set forth herein. It would follow therefore that the

instant claims recite prima facie obvious subject matter and are properly rejected under 35 USC 103.

The declaration under 37 CFR 1.132 has been considered but is not deemed probative. It is well settled patent law that claimed compounds are deemed optical isomer mixtures, absent information to the contrary. Additionally, the claimed compound is seen as an optical isomer mixture, wherein the individual isomers have various biological activity levels. Any information proffered to demonstrate unexpected benefits residing in any isomer must be compared to the natural racemic mixture. In the instant declaration applicants optical isomer comparison is devoid probative moment. Absent information to support unexpected benefits residing in the old and well known compositions and their methods of use, the instant claims are properly rejected under 35 USC 103.

NO claims are allowed.

Any inquiry concerning this communication should be directed to Russell Travers at telephone number (703) 308-4603.

Frederick E. Waddell
Supervisory Patent Examiner
Group 120

Russell Travers

JAB 775

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Raymond Mathieu Xhonneux et al.

Serial No.: 07/825,488 Art Unit: 125

Filed : January 24, 1992 Examiner: R. Travers

For : METHOD OF LOWERING THE BLOOD PRESSURE

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on August 28, 1992
(Date of Deposit)

Charles J. Metz
Name of Registered Representative

(Signature)
August 28, 1992
(Date of Signature)

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

AMENDMENT

In response to the Office Action of May 29, 1992, please amend the above-identified application as follows:

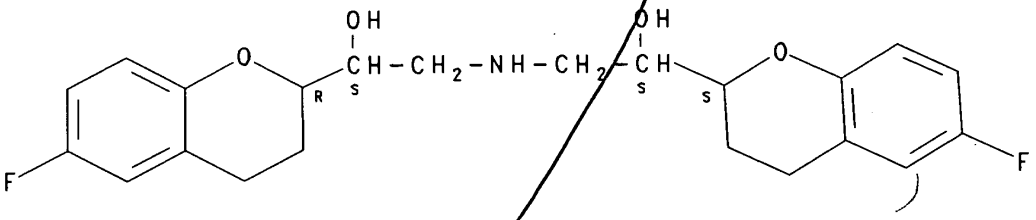
In The Specification

Page 1, in the second line of the paragraph added in the PRELIMINARY AMENDMENT, after "1989", insert --- (now abandoned) ---.

In The Claims

Please cancel Claims 18 and 19 and rewrite as new Claims 25 and 26, as follows:

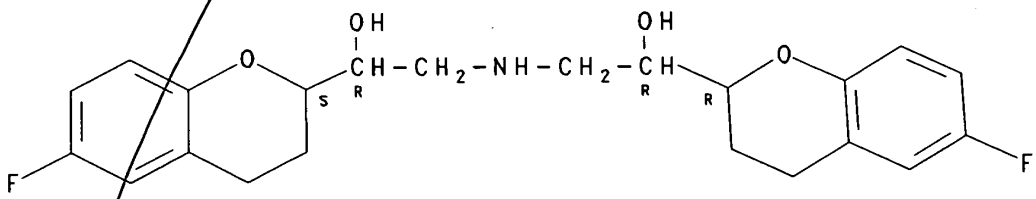
25. A composition consisting essentially of the compound [2R,αS,2'S,α'S]-α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol] having the formula:



or a pharmaceutically acceptable acid addition salt thereof.

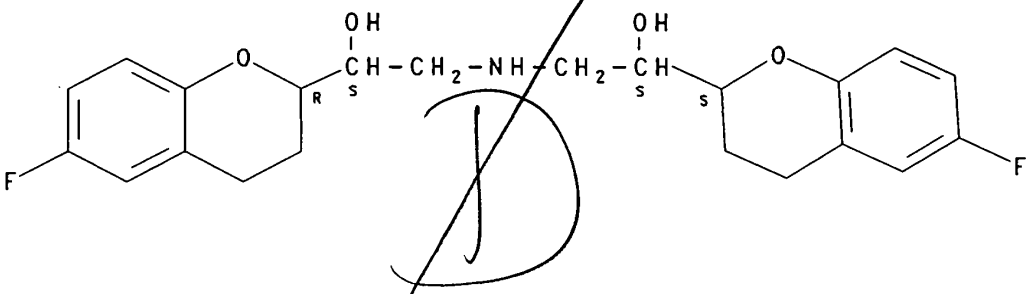
26. A pharmaceutical composition consisting essentially of a pharmaceutically acceptable carrier and, as active ingredients:

(a) the blood pressure reducing compound [2S,αR,2'R,α'R]-α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol] having the formula:



or a pharmaceutically acceptable acid addition salt thereof; and

(b) the compound [2R,αS,2'S,α'S]-α,α'-[iminobismethylene]-bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol] having the formula:



or a pharmaceutically acceptable acid addition salt thereof,

Compound (b) being present in an amount capable of potentiating the blood pressure lowering effect of compound (a), above.

Claims 20 and 21, first line of each claim, and Claim 22, last line, after the word "Claim" at each occurrence, delete "19" and insert therefor --- 26 ---.

REMARKS

In the specification, the status of the immediate parent application has been brought up to date.

Claims 18 and 19 have been rewritten as new Claims 25 and 26. Claim 25 recites "A composition consisting essentially of the compound ...", and Claim 26 recites "A pharmaceutical composition consisting essentially of ... [the two compounds (a) and (b)]". This amendment is being made to more clearly distinguish the claimed

invention over the prior art which, as is explained in detail below, discloses undefined mixtures that may include the presently claimed compounds in admixture with other stereoisomers of the Base Compound (the "Base Compound" is defined below). Favorable consideration of the amended claims is respectfully requested.

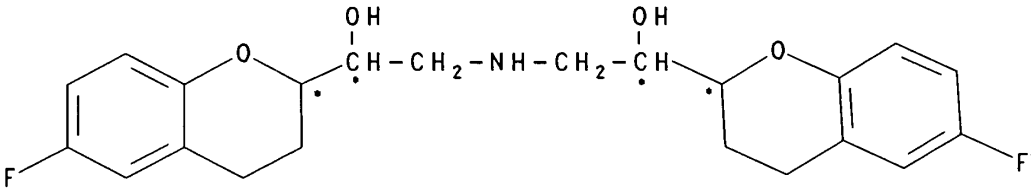
The claims in the application are Nos. 20-26. All the claims in the application have been rejected under 35 U.S.C. 101 as claiming the same invention as Claims 1-12 of Van Lommen et al., U.S. Patent No. 4,654,362 (a double patenting rejection), under both 35 U.S.C. 102(a) and 35 U.S.C. 102(b) as being anticipated by Van Lommen et al., and under 35 U.S.C. 103 as being obvious over Van Lommen et al. **[In the Office Action, the reference cited in support of the Section 102 and 103 rejections is referred to as "Xhonneux et al." Applicants assume that this is in error and that the Van Lommen et al. patent is intended, since there is no prior art Xhonneux et al. reference of record. Correction for the record is respectfully requested.]** These rejections are respectfully traversed, for the reasons that are set forth below.

Background Discussion of the Applicable Stereochemistry

The claimed invention relates to a particular stereochemically isomeric form (i.e., *stereoisomer*) of the compound α,α'-[iminobis-methylene]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol], to a pharmaceutical composition consisting essentially of said stereoisomer plus a particular blood pressure reducing agent [the mirror image stereoisomer (or *enantiomer*) of the subject claimed

stereoisomer], and to a method of treating hypertension in warm blooded animals which comprises administering to warm blooded animals in need of such treatment an effective amount of said pharmaceutical composition.

The compound α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol] has the following molecular structure:



This compound (which *per se*, without regard to its stereochemical configuration, will be referred to herein as the "Base Compound") has four chiral centers, which are indicated in the formula with asterisks ("*"). Each chiral center can have either of two absolute spatial configurations, designated by convention as "R" or "S" (for *rectus* and *sinister*), in accordance with the rules of Cahn, Ingold and Prelog (Cahn et al., *Angew. Chem.*, 1966, **78**, 413; *Angew. Chem. Int. Ed.*, 1966, **5**, 385). Thus, a specific stereoisomer of the Base Compound could be referred to, for example, as the "RRRR stereoisomer", if each chiral center had the R absolute configuration. Theoretically, a compound having 4 chiral centers, each of which can have 2 absolute spatial configurations, would have sixteen [i.e., 2^4] possible stereoisomers. The present Base Compound, however, has only ten. This is so because the two moieties of the Base Compound that are bonded to the central -NH- group are

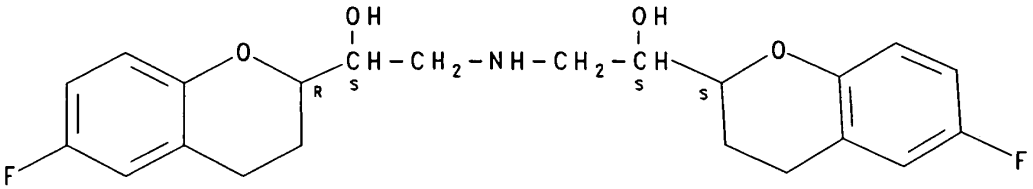
geometrically identical (as distinguished from "stereochemically identical"). By virtue of having two geometrically identical moieties bonded to the central -NH- group, the formula used to calculate the number of theoretically possible stereochemical configurations "degenerates" so that there are in fact fewer such configurations than the formula predicts. This is so because the members of certain pairs of the sixteen theoretically possible stereoisomers are identical to each other. I.e., they are the same stereoisomer but "written" forwards and backwards (analogously to the word "radar"). The ten possible stereoisomers (and, where appropriate, their "written backwards" equivalents) are:

1. SRRR [same as RRRS]
2. RSSS [same as SSSR]
3. SRRS
4. RSSR
5. SRSR [same as RSRS]
6. SRSS [same as SSRS]
7. RSRR [same as RRSR]
8. RRSS [same as SSRR]
9. SSSS
10. RRRR

For the information of the Examiner, these ten possible stereoisomers are identified in Table 2, on page 847, of the Pauwels et al. article enclosed with the Pauwels Declaration that was submitted with the PRELIMINARY AMENDMENT AND INFORMATION DISCLOSURE STATEMENT.

The present invention is based on the discovery that one of the ten possible stereoisomers, the RSSS isomer, possesses unexpected properties, as is discussed more fully below.

The specific stereoisomeric compound of the invention is represented by the formula:



It will be seen that the four chiral centers, reading from left to right in the formula, have, respectively, the R, S, S, and S absolute configurations. For brevity, this specific stereoisomeric form of the Base Compound will be referred to herein as the "RSSS isomer", and its mirror image (or enantiomer) will be referred to herein to as the "SRRR isomer".

Relation of Claimed Invention to Van Lommen et al.

Neither a composition consisting essentially of the RSSS isomer, nor a composition consisting essentially of the RSSS isomer and its enantiomer the SRRR isomer, are disclosed in Van Lommen et al. The patentees disclose the Base Compound, **as an undefined mixture of stereoisomers**, as compound Nos. 84 (designated as "AB") and 87 (designated as "AA"), shown in the table in Col. 21 of the patent. There is no way that one can determine from the teachings

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of the patent the specific stereoisomeric configurations of Van Lommen et al's compound Nos. 84 and 87, as will be explained below.

At Col. 4, lines 59 et seq., in referring to the two intermediates used to prepare the final compounds, each [intermediate] of which forms half the final compound, the patentees disclose that "...it is conventionally agreed to designate the stereochemically isomeric form [of the intermediate] which is first isolated as 'A' and the second as 'B', **without further reference to the actual stereochemical configuration.**" (Emphasis supplied.) With respect to the patentees' preferred compound, α,α'-[iminobismethylene]bis-[3,4-dihydro-2*H*-1-benzopyran-2-methanol], the patentees disclose that "... it has experimentally been determined that the 'A' form corresponds with the RS or SR configuration at the chiral centers 1 and 2 or 3 and 4 while the 'B' form corresponds with the SS or RR configuration at the said chiral centers." Thus "A" means RS or SR or both RS and SR, and "B" means SS or RR or both SS and RR.

Employing these definitions wherein A = RS or SR or both, and B = SS or RR or both, the patentees' Compound 84, designated as "AB", is an undefined mixture of the RSRR, RSSS, SRSS and SRRR isomers, and Compound 87, designated as "AA", is an undefined mixture of the RSRS, RSSR, and SRRS isomers.

Some of the compounds in the cited patent were recovered as pure stereoisomers. Such compounds are indicated in the examples by designations such as A+B+, A+B-, etc. Illustrations include Compound Nos. 14-17, 22-23, 42, 78-83, 88, 107-109, and 129-130.

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While these compounds were recovered as pure stereoisomers, the patent does not disclose whether, for instance, A+ = RS or A+ = SR. Therefore, even with respect to the compounds of the patent that were separated into pure stereoisomers, the absolute spatial configurations (i.e., R or S) at each chiral center of these compounds are not deducible from the teachings of the patent.

From the above discussion, it is clear that the cited Van Lommen et al. patent discloses neither a composition consisting essentially of the RSSS stereoisomer of the Base Compound, nor a composition consisting essentially of the RSSS and SRRR isomers.

The Unobvious and Valuable Properties of the RSSS Isomer

The RSSS isomer has an unobvious and valuable potentiating effect on blood pressure reducing compounds, and in particular, on its enantiomer (i.e., mirror image stereoisomer), the SRRR isomer. This unexpected potentiating effect will be explained below.

The Examiner's attention is again respectfully directed to the Rule 132 Declarations that were submitted with the PRELIMINARY AMENDMENT AND INFORMATION DISCLOSURE STATEMENT, one by Applicant Xhonneux and one by Petrus J. Pauwels. Please refer first to Mr. Xhonneux' Declaration, in which biological data demonstrating the potentiating effect of the subject RSSS isomer is presented. Table 1 presents data showing the effect of various dosages of the subject RSSS isomer alone on spontaneously hypertensive rats "SHR". It is seen that (i) at dosages of up to 5 mg/kg, there is no significant

effect on diastolic blood pressure, (ii) at a dosage of 2.5 mg/kg, there is only a slight effect on systolic blood pressure, and (iii) at a dosage of 5 mg/kg there is only a slight effect on heart rate. Thus, it is clear that the subject RSSS isomer only minimally affects blood pressure and heart rate when given alone.

The Examiner's attention is now respectfully invited to Tables 2 and 3. Table 2 presents data in which SHR were given the mirror image SRRR isomer alone at varying dosages. Table 2 shows that a significant systolic blood pressure reduction is obtained at a dosage of 0.63 mg/kg of the SRRR isomer and a significant diastolic blood pressure reduction is obtained at a dosage of 1.25 mg/kg of the SRRR isomer.

Table 3 presents data in which SHR were given a dosage of 1.25 mg/kg of the SRRR isomer, and varying dosages of the subject RSSS isomer, from 0 up to 5 mg/kg. As can be seen from the data in which no RSSS isomer is added to the SRRR isomer (and also from the data presented in Table 2), the SRRR isomer is a potent blood pressure reducing agent when used by itself. However, please note that a significant reduction in systolic blood pressure is seen when 0.16 mg/kg of the subject RSSS isomer is added to the 1.25 mg/kg of the SRRR isomer; a significant reduction is diastolic blood pressure is seen when 0.31 mg/kg of the subject RSSS isomer is added to the 1.25 mg/kg of the SRRR isomer; but significant additional heart rate reduction is not seen until a dosage of 2.5 mg/kg of the subject RSSS isomer is added to the 1.25 mg/kg of the SRRR isomer. As this data demonstrates, at dosages in which the subject RSSS isomer has

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little or no effect when used alone, when it is combined with the SRRR isomer, significant additional blood pressure reducing effect is obtained. Also, please compare, for instance, the data from Table 3 wherein 1.25 mg/kg of each compound was administered (i.e., a total dosage of the mixture of the two isomers of 2.5 mg/kg) with the results shown in Table 2 wherein 2.5 mg/kg of the SRRR isomer was used (again, a total dosage of 2.5 mg/kg). It is seen that when the mixture of the two compounds is used, a significantly greater decrease in blood pressure is obtained than when the SRRR isomer is used alone in an equimolar amount, and at this optimum ratio of the two isomers, the significant blood pressure reduction is obtained without significant additional heart rate reduction.

The experimental results presented in the Xhonneux Declaration are shown graphically on page 264 of the Xhonneux et al. article that is appended to the Xhonneux Declaration. It is believed that the data presented in the Xhonneux Declaration and shown in the said article illustrate a classic case of synergistic results wherein the benefits of the two materials used in combination far exceed the additive effect that would have been expected from the properties exhibited by each alone.

The Examiner's attention is now respectfully directed to the Pauwels Declaration and the Pauwels et al. article that is appended thereto. This article relates to the receptor binding profile of the stereoisomers of the compound α,α'-[iminobis(methylene)]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol], the Base Compound of the subject claimed RSSS isomer, and the SRRR isomer. In the

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article, the RSSS isomer is identified as R 67,145 and the SRRR isomer is identified as R 67,138. First, please refer to page 848, right hand column, at lines 2-6. As disclosed here in the article, the 1:1 mixture of these two enantiomers, identified by the generic name "nebivolol", is found to be a potent β_1-adrenergic blocker as tested by binding studies on receptors in rabbit lung, the SRRR isomer (R 67,138) is equally potent (and therefore is a conventional β-adrenergic blocking agent), whereas the RSSS isomer (R 67,145) is 175-fold less potent. Thus, while the subject RSSS isomer does have β-adrenergic blocking activity, it is considerably less potent than conventional β-blockers. Therefore, it is surprising that when it is mixed with a conventional β-blocker, the beneficial effects of the said β-blocker is significantly potentiated.

The Examiner's attention is now respectfully directed to page 849 of the Pauwels et al. article. Please note the discussion beginning in the middle of the right hand column. The following quotation is significant:

> **Mode of action of nebivolol as antihypertensive agent.** Clinical and *in vivo* pharmacological studies with nebivolol revealed an interesting hemodynamic profile, different from that of classical β-adrenergic blockers (see introduction). Observed reductions in heart rate can probably be attributed to β_1-adrenergic receptor blockade. However, improved left ventricular function, reduction in systemic vascular resistance, and related cardiac output seen with nebivolol are not properties of classical β-adrenergic blockers. Also, the immediate reduction in blood pressure, obtained after administration of nebivolol to conscious spontaneous hypertensive rats, has not been observed with known β-adrenergic blockers. Recent observations have revealed that the particular hemodynamic profile is specifically obtained with nebivolol, whereas the β_1-adrenergic active enantiomer R 67,138 (S,R,R,R) showed the activities of a typical

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> β-adrenergic blocker. Hence the properties of nebivolol apparently resulted from the combined activities of the two enantiomers. (Underscoring added.)

The underscored matter in this quotation speaks for itself. However, it is clear that the combination of the two enantiomers, i.e., the SRRR and the RSSS enantiomers, do not behave like the heretofore known β-blockers. It is also clear that the unusual activity of the combination is due in large part to the subject claimed RSSS isomer. These effects are entirely unexpected and could not have been predicted from the known prior art.

Applicants will now discuss the three rejections, in turn.

The Double Patenting Rejection

The Examiner's attention is respectfully directed to the discussion of "same invention" type double patenting appearing in MPEP, Section 804, at page 800-4. It is there stated that:

> "A good test for double patenting under 35 U.S.C. 101 is whether one of the claims could be literally infringed without literally infringing the other. *In re Vogel*, 164 USPQ 619 (CCPA 1970)."

It is respectfully submitted that it is possible to literally infringe every single one of the claims of the cited Van Lommen et al. patent without at the same time infringing any of the claims pending herein. For instance, the RRRR stereoisomer of the base compound (along with its use in the treatment of coronary vascular

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disorders) would not infringe any of the presently pending claims, but it would literally infringe Claims 1, 3, 5, 7, 9 and 11 of the cited patent. The patentees' preferred compound, namely, α,α'-[iminobismethylene]bis[3,4-dihydro-2*H*-1-benzopyran-2-methanol],and its use in the treatment of coronary vascular disorders, would literally infringe every claim of the cited patent, but would not infringe any of the presently pending claims. From the foregoing facts, it is seen that it is possible to literally infringe all the claims of the cited patent without literally infringing any of the subject claims. Consequently, the test suggested by *In re Vogel* and endorsed by MPEP is NOT met, and for this reason it is urged that the double patenting rejection is in error. Favorable reconsideration and withdrawal of this rejection is respectfully requested.

The Anticipation Rejections

Applicants strenuously urge that the subject claimed invention is not anticipated by Van Lommen et al. The present invention is directed to a composition consisting essentially of the RSSS isomer, to a pharmaceutical composition consisting essentially of the RSSS isomer and its enantiomer (the SRRR isomer), and to a method of treating hypertension comprising administering said pharmaceutical composition. While this invention is within the scope of the generic disclosure and claims of the Van Lommen et al. patent, it is not disclosed therein. Applicants' view on this point is supported by the following facts:

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The RSSS isomer is one of ten possible stereoisomers of the Base Compound. The Base Compound, as an undefined mixture of stereoisomers, is disclosed by Van Lommen et al. However, there is nothing in the patent to lead one to single out said Base Compound. It is disclosed in the patent as one of more than 100 compounds specifically disclosed therein [the compound numbers in the patent go up to 143, but there is some duplication since different salts, esters, or (unresolved) stereoisomers of particular basic compounds are assigned different compound numbers]. Further, the subject Base Compound is not the preferred compound in the patent. Since it is not the preferred compound disclosed in the patent, and since it is only one of at least 100 different compounds disclosed in the patent, it is clear that there are no teachings in the patent that would lead one of ordinary skill in the art to specifically select the Base Compound for further investigation.

As Applicants have pointed out above in the section of this AMENDMENT entitled "Relation of Claimed Invention to Van Lommen et al.", [which section is incorporated by reference herein] it is absolutely clear that the Van Lommen et al. patent does not disclose a composition consisting essentially of the RSSS isomer. It is also clear that the reference does not disclose the presently claimed mixture consisting essentially of the RSSS isomer and its enantiomer, the SRRR isomer. It follows *a fortiori* that the patent does not anticipate the subject claimed invention.

For the above reasons, it is respectfully urged that Van Lommen et al. does not anticipate the subject claimed invention. There-

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fore, the rejection of all the claims under 35 U.S.C. 102 (a or b) is in error and favorable reconsideration and withdrawal of the two anticipation rejections is respectfully requested.

The Obviousness Rejection

It is urged that the subject claimed invention is unobvious on the basis of unobvious and valuable pharmacological properties. These properties were discussed above in this AMENDMENT in the section entitled "The Unobvious and Valuable Properties of the RSSS Isomer". The Examiner's attention is again respectfully directed to the matter presented in that section, which is incorporated herein by reference.

The Examiner has criticized the probative value of Applicants' experimental showing on a number of grounds. For instance, it is urged in the Office Action that:

> "Any information proffered to demonstrate unexpected benefits residing in any isomer must be compared to the natural racemic mixture."

Applicants respectfully but strenuously contend that there is no such mechanistic legal requirement that mandates what must be shown in seeking to establish unexpected results. For instance, in the present case, Applicants respectfully urge that there is no "natural racemic mixture" of the Base Compound, and certainly none is so identified in the prior art. The Examiner is respectfully reminded that the Base Compound has ten possible stereoisomers, so

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the number of possible mixtures of two or more (up to all ten!) of these stereoisomers is very large indeed. The prior art does not teach which of these many possible mixtures would be considered by the artisan to be the natural racemic mixture. Since the natural racemic mixture is not known, the comparison requested in the Office Action is impossible to make.

In the Office Action, the following is also stated in support of the Section 103 rejection:

> "Absent information to support unexpected benefits residing in the old and well known compositions and their methods of use, the instant claims are properly rejected under 35 U.S.C. 103." (Emphasis added.)

Applicants respectfully urge that the subject claimed compositions consisting essentially of the RSSS isomer and the pharmaceutical composition consisting essentially of a mixture of the RSSS isomer and its enantiomer, are not "old and well known composition[s]...". The Base Compound, as an undefined mixture of stereoisomers, is disclosed in the Van Lommen et al. patent. The exact content of these mixtures cannot be deduced from the disclosure of the patent. It follows that the subject claimed compositions are not disclosed therein and are not "old and well known".

Applicants respectfully disagree with the premise implied in the above-quoted phrase "Absent information to support unexpected results...." The unexpected properties possessed by the RSSS isomer have clearly been demonstrated by the experimental results

presented in the two Rule 132 Declarations and appended journal articles that were submitted with the PRELIMINARY AMENDMENT AND INFORMATION DISCLOSURE STATEMENT in this application. There is no teaching of the prior art that renders these properties obvious, and no such teaching has been called to Applicants' attention in the Office Action.

In support of Applicants' position on this point, consider what is and is not disclosed in the prior art. First, the cited patent discloses the Base Compound (as an undefined mixture of stereo-isomers) as one of at least 100 other compounds that are specifically mentioned in the patent. Along with the other compounds disclosed in Van Lommen et al., the Base Compound is disclosed as being a β-adrenergic blocker that is useful in the treatment of disorders of the coronary vascular system.

However, it is significant that the patent does not disclose the following:

1. The patent does not disclose a composition consisting essentially of the RSSS isomer or a composition consisting essentially of the RSSS isomer and the SRRR isomer;
2. The patent does not disclose that the RSSS isomer is a rather poor β-adrenergic blocker with only moderate blood pressure lowering effects; and
3. The patent does not disclose that, despite being a poor β-adrenergic blocker itself, the RSSS isomer significantly potentiates the blood pressure lowering effect of its enantio-

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mer, the SRRR isomer (itself an excellent β-adrenergic blocker), such that a mixture consisting essentially of the two compounds exhibits significantly greater blood pressure lowering effects than an equimolar amount of the SRRR isomer alone.

In view of the foregoing, it is respectfully urged that Applicants have clearly demonstrated "unexpected results" that supports the patentability of the subject claimed invention under 35 U.S.C. 103.

In the Office Action it is contended as follows:

> "... [the cited patent] teach[es] the claim designated compounds as old, well known and in combination with various carriers and excipients as useful for the claimed utility. This teaching includes all ... [stereo]isomers inherent in the claimed compound. The skilled artisan would have known that various isomers would exhibit biological activity at various levels."

The present invention is a "selection" invention in which a species that falls within a known genus has been found to have unexpected properties, and therefore has been selected. The particular selection that has been made here is a stereoisomer of a compound disclosed in the prior art, but which was not disclosed in the prior art as having been resolved into particular stereoisomers. The situation is not materially different from that wherein a genus of compounds is known in the prior art, but wherein the invention sought to be patented is a species within the known genus. There are many examples of situations where such a selected

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species within a known genus has been found to be patentable. The recent decision in *In re Jones*, 21 USPQ2d 1941 (Fed. Cir.) (1992), is illustrative. The following quotation from page 1944 of this decision is applicable to the situation in this case:

> "Conspicuously missing from this record is any *evidence*, other than the PTO's speculation (if it be called evidence) that one of ordinary skill in the herbicidal art would have been motivated to make the modifications of the prior art salts necessary to arrive at the claimed ... salt." (Emphasis in the original.)

In the present case, the fact that one could have deduced all ten of the individual stereoisomers from the disclosure in the prior art of the Base Compound is not controlling on the question of patentability, since it is clear that there are no teachings in the prior art that would have motivated the artisan to first single out the Base Compound and to then prepare any of the ten stereoisomers of the Base Compound, and certainly not specifically the RSSS isomer.

In the quotation from the Office Action most recently cited above, it is contended that "The skilled artisan would have known that various isomers would exhibit biological activity at various levels." Perhaps some variation in biological activity among the ten stereoisomers might not be surprising. However, the unusual properties exhibited by the RSSS isomer that have been demonstrated on this record is certainly surprising, unexpected and unobvious, and could not have been predicted from any teachings found in the prior art. It is respectfully but strenuously urged that any

contention to the contrary is mere speculation, unsupported by any evidence that has been placed on the record.

For all of the reasons that have been set forth above, it is respectfully urged that the rejection of all the claims under 35 U.S.C. 103 as being unpatentable over Van Lommen et al., U.S. Patent No. 4,654,362, is in error. Accordingly, favorable reconsideration and withdrawal of this rejection is respectfully requested.

In view of the foregoing amendments and remarks, it is urged that it has been demonstrated that all of the rejections that have been applied against the claims of this application are in error, and that this application is in condition for allowance. Early favorable action is respectfully requested.

Respectfully submitted,

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August 28, 1992

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TRAVERS, R

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DATE MAILED: 11/10/92

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 8/3/92 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 20-26 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 20-26 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

The amendment filed August 31, 1992 has been received and entered into the file.

Claims 20-26 are presented for examination.

35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 20-26 are rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 1-12 of prior U.S. Patent No. 4,654,362. This is a double patenting rejection.

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

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 20-26 are rejected under 35 U.S.C. § 102(a) as being anticipated by Van de Water et al.

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

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

Claims 20-26 are rejected under 35 U.S.C. § 102(b) as being anticipated by Van de Water et al.

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

action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 20-26 are rejected under 35 U.S.C. § 103 as being unpatentable over Van Lommen et al in view of Van de Water.

Van Lommen et al and Van de Water et al teach the claim designated compounds as old, well known and in combination with various carriers and excipients as useful for the claimed utility. This teaching includes all position isomers inherent in the claimed compound. The skilled artisan would have known that various isomers would exhibit biological activity at various levels. Absent information to the contrary, the skilled artisan would have seen optical isomer separation as a routine procedure leading to the compounds claimed herein. Biological testing for the claimed compounds would have been well within the skill of the artisan,a and such artisan would have expected the various biological activity levels set forth herein. It would follow therefore that the instant claims recite prima facie obvious

subject matter and are properly rejected under 35 USC 103.

The declaration under 37 CFR 1.132 has been considered but is not deemed probative. It is well settled patent law that claimed compounds are deemed optical isomer mixtures, absent information to the contrary. Additionally, the claimed compound is seen as an optical isomer mixture, wherein the individual isomers have various biological activity levels. Any information proffered to demonstrate unexpected benefits residing in any isomer must be compared to the natural racemic mixture. In the instant declaration applicants optical isomer comparison is devoid probative moment. Absent information to support unexpected benefits residing in the old and well known compositions and their methods of use, the instant claims are properly rejected under 35 USC 103.

The instant claims are directed to effecting a biochemical pathway with an old and well known compound. Applicant's arguments that differental biological effects for rotational isomers are unexpected are not probative. Applicant's attention is directed to In re Swinehart, (169 USPQ 226 at 229) where the Court of Customs and Patent Appeals stated "is elementary that the mere recitation of a newly discovered function or property, inherently possessed by things in the prior art, does not cause a claim drawn to those things to distinguish over the prior art. Additionally, where the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing

novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to requires the applicant to prove that the subject matter shown to be in the prior art dose not posses the characteristic relied on. IN the instant invention the claims are directed to the ultimate utility set forth in the prior art, abet distanced by various biochemical intermediates. The ultimate utility for the claimed compounds, to include all isomers for such compounds, is old and well known, rendering the claimed subject matter obvious to the skilled artisan. It would follow therefore that the instant claims are properly rejected under 35 USC 103.

NO claims are allowed.

Any inquiry concerning this communication should be directed to Russell Travers at telephone number (703) 308-4603.

Russell Travers

Frederick E. Waddell
Supervisory Patent Examiner
Group 120

JAB 775

#10
JRP
3/10/93

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Raymond Mathieu Xhonneux et al.

Serial No.: 07/825,488 Art Unit: 1205

Filed : January 24, 1992 Examiner: R. Travers

For : METHOD OF LOWERING THE BLOOD PRESSURE

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on February 17, 1993
(Date of Deposit)

Charles J. Metz
Name of Registered Representative

Charles J. Metz
(Signature)

February 17, 1993
(Date of Signature)

93 MAR -9 AM 6:40

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

RESPONSE

This letter is responsive to the Office Action of November 10, 1993.

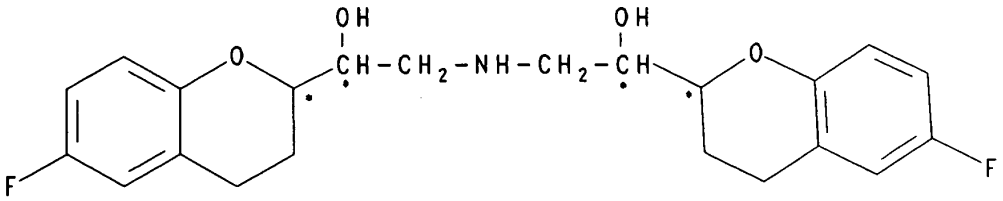
The claims in the application are Nos. 20-26. All the claims in the application have been rejected under 35 U.S.C. 101 as claiming the same invention as Claims 1-12 of Van Lommen et al., U.S. Patent No. 4,654,362 (a double patenting rejection), under both 35 U.S.C. 102(a) and 35 U.S.C. 102(b) as being anticipated by Van de Water et al., **Pharmacological and Hemodynamic Profile of Nebivolol, a Chemically**

Novel, Potent, and Selective B_1-Adrenergic Antagonist, *Journal of Cardiovascular Pharmacology*, **11**, No.. 5, 552-563 (1988) Lommen et al., and under 35 U.S.C. 103 as being obvious over Van Lommen et al. in view of Van de Water et al. These rejections are respectfully traversed, for the reasons that are set forth below.

Background Discussion

The claimed invention relates to a particular stereochemically isomeric form (i.e., *stereoisomer*) of the compound α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol], to a pharmaceutical composition consisting essentially of said stereoisomer plus a particular blood pressure reducing agent [the mirror image stereoisomer (or *enantiomer*) of the subject claimed stereoisomer], and to a method of treating hypertension in warm blooded animals which comprises administering to warm blooded animals in need of such treatment an effective amount of said pharmaceutical composition.

The compound α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol] has the following molecular structure:

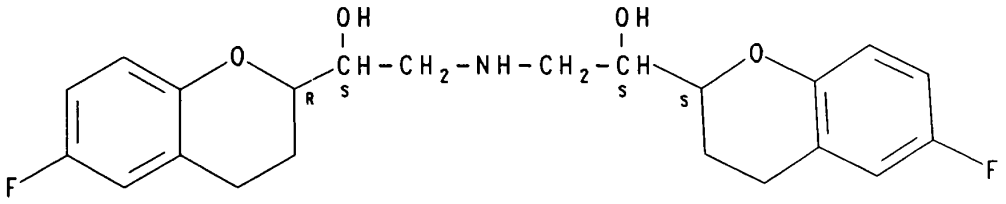


This compound (which *per se*, without regard to its stereochemical configuration, will be referred to herein as the "Base Compound") has four chiral centers, which are indicated in the formula with asterisks ("*"). Each chiral center can have either of two absolute spatial configurations, designated by convention as "R" or "S". Thus, a specific stereoisomer of the Base Compound could be referred to, for example, as the "RRRR stereoisomer", if each chiral center had the R absolute configuration. Theoretically, a compound having 4 chiral centers, each of which can have 2 absolute spatial configurations, would have sixteen [i.e., 2^4] possible stereoisomers. The present Base Compound, however, has only ten. This is so because the two moieties of the Base Compound that are bonded to the central -NH- group are geometrically identical (as distinguished from "stereochemically identical"). By virtue of having two geometrically identical moieties bonded to the central -NH- group, the formula used to calculate the number of theoretically possible stereochemical configurations "degenerates" so that there are in fact fewer such configurations than the formula predicts. This is so because the members of certain pairs of the sixteen theoretically possible stereoisomers are identical to each other. I.e., they are the same stereoisomer but "written" forwards and backwards (analogously to the word "radar"). The ten possible stereoisomers (and, where appropriate, their "written backwards" equivalents) are:

1. SRRR [same as RRRS]
2. RSSS [same as SSSR]
3. SRRS
4. RSSR
5. SRSR [same as RSRS]
6. SRSS [same as SSRS]
7. RSRR [same as RRSR]
8. RRSS [same as SSRR]
9. SSSS
10. RRRR

The present invention is based on the discovery that one of the ten possible stereoisomers, the RSSS isomer, possesses unexpected properties, as was discussed in detail in Applicants' response to the previous Office Action.

The specific stereoisomeric compound of the invention is represented by the formula:



It will be seen that the four chiral centers, reading from left to right in the formula, have, respectively, the R, S, S, and S absolute configurations. For brevity, this specific stereoisomeric

form of the Base Compound will be referred to herein as the "RSSS isomer", and its mirror image (or enantiomer) will be referred to herein to as the "SRRR isomer".

Relation of Claimed Invention to Van Lommen et al.

Neither a composition consisting essentially of the RSSS isomer, nor a composition consisting essentially of the RSSS isomer and its enantiomer the SRRR isomer, are disclosed in Van Lommen et al. The patentees disclose the Base Compound, **as an undefined mixture of stereoisomers**, as compound Nos. 84 (designated as "AB") and 87 (designated as "AA"), shown in the table in Col. 21 of the patent. There is no way that one can determine from the teachings of the patent the specific stereoisomeric configurations of Van Lommen et al's compound Nos. 84 and 87, as will be explained below.

At Col. 4, lines 59 et seq., in referring to the two intermediates used to prepare the final compounds, each [intermediate] of which forms half the final compound, the patentees disclose that "...it is conventionally agreed to designate the stereochemically isomeric form [of the intermediate] which is first isolated as 'A' and the second as 'B', **without further reference to the actual stereochemical configuration.**" (Emphasis supplied.) With respect to the patentees' preferred compound, α,α'-[iminobismethylene]bis[3,4-dihydro-2*H*-1-benzopyran-2-methanol], the patentees disclose that "... it has experimentally been determined that the 'A' form corresponds with the

RS or SR configuration at the chiral centers 1 and 2 or 3 and 4 while the 'B' form corresponds with the SS or RR configuration at the said chiral centers." Thus "A" means RS or SR or both RS and SR, and "B" means SS or RR or both SS and RR.

Employing these definitions wherein A = RS or SR or both, and B = SS or RR or both, the patentees' Compound 84, designated as "AB", is an undefined mixture of the RSRR, RSSS, SRSS and SRRR isomers, and Compound 87, designated as "AA", is an undefined mixture of the RSRS, RSSR, and SRRS isomers.

Some of the compounds in the cited patent were recovered as pure stereoisomers. Such compounds are indicated in the examples by designations such as A+B+, A+B-, etc. Illustrations include Compound Nos. 14-17, 22-23, 42, 78-83, 88, 107-109, and 129-130. While these compounds were recovered as pure stereoisomers, the patent does not disclose whether, for instance, A+ = RS or A+ = SR. Therefore, even with respect to the compounds of the patent that were separated into pure stereoisomers, the absolute spatial configurations (i.e., R or S) at each chiral center of these compounds are not deducible from the teachings of the patent.

From the above discussion, it is clear that the cited Van Lommen et al. patent discloses neither a composition consisting essentially of the RSSS stereoisomer of the Base Compound, nor a composition consisting essentially of the RSSS and SRRR isomers.

The Double Patenting Rejection

The Examiner's attention is respectfully directed to the discussion of "same invention" type double patenting appearing in MPEP, Section 804, at page 800-4. It is there stated that:

> "A good test for double patenting under 35 U.S.C. 101 is whether one of the claims could be literally infringed without literally infringing the other. *In re Vogel*, 164 USPQ 619 (CCPA 1970)."

It is respectfully submitted that it is possible to literally infringe every single one of the claims of the cited Van Lommen et al. patent without at the same time infringing any of the claims pending herein. For instance, the RRRR stereoisomer of the base compound (along with its use in the treatment of coronary vascular disorders) would not infringe any of the presently pending claims, but it would literally infringe Claims 1, 3, 5, 7, 9 and 11 of the cited patent. The patentees' preferred compound, namely, α,α'-[iminobis-methylene]bis[3,4-dihydro-2*H*-1-benzopyran-2-methanol], and its use in the treatment of coronary vascular disorders, would literally infringe every claim of the cited patent, but would not infringe any of the presently pending claims. From the foregoing facts, it is seen that it is possible to literally infringe all the claims of the cited patent without literally infringing any of the subject claims. Consequently, the test suggested by *In re Vogel* and endorsed by MPEP

is NOT met, and for this reason it is urged that the double patenting rejection is in error.

Applicants presented the foregoing argument in response to the double patenting rejection in the previous Office Action. In the present Office Action, no reasons are presented to explain why the rule of *In re Vogel*, which is endorsed in MPEP, should not govern the present situation. In the absence of any reason why the rule of *In re Vogel* should not apply to the facts here, it is urged that the double patent rejection should be withdrawn. Accordingly, favorable reconsideration and withdrawal of this rejection is respectfully requested.

The Section 102 and 103 Rejections

The § 102 and 103 rejections depend upon the premise that the Van de Water et al. journal article is a reference against Applicants. However, it is respectfully pointed out that this article was published in May, 1988 (see copy of FAXed transmission from *Information Research Services Inc.*), whereas Applicants are entitled to the filing date of their parent application Serial No. 172,747, which was March 23, 1988. The invention claimed herein is fully supported in application Serial No. 172,747. See, for example, Claims 8-10 of the said parent application. Since both Section 102 rejections and the Section 103 rejection require the use of the Van de Water et al. article as a reference, and since it is not available as

a reference against Applicants herein, it is respectfully urged that all of these rejections are in error. Favorable reconsideration and withdrawal of these rejections is respectfully requested.

In view of the foregoing remarks, it is urged that this application is in condition for allowance. Early favorable action is respectfully requested.

Respectfully submitted,

Charles J. Metz

Charles J. Metz
Attorney for Applicants
Registration #20,359

Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933

(908) 524-2814

February 17, 1993

V.K.

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address : COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/825,488	01/24/92	XHONNEUX R	JAB-775

EXAMINER
TRAVERS, R

12M2

ROBERT L. MINIER
JOHNSON & JOHNSON
ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, NJ 08933-7003

ART UNIT	PAPER NUMBER
1205	11

DATE MAILED: 05/14/93

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 2/22/93 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 20-26 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 20-26 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER

(Rev. 9-89)

The amendment filed February 22 1993 has been received and entered into the file.

Claims 20-26 are presented for examination.

35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 20-26 are rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 1-12 of prior U.S. Patent No. 4,654,362. This is a double patenting rejection.

It is well settled patent law that the skilled artisan, possessing a compound, possesses all the possible isomers imposed by optically active centers. The skilled artisan would have also known that each isomer would inherently produce different biological effect levels. Absent some unexpected benefit residing in one isomer or anther, the instant claims remain properly rejected under 35 USC 101.

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

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 20-26 are rejected under 35 U.S.C. § 102(a) as being anticipated by Van Lommen et al.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under

this section made in this Office action:

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

Claims 20-26 are rejected under 35 U.S.C. § 102(b) as being anticipated by Van Lommen et al.

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

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 20-26 are rejected under 35 U.S.C. § 103 as being unpatentable over Van Lommen et al in view of Van de Water (newly cited).

Van Lommen et al and Van de Water et al teach the claim designated compounds as old, well known and in combination with various carriers and excipients as useful for the claimed utility. This teaching includes all position isomers inherent in the claimed compound. The skilled artisan would have known that

various isomers would exhibit biological activity at various levels. Absent information to the contrary, the skilled artisan would have seen optical isomer separation as a routine procedure leading to the compounds claimed herein. Biological testing for the claimed compounds would have been well within the skill of the artisan,a and such artisan would have expected the various biological activity levels set forth herein. It would follow therefore that the instant claims recite prima facie obvious subject matter and are properly rejected under 35 USC 103.

The declaration under 37 CFR 1.132 has been considered but is not deemed probative. It is well settled patent law that claimed compounds are deemed optical isomer mixtures, absent information to the contrary. Additionally, the claimed compound is seen as an optical isomer mixture, wherein the individual isomers have various biological activity levels. Any information proffered to demonstrate unexpected benefits residing in any isomer must be compared to the natural racemic mixture. In the instant declaration applicants optical isomer comparison is devoid probative moment. Absent information to support unexpected benefits residing in the old and well known compositions and their methods of use, the instant claims are properly rejected under 35 USC 103.

Claims 20-26 are rejected under 35 U.S.C. § 103 as being unpatentable over Van Lommen et al.

Van Lommen et al teach the claim designated compounds as

old, well known and in combination with various carriers and excipients as useful for the claimed utility. This teaching includes all position isomers inherent in the claimed compound. The skilled artisan would have known that various isomers would exhibit biological activity at various levels. Absent information to the contrary, the skilled artisan would have seen optical isomer separation as a routine procedure leading to the compounds claimed herein. Biological testing for the claimed compounds would have been well within the skill of the artisan,a and such artisan would have expected the various biological activity levels set forth herein. It would follow therefore that the instant claims recite prima facie obvious subject matter and are properly rejected under 35 USC 103.

The instant claims are directed to effecting a biochemical pathway with an old and well known compound. Applicant's arguments that differential biological effects for rotational isomers are unexpected are not probative. Applicant's attention is directed to In re Swinehart, (169 USPQ 226 at 229) where the Court of Customs and Patent Appeals stated "is elementary that the mere recitation of a newly discovered function or property, inherently possessed by things in the prior art, does not cause a claim drawn to those things to distinguish over the prior art. Additionally, where the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an

inherent characteristic of the prior art, it possesses the authority to requires the applicant to prove that the subject matter shown to be in the prior art dose not posses the characteristic relied on. IN the instant invention the claims are directed to the ultimate utility set forth in the prior art, abet distanced by various biochemical intermediates. The ultimate utility for the claimed compounds, to include all isomers for such compounds, is old and well known, rendering the claimed subject matter obvious to the skilled artisan. It would follow therefore that the instant claims are properly rejected under 35 USC 103.

NO claims are allowed.

Any inquiry concerning this communication should be directed to Russell Travers at telephone number (703) 308-4603.

Russell Travers

Frederick E. Waddell
Supervisory Patent Examiner
Group 120

JAB 775

#13/9/21/93

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Raymond Mathieu Xhonneux et al.

Serial No.: 07/825,488 Art Unit: 1205

Filed : January 24, 1992 Examiner: R. Travers

For : METHOD OF LOWERING THE BLOOD PRESSURE

I, Charles J. Metz, Registration No. 20,359, certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to:
Commissioner of Patents and Trademarks,
Washington, D.C. 20231.

On: August 26, 1993

Charles J. Metz

Charles J. Metz, Reg. No. 20,359

In re may PO 197/601

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

RESPONSE

This letter is responsive to the Office Action of May 14, 1993.

The claims in the application are Nos. 20-26. All the claims in the application have been rejected (I) under 35 U.S.C. 101 as claiming the same invention as Claims 1-12 of Van Lommen et al., U.S. Patent No. 4,654,362 (a double patenting rejection); (II) under both 35 U.S.C. 102(a) and 35 U.S.C. 102(b) as being anticipated by Van Lommen et al., U.S. Patent No. 4,654,362; and (III) under 35 U.S.C. 103 as being obvious over Van Lommen et al., U.S. Patent No. 4,654,362, either alone or in view of Van de Water et al., *Eur. J.*

Pharmacol. **1988**, 156(1), 95-103. These rejections are respectfully traversed, for the reasons that are set forth below. For the convenience of the Examiner, the Background Discussion and Relation of the Claimed Invention to Van Lommen et al. that were included in the previous RESPONSE is attached hereto in an APPENDIX.

I. THE DOUBLE PATENTING REJECTION

A. **The Legal Test for Double Patenting**

In responding to the double patenting rejection, Attorney for Applicants assumes that the rejection is a same invention type double patenting rejection rather than a rejection under the judicially created doctrine of obviousness-type double patenting.

The Examiner's attention is respectfully invited to the decision in *In re Vogel et al.*, 164 USPQ 619 (CCPA 1970). At 622, the Court stated:

> "A good test, and probably the only objective test, for 'same invention' [i.e., same invention type double patenting], is whether one of the claims could be literally infringed without literally infringing the other. If it could be, the claims do not define identically the same invention."

This test for double patenting has been endorsed by the Court of Appeals for the Federal Circuit. See, for Example, *Studiengesell-*

schaft Kohle mbH v. Northern Petrochemical Company, 228 USPQ 837 (CAFC 1986), at 840. It is also endorsed by MPEP, Section 804, at page 800-4.

B. **The Test Applied to the Facts in this Case**

It is respectfully submitted that it is possible to literally infringe every single one of the claims of the cited Van Lommen et al. patent without at the same time infringing any of the claims pending herein. For instance, the RRRR stereoisomer of the base compound (see the attached APPENDIX), along with its use in the treatment of coronary vascular disorders, would not infringe any of the presently pending claims, but it would literally infringe Claims 1, 3, 5, 7, 9 and 11 of the cited patent. The patentees' preferred compound, namely, α,α'-[iminobismethylene]bis[3,4-dihydro-2*H*-1-benzopyran-2-methanol], and its use in the treatment of coronary vascular disorders, would literally infringe every claim of the cited patent, but would not infringe any of the presently pending claims. From the foregoing facts, it is seen that it is possible to literally infringe all the claims of the cited patent without literally infringing any of the subject claims. Consequently, the test suggested by *In re Vogel* and endorsed by the CAFC and by MPEP is NOT met, and for this reason and applying the legally mandated test, it is respectfully but strenuously urged that there is no double patenting in this case.

C. **Stereoisomer Issue**

In the Office Action, on page 2, it is argued (with no authority cited) that the double patenting rejection is proper because:

> "It is well settled patent law that the skilled artisan, possessing a compound, possesses all the possible isomers imposed by optically active centers."

Applicants respectfully submit that it is NOT "well settled patent law that the skilled artisan, possessing a compound, possesses all the possible isomers imposed by optically active centers". In fact, it is urged that the law is to the contrary. For instance, the Examiner's attention is respectfully invited to the decision in *In re May and Eddy*, 197 USPQ 601 (CCPA, 1978), at page 607, wherein it is stated:

> "The remaining method of use claims ... critically differ from Claims 1 and 6 in that they recite the use of a *novel* compound. As recognized in In re Williams ... , **the novelty of an optical isomer is not negated by the prior art disclosure of its racemate.**" (Italics in original; bold emphasis added.)

As applied to the present case, it is respectfully urged that the novelty of the subject claimed RSSS isomer is not negated by the disclosure of the Base Compound. The morphine derivative that was at issue in the In re May et al. decision had only two chiral centers, and hence only 4 [2^2] possible stereoisomers. In the present case,

the Base Compound has 4 chiral centers and 10 possible stereoisomers. Furthermore, only the Base Compound, not the racemate of the RSSS isomer (which would be an equimolar mixture of the RSSS and the SRRR isomers), is disclosed in the reference. Thus, the facts here are even more favorable to a finding of novelty than in the May et al. decision.

D. **"Unexpected Benefit" Issue**

In further support of the double patenting rejection, on page 2 of the Office Action the following argument is presented:

> "The skilled artisan would have also known that each isomer would inherently produce different biological effect levels. Absent some unexpected benefit residing in one isomer or another, the instant claims remain properly rejected under 35 U.S.C. 101."

It is first respectfully submitted that this argument is NOT RELEVANT to a Section 101 same invention type double patenting rejection. Rather, issues concerning unexpected benefits [or unexpected properties] are relevant to patentability under Section 103, or to a rejection under the judicially created doctrine of obviousness-type double patenting.

However, regardless of whether this issue is relevant to the present rejection, it is respectfully submitted that Applicants have demonstrated unexpected properties with the data of record. In this

respect, the Examiner's attention is again respectfully invited to the Rule 132 Declarations of Applicant Xhonneux and Petrus J. Pauwels that were submitted with the PRELIMINARY AMENDMENT AND INFORMATION DISCLOSURE STATEMENT.

1. UNEXPECTED POTENTIATING EFFECT

Please refer first to Mr. Xhonneux' Declaration, in which biological data demonstrating the potentiating effect of the subject RSSS isomer is presented. Table 1 presents data showing the effect of various dosages of the subject RSSS isomer alone on spontaneously hypertensive rats "SHR". It is seen that (i) at dosages of up to 5 mg/kg, there is no significant effect on diastolic blood pressure, (ii) at a dosage of 2.5 mg/kg, there is only a slight effect on systolic blood pressure, and (iii) at a dosage of 5 mg/kg there is only a slight effect on heart rate. Thus, it is clear that the subject RSSS isomer only minimally affects blood pressure and heart rate when given alone.

The Examiner's attention is now respectfully invited to Tables 2 and 3. Table 2 presents data in which SHR were given the mirror image SRRR isomer alone at varying dosages. Table 2 shows that a significant systolic blood pressure reduction is obtained at a dosage of 0.63 mg/kg of the SRRR isomer and a significant diastolic blood pressure reduction is obtained at a dosage of 1.25 mg/kg of the SRRR isomer.

Table 3 presents data in which SHR were given a dosage of 1.25 mg/kg of the SRRR isomer, and varying dosages of the subject RSSS isomer, from 0 up to 5 mg/kg. As can be seen from the data in which no RSSS isomer is added to the SRRR isomer (and also from the data presented in Table 2), the SRRR isomer is a potent blood pressure reducing agent when used by itself. However, please note that a significant reduction in systolic blood pressure is seen when 0.16 mg/kg of the subject RSSS isomer is added to the 1.25 mg/kg of the SRRR isomer; a significant reduction is diastolic blood pressure is seen when 0.31 mg/kg of the subject RSSS isomer is added to the 1.25 mg/kg of the SRRR isomer; but significant additional heart rate reduction is not seen until a dosage of 2.5 mg/kg of the subject RSSS isomer is added to the 1.25 mg/kg of the SRRR isomer. As this data demonstrates, at dosages in which the subject RSSS isomer has little or no effect when used alone, when it is combined with the SRRR isomer, significant additional blood pressure reducing effect is obtained. Also, please compare, for instance, the data from Table 3 wherein 1.25 mg/kg of each compound was administered (i.e., a total dosage of the mixture of the two isomers of 2.5 mg/kg) with the results shown in Table 2 wherein 2.5 mg/kg of the SRRR isomer was used (again, a total dosage of 2.5 mg/kg). It is seen that when the mixture of the two compounds is used, a significantly greater decrease in blood pressure is obtained than when the SRRR isomer is used alone in an equimolar amount, and at this optimum ratio of the two isomers, the significant blood pressure reduction is obtained without significant additional heart rate reduction.

The experimental results presented in the Xhonneux Declaration are shown graphically on page 264 of the Xhonneux et al. article that is appended to the Xhonneux Declaration. It is believed that the data presented in the Xhonneux Declaration and shown in the said article illustrate a classic case of synergistic results wherein the benefits of the two materials used in combination far exceed the additive effect that would have been expected from the properties exhibited by each alone.

2. BEHAVIOR UNLIKE KNOWN β-BLOCKERS

The Examiner's attention is now respectfully directed to the Pauwels Declaration and the Pauwels et al. article that is appended thereto. This article relates to the receptor binding profile of the stereoisomers of the compound α,α'-[iminobis(methylene)]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol], the Base Compound of the subject claimed RSSS isomer, and the SRRR isomer. In the article, the RSSS isomer is identified as R 67,145 and the SRRR isomer is identified as R 67,138. First, please refer to page 848, right hand column, at lines 2-6. As disclosed here in the article, the 1:1 mixture of these two enantiomers, identified by the generic name "nebivolol", is found to be a potent β_1-adrenergic blocker as tested by binding studies on receptors in rabbit lung, the SRRR isomer (R 67,138) is equally potent (and therefore is a conventional β-adrenergic blocking agent), whereas the RSSS isomer (R 67,145) is 175-fold less potent. Thus, while the subject RSSS isomer does have β-adrenergic blocking

activity, it is considerably less potent than conventional β-blockers. Therefore, it is surprising that when it is mixed with a conventional β-blocker, the beneficial effects of the said β-blocker is significantly potentiated.

The Examiner's attention is now respectfully directed to page 849 of the Pauwels et al. article. Please note the discussion beginning in the middle of the right hand column. The following quotation is significant:

> **Mode of action of nebivolol as antihypertensive agent.** Clinical and *in vivo* pharmacological studies with nebivolol revealed an interesting hemodynamic profile, different from that of classical β-adrenergic blockers (see introduction). Observed reductions in heart rate can probably be attributed to β_1-adrenergic receptor blockade. However, improved left ventricular function, reduction in systemic vascular resistance, and related cardiac output seen with nebivolol are not properties of classical β-adrenergic blockers. Also, the immediate reduction in blood pressure, obtained after administration of nebivolol to conscious spontaneous hypertensive rats, has not been observed with known β-adrenergic blockers. Recent observations have revealed that the particular hemodynamic profile is specifically obtained with nebivolol, whereas the β_1-adrenergic active enantiomer R 67,138 (S,R,R,R) showed the activities of a typical β-adrenergic blocker. Hence the properties of nebivolol apparently resulted from the combined activities of the two enantiomers. (Underscoring added.)

The underscored matter in this quotation speaks for itself. However, it is clear that the combination of the two enantiomers, i.e., the SRRR and the RSSS enantiomers, do not behave like the heretofore known β-blockers. It is also clear that the unusual activity of the combination is due in large part to the subject

claimed RSSS isomer. These effects are entirely unexpected and could not have been predicted from the known prior art.

From the foregoing, it is respectfully submitted that it is clear that the presently claimed RSSS isomer possesses an unexpected benefit that could not have been predicted from the prior art.

In view of the foregoing discussion, it is respectfully urged that the rejection of claims 20-26 under 35 U.S.C. 101 as claiming the same invention as Claims 1-12 of Van Lommen et al., U.S. Patent No. 4,654,362, is in error. Favorable reconsideration and withdrawal of this rejection is respectfully requested.

II. THE SECTION 102 REJECTIONS

Claims 20-26 are rejected under both 35 U.S.C. 102(a) and 35 U.S.C. 102(b) as being anticipated by Van Lommen et al., U.S. Patent No. 4,654,362. These rejections are respectfully traversed, for the reasons that are set forth below.

As was presented above in Applicants' discussion of the double patenting rejection, it is respectfully urged that the law is clear that "... **the novelty of an optical isomer is not negated by the prior art disclosure of its racemate** ....", *In re May and Eddy*, 197 USPQ 601 (CCPA, 1978), at page 607 (emphasis added.) In the present case, only the Base Compound is disclosed (not the racemate), and whereas the

compound at issue in the May et al. case had only two chiral centers, the Base Compound here has four. Thus, it is respectfully urged that it is even clearer than it was in the In re May et al. case that the present RSSS isomer, the mixture of the RSSS and the SRRR isomers, and their use in treating hypertension are novel. Accordingly, it is respectfully urged that the rejection of Claims 20-26 under both 35 U.S.C. 102(a) and 35 U.S.C. 102(b) as being anticipated by Van Lommen et al., U.S. Patent No. 4,654,362, is in error. Favorable reconsideration and withdrawal of these rejections is respectfully requested.

III. THE SECTION 103 REJECTIONS

A. **The § 103 Rejection over Van Lommen in view of Van de Water et al.**

The § 103 rejection over Van Lommen in view of the Van de Water et al. article depends upon the premise that said article is a reference against Applicants. However, it is respectfully pointed out that this article was published on November 2, 1988 (see enclosed copy of FAXed transmission from *Information Research Services Inc.*), whereas Applicants are entitled to the filing date of their parent application Serial No. 172,747, which was March 23, 1988. The invention claimed herein is fully supported in application Serial No. 172,747. See, for example, Claims 8-10 of the said parent application. Since the Section 103 rejection requires the use of the Van de

Water et al. article as a reference, and since it is not available as a reference against Applicants herein, it is respectfully urged that this rejection cannot be maintained. Favorable reconsideration and withdrawal of the rejection of Claims 20-26 under 35 U.S.C. 103 as being obvious over Van Lommen et al., U.S. Patent No. 4,654,362, in view of Van de Water et al., *Eur. J. Pharmacol.* **1988**, 156(1), 95-103, is respectfully requested.

B. **The § 103 Rejection over Van Lommen et al.**

It is the position of the Examiner that because the Base Compound is known, it follows that the various isomers are inherently known and the artisan would expect that the several isomers would have different biological activity. It is respectfully urged, however, that it was not known, and could not have been predicted from the knowledge of the prior art, that the subject claimed RSSS isomer would have the unexpected properties that have been demonstrated on the record herein. These unexpected properties include an unexpected potentiating effect when combined with its mirror image stereoisomer, the SRRR isomer, and the behavior of the mixture of the RSSS and the SRRR isomers that is unlike that of conventional β-blockers. (Please see the discussion above re unexpected results in the section on the double patenting rejection.)

The Examiner has criticized Applicants' presentation of data because no comparison has been made with the "natural racemic

mixture". Applicants respectfully request the Examiner to identify the natural racemic mixture. The Base Compound has 10 possible stereoisomers; hence, an exceedingly large number of mixtures of two or more of these isomers is possible. Which of this large number is the natural racemic mixture?

It is further argued in the Office Action (citing *In re Swinehart et al.*, 169 USPQ 226 at 229) that it "is elementary that the mere recitation of a newly discovered function or property, inherently possessed by things in the prior art, does not cause a claim drawn to those things to distinguish over the prior art".

The Swinehart et al. decision involved the propriety of the use of functional language to distinguish over the prior art. It is believed that the following quotation from pages 228-229 (from which the quote cited in the Office Action was taken), epitomizes the holding in the case:

> "Our study of these cases has satisfied us ... that any concern over the use of functional language at the so-called 'point of novelty' stems largely from the fear that an applicant will attempt to distinguish over a reference disclosure by emphasizing a property or function which may not be mentioned by the reference and thereby assert that his claimed subject matter is novel. Such a concern is not only irrelevant, it is misplaced. In the first place, it is elementary that the mere recitation of a newly discovered function or property, inherently possessed by things in the prior art, does not cause a claim drawn to those things to distinguish over the prior art. Additionally, where the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent

characteristic of the prior art, it possesses the authority to require the applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on."

The only functional language in the pending claims has to do with amounts of ingredients used in the composition and method-of-use claims. However, Applicants do not rely on this functional language to distinguish over the prior art. Rather, Applicants distinguish over the prior art in the selection of a particular stereoisomer of a Base Compound. (In this respect, please see below in the APPENDIX, especially the discussion under the heading Relation of Claimed Invention to Van Lommen et al., and the matter presented above re novelty in the discussions of the double patenting rejection and the § 102 rejections.) Since Applicants do not rely on functional language to distinguish over the prior art, it is respectfully urged that the Swinehart et al. case does not apply to the facts herein.

For the reasons that are set forth above, it is respectfully urged that the rejection of Claims 20-26 under 35 U.S.C. 103 as being unpatentable over Van Lommen et al., U.S. Patent No. 4,654,362, is in error. Favorable reconsideration and withdrawal of this rejection is respectfully requested.

CONCLUSION

It is respectfully submitted that the foregoing discussion has demonstrated the patentability of the claimed subject matter. Accordingly, early favorable action is respectfully requested.

Respectfully submitted,

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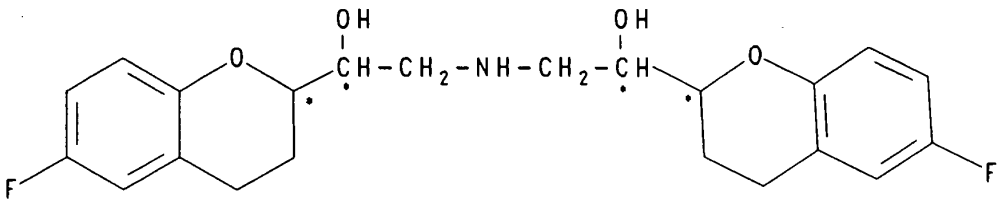
APPENDIX

Background Discussion

The claimed invention relates to a particular stereochemically isomeric form (i.e., *stereoisomer*) of the compound α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol], to a pharmaceutical composition consisting essentially of said stereoisomer plus a particular blood pressure reducing agent [the mirror image stereoisomer (or *enantiomer*) of the subject claimed stereoisomer], and to a method of treating hypertension in warm blooded animals which comprises administering to warm blooded animals in need of such treatment an effective amount of said pharmaceutical composition.

The compound α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol] has the following molecular structure:



This compound (which *per se*, without regard to its stereochemical configuration, will be referred to herein as the "Base Compound") has four chiral centers, which are indicated in the formula with asterisks ("*"). Each chiral center can have either of two absolute spatial configurations, designated by convention as "R" or "S". Thus, a specific stereoisomer of the Base Compound could be referred to, for

example, as the "RRRR stereoisomer", if each chiral center had the R absolute configuration. Theoretically, a compound having 4 chiral centers, each of which can have 2 absolute spatial configurations, would have sixteen [i.e., 2^4] possible stereoisomers. The present Base Compound, however, has only ten. This is so because the two moieties of the Base Compound that are bonded to the central -NH- group are geometrically identical (as distinguished from "stereochemically identical"). By virtue of having two geometrically identical moieties bonded to the central -NH- group, the formula used to calculate the number of theoretically possible stereochemical configurations "degenerates" so that there are in fact fewer such configurations than the formula predicts. This is so because the members of certain pairs of the sixteen theoretically possible stereoisomers are identical to each other. That is, they are the same stereoisomer but "written" forwards and backwards (analogously to the word "radar"). The ten possible stereoisomers, which are disclosed in TABLE 2 on page 847 of the Pauwels et al. article that is appended to the Pauwels Declaration, and, where appropriate, their "written backwards" equivalents, are:

1. SRRR [same as RRRS]
2. RSSS [same as SSSR]
3. SRRS
4. RSSR
5. SRSR [same as RSRS]
6. SRSS [same as SSRS]

7. RSRR [same as RRSR]

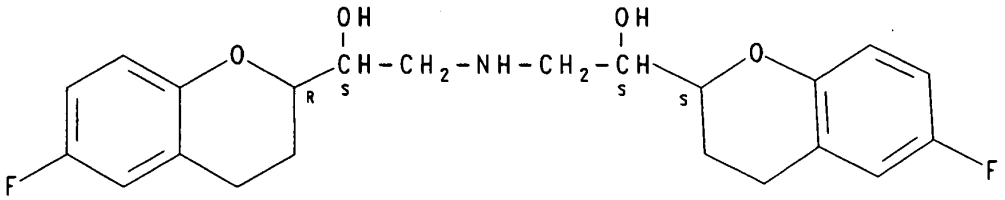
8. RRSS [same as SSRR]

9. SSSS

10. RRRR

The present invention is based on the discovery that one of the ten possible stereoisomers, the RSSS isomer, possesses unexpected properties, as was discussed in detail in Applicants' response to the previous Office Action.

The specific stereoisomeric compound of the invention is represented by the formula:



It will be seen that the four chiral centers, reading from left to right in the formula, have, respectively, the R, S, S, and S absolute configurations. For brevity, this specific stereoisomeric form of the Base Compound will be referred to herein as the "RSSS isomer", and its mirror image (or enantiomer) will be referred to herein to as the "SRRR isomer".

Relation of Claimed Invention to Van Lommen et al.

Neither a composition consisting essentially of the RSSS isomer, nor a composition consisting essentially of the RSSS isomer and its enantiomer the SRRR isomer, are disclosed in Van Lommen et al. The patentees disclose the Base Compound, **as an undefined mixture of stereoisomers**, as compound Nos. 84 (designated as "AB") and 87 (designated as "AA"), shown in the table in Col. 21 of the patent. There is no way that one can determine from the teachings of the patent the specific stereoisomeric configurations of Van Lommen et al's compound Nos. 84 and 87, as will be explained below.

At Col. 4, lines 59 et seq., in referring to the two intermediates used to prepare the final compounds, each [intermediate] of which forms half the final compound, the patentees disclose that "...it is conventionally agreed to designate the stereochemically isomeric form [of the intermediate] which is first isolated as 'A' and the second as 'B', **without further reference to the actual stereochemical configuration.**" (Emphasis supplied.) With respect to the patentees' preferred compound, α,α'-[iminobismethylene]bis[3,4-dihydro-2*H*-1-benzopyran-2-methanol], the patentees disclose that "... it has experimentally been determined that the 'A' form corresponds with the RS or SR configuration at the chiral centers 1 and 2 or 3 and 4 while the 'B' form corresponds with the SS or RR configuration at the said chiral centers." Thus "A" means RS or SR or both RS and SR, and "B" means SS or RR or both SS and RR.

Employing these definitions wherein A = RS or SR or both, and B = SS or RR or both, the patentees' Compound 84, designated as "AB", is an undefined mixture of the RSRR, RSSS, SRSS and SRRR isomers, and Compound 87, designated as "AA", is an undefined mixture of the RSRS, RSSR, and SRRS isomers.

Some of the compounds in the cited patent were recovered as pure stereoisomers. Such compounds are indicated in the examples by designations such as A+B+, A+B-, etc. Illustrations include Compound Nos. 14-17, 22-23, 42, 78-83, 88, 107-109, and 129-130. While these compounds were recovered as pure stereoisomers, the patent does not disclose whether, for instance, A+ = RS or A+ = SR. Therefore, even with respect to the compounds of the patent that were separated into pure stereoisomers, the absolute spatial configurations (i.e., R or S) at each chiral center of these compounds are not deducible from the teachings of the patent.

From the above discussion, it is clear that the cited Van Lommen et al. patent discloses neither a composition consisting essentially of the RSSS stereoisomer of the Base Compound, nor a composition consisting essentially of the RSSS and SRRR isomers.

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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/825,488	01/24/92	XHONNEUX	R JAB-775

EXAMINER
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ART UNIT	PAPER NUMBER
1205	14

DATE MAILED: 02/15/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 8/30/93 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 20-26 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 20-26 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMI

The arguments filed August 30, 1993 have been received and entered into the file.

Applicant's arguments filed August 30, 1993 have been fully considered but they are not deemed to be persuasive.

Claims 20-26 are presented for examination.

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

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 20-26 are rejected under 35 U.S.C. § 102(a) as being anticipated by Van Lommen et al. col 4 l 34-48

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

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

Claims 20-26 are rejected under 35 U.S.C. § 102(b) as being anticipated by Van Lommen et al.

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

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section

> 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 20-26 are rejected under 35 U.S.C. § 103 as being unpatentable over Van Lommen et al in view of Van de Water, all of record, for reasons of record.

Van Lommen et al and Van de Water et al teach the claim designated compounds as old, well known and in combination with various carriers and excipients as useful for the claimed utility. This teaching includes all position isomers inherent in the claimed compound. The skilled artisan would have known that various isomers would exhibit biological activity at various levels. Absent information to the contrary, the skilled artisan would have seen optical isomer separation as a routine procedure leading to the compounds claimed herein. Biological testing for the claimed compounds would have been well within the skill of the artisan,a and such artisan would have expected the various biological activity levels set forth herein. It would follow therefore that the instant claims recite prima facie obvious subject matter and are properly rejected under 35 USC 103.

The declaration under 37 CFR 1.132 has been considered but is not deemed probative. It is well settled patent law that claimed compounds are deemed optical isomer mixtures, absent information to the contrary. Additionally, the claimed compound is seen as an optical isomer mixture, wherein the individual isomers have various biological activity levels. Any information proffered to demonstrate unexpected benefits residing in any isomer must be compared to the natural racemic mixture. In the instant declaration applicants optical isomer comparison is devoid probative moment. Absent information to support unexpected benefits residing in the old and well known compositions and their methods of use, the instant claims are properly rejected under 35 USC 103.

Claims 20-26 are rejected under 35 U.S.C. § 103 as being unpatentable over Van Lommen et al.

Van Lommen et al teach the claim designated compounds as old, well known and in combination with various carriers and excipients as useful for the claimed utility. This teaching includes all position isomers inherent in the claimed compound. The skilled artisan would have known that various isomers would exhibit biological activity at various levels. Absent information to the contrary, the skilled artisan would have seen optical isomer separation as a routine procedure leading to the compounds claimed herein. Biological testing for the claimed compounds would have been well within the skill of the artisan, and such

artisan would have expected the various biological activity levels set forth herein. It would follow therefore that the instant claims recite prima facie obvious subject matter and are properly rejected under 35 USC 103.

The instant claims are directed to effecting a biochemical pathway with an old and well known compound. Applicant's arguments that differential biological effects for rotational isomers are unexpected are not probative. Applicant's attention is directed to In re Swinehart, (169 USPQ 226 at 229) where the Court of Customs and Patent Appeals stated "is elementary that the mere recitation of a newly discovered function or property, inherently possessed by things in the prior art, does not cause a claim drawn to those things to distinguish over the prior art. Additionally, where the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to requires the applicant to prove that the subject matter shown to be in the prior art dose not posses the characteristic relied on. IN the instant invention the claims are directed to the ultimate utility set forth in the prior art, abet distanced by various biochemical intermediates. The ultimate utility for the claimed compounds, to include all isomers for such compounds, is old and well known, rendering the claimed subject matter obvious to the skilled artisan. It would follow

therefore that the instant claims are properly rejected under 35 USC 103.

Reliance on *In re May and Eddy*, 197 USPQ 601 (CCPA 1978) in the instant case is ill advised. Applicants' attention is directed to *In re Adamson and Duffin*, 125 USPQ 233 (CCPA 1960) which would be seen as controlling in the instant case. *In re Williams*, 80 USPQ 150, quoted but not cited by Applicant, was differentiated by the Adamson court for reasons applicable in the instant case. Compounds at issue in the Williams case were not known to possess optical isomers, clearly a different situation than the instant case. The skilled artisan would have known the instant compounds contain asymmetric centers, rendering arguments based on *In re Williams*, supra, moot. It is well settled patent law that the skilled artisan possessing the racemate, possesses the optical isomers.

It is well settled patent law that the skilled artisan would have expected each isomer to exhibit biological activity at different levels. Applicants aver differences between optical isomers support patentability, this position is not well taken. In the instant case the stated differences are differences in degree, not patentably distinct differences in kind. Absent different biological activities for each isomer, patentability for optical isomers does not lie.

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

The practice of automatically extending the shortened statutory period an additional month upon the filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication should be directed to Russell Travers at telephone number (703) 308-4603.

Russell Travers

MARIANNE M. CINTINS
SUPERVISORY PATENT EXAMINER
GROUP 120

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

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	15

DATE MAILED:

EXAMINER INTERVIEW SUMMARY RECORD

All participants (applicant, applicant's representative, PTO personnel):

(1) Charles Mieth (3) _____

(2) Russell Travis (4) _____

Date of interview 5/4/94

Type: ☐ Telephonic ☑ Personal (copy is given to ☐ applicant ☐ applicant's representative).

Exhibit shown or demonstration conducted: ☐ Yes ☑ No. If yes, brief description: _____

Agreement ☐ was reached with respect to some or all of the claims in question. ☑ was not reached.

Claims discussed: all claims

Identification of prior art discussed: all prior art

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: Examiner would favorably consider data supporting unexpected benefits results in claimed subject matter filed under 37 CFR 1.132

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

Unless the paragraphs below have been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW (e.g., items 1–7 on the reverse side of this form). If a response to the last Office action has already been filed, then applicant is given one month from this interview date to provide a statement of the substance of the interview.

☑ It is not necessary for applicant to provide a separate record of the substance of the interview.

☐ Since the examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action.

Russell Travis
Examiner's Signature

PTOL-413 (REV. 1-84)

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#17
JRP
7/12/94

JAB 775

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

RESPONSE UNDER 37 CFR 1.116
EXPEDITED PROCEDURE
EXAMINING GROUP 1205

Applicant : Raymond Mathieu Xhonneux et al.

Serial No.: 07/825,488 Art Unit: 125

Filed : January 24, 1992 Examiner: R. Travers

For : METHOD OF LOWERING THE BLOOD PRESSURE

I, Charles J. Metz, Reg. No. 20,359, certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231.

On: June 27, 1994

Charles J. Metz

Charles J. Metz, Reg. No. 20,359

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

RESPONSE UNDER 37 CFR 1.116

This letter is in response to the Office Action of February 15, 1994.

The courtesies extended by the Examiner to the undersigned Attorney for Applicants at the interview held on May 4, 1994, are gratefully acknowledged.

The following rejections remain at issue:

1. All the claims in the application (Claims 20-26) are rejected under both 35 U.S.C. 102(a) and 35 U.S.C. 102(b) as being anticipated by Van Lommen et al., U.S. Patent No. 4,654,362 ("Van Lommen");

2. All the claims in the application are rejected under 35 U.S.C. 103 over Van Lommen, in view of Van de Water et al., **Pharmacological and Hemodynamic Profile of Nebivolol, a Chemically Novel, Potent, and Selective B_1-Adrenergic Antagonist**, *Journal of Cardiovascular Pharmacology*, **11**, No. 5, 552-563 (1988); and

3. All the claims in the application are rejected under 35 U.S.C. 103 over Van Lommen.

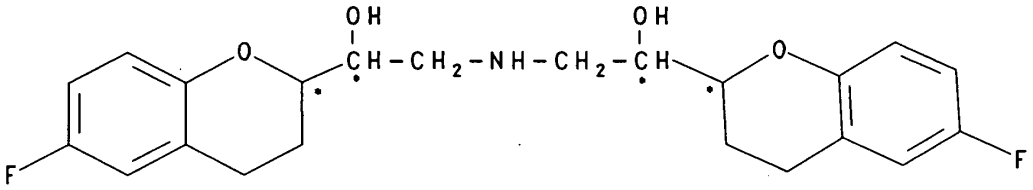
Applicants present below a background discussion, followed by a discussion of the above-identified three issues.

I. Background Discussion

The claimed invention relates to a particular stereochemically isomeric form (i.e., *stereoisomer*) of the compound α,α'-[iminobis-methylene]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol], to a pharmaceutical composition consisting essentially of said stereoisomer plus a particular blood pressure reducing agent [the mirror image stereoisomer (or *enantiomer*) of the subject claimed stereoisomer], and to a method of treating hypertension in warm blooded animals which comprises administering to warm blooded

animals in need of such treatment an effective amount of said pharmaceutical composition.

The compound α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol] has the following molecular structure:



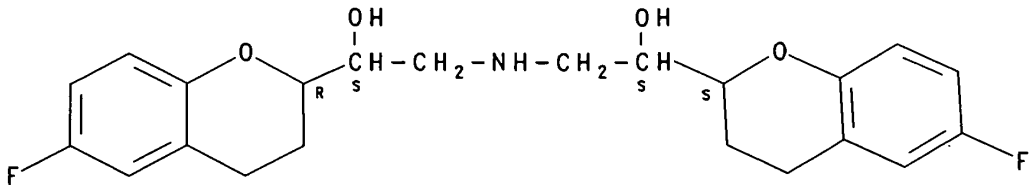
This compound (which *per se*, without regard to its stereochemical configuration) will be referred to herein as the "Base Compound"). The Base Compound, which is disclosed by Van Lommen, has four chiral centers, which are indicated in the formula with asterisks ("*"). Each chiral center can have either of two absolute spatial configurations, designated by convention as "R" or "S". Theoretically, a compound having 4 chiral centers, each of which can have 2 absolute spatial configurations, would have sixteen [i.e., 2^4] possible stereoisomers. The present Base Compound, however, has only ten because the two moieties of the Base Compound that are bonded to the central -NH- group are geometrically identical (as distinguished from "stereochemically identical"). By virtue of having two geometrically identical moieties bonded to the central -NH- group, the formula used to calculate the number of theoretically possible stereochemical configurations "degenerates" so that there are in fact fewer such configurations than the formula predicts because the members of certain pairs of the sixteen

theoretically possible stereoisomers are identical to each other. I.e., they are the same stereoisomer but "written" forwards and backwards (analogously to the word "radar"). The ten possible stereoisomers (and, where appropriate, their "written backwards" equivalents) are:

1. SRRR [same as RRRS]
2. RSSS [same as SSSR]
3. SRRS
4. RSSR
5. SRSR [same as RSRS]
6. SRSS [same as SSRS]
7. RSRR [same as RRSR]
8. RRSS [same as SSRR]
9. SSSS
10. RRRR

The present invention is based on the discovery that one of the ten possible stereoisomers, the RSSS isomer, possesses unexpected properties, which will be discussed in more detail below in the section relating to the Section 103 rejection over Van Lommen.

The specific stereoisomeric compound of the invention is represented by the formula:



It will be seen that the four chiral centers, reading from left to right in the formula, have, respectively, the R, S, S, and S absolute configurations. This stereoisomer of the Base Compound will be referred to as the "RSSS isomer", and its mirror image (enantiomer) will be referred to herein as the "SRRR isomer".

II. The Section 102 Rejections

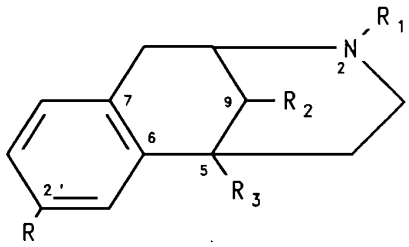
It is respectfully submitted that the Section 102 issues are controlled by the decision in *In re May and Eddy*, 197 USPQ 601 (CCPA 1978) ["May et al."]

Discussion of May et al.

The point of law brought out by May et al. that is applicable to the facts of this case is that the novelty of optical isomers is not negated by the prior art disclosure of the racemate. The CCPA so held in May et al., and cited *In re Williams*, 80 USPQ 150 (CCPA 1948), on page 607 in support thereof. The Examiner has criticized *In re Williams* on the grounds that in the 1948 decision the court stated that there was "no evidence of record to show actual knowledge of the racemic nature of the ... [prior art compound]".

Regardless of whether the state of the art in 1948 would have led those skilled in the art to know that the prior art compound was a racemate that contained a laevo and a dextro isomer, in May et al., the prior art actually disclosed that the racemate compounds of the prior art can be separated into optical isomers. Therefore, it is clear that the holding in May et el. that the novelty of optical isomers is not negated by the prior art disclosure of the racemate did not depend upon any lack of knowledge in the prior art that the racemate could be resolved into its isomers. The following is a brief summary of the prior art that was applied against the application of May et al., and a summary of the claimed subject matter that was found patentable over that prior art:

The prior art in May et al. showed compounds of the formula:



wherein:

R = hydrogen or **hydroxy**;

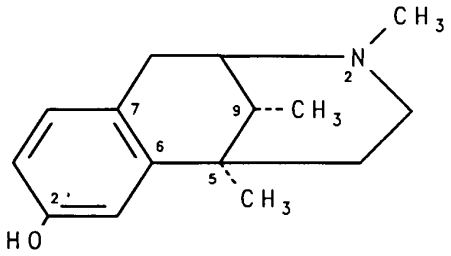
R_1 = hydrogen, **methyl**, straight chain alkyl or aralkyl;

R_2 = **hydrogen**, **alkyl**, methylene or substituted methylene; and

R_3 = hydrogen or **alkyl**.

[Variables that are particularly relevant to the subject matter sought to be patented by May et al. are shown in **bold faced type.**]

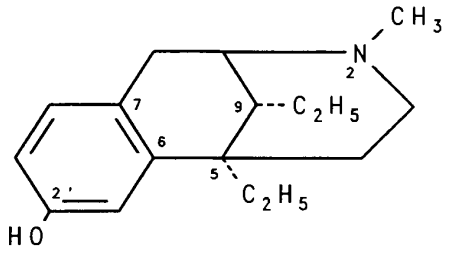
The prior art specifically disclosed the compound α-(-)-2'-hydroxy-2,5,9-trimethyl-6,7-benzomorphan, a compound of the formula:



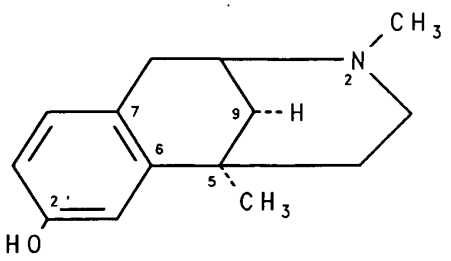
The prior art also disclosed that "virtually all of the ... activity is due to the levo, as opposed to the dextro, isomer."

The following levo isomers were found to be patentable to May et al. (a copy of their issued patent, No. 4,159,333, is enclosed):

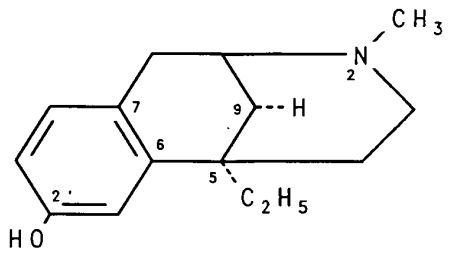
α-(-)-5,9-diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan:



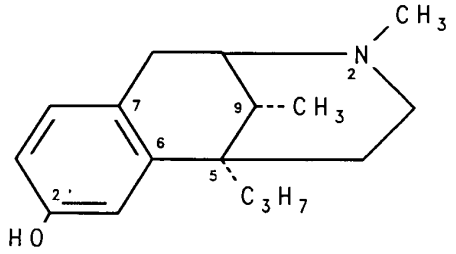
(-)-5-methyl-2'-hydroxy-2-methyl-6,7-benzomorphan:



(-)-5-ethyl-2'-hydroxy-2-methyl-6,7-benzomorphan:



α-(-)-5-propyl-9-methyl-2'-hydroxy-2-methyl-6,7-benzomorphan:



It is urged that it is clear from the facts and the holding in May et al. that a Section 102 rejection of a stereoisomer, based upon the premise that the disclosure in the prior art of its racemate anticipates the stereoisomer, is error. Accordingly, favorable reconsideration and withdrawal of the rejection of all the claims under both 35 U.S.C. 102(a) and 35 U.S.C. 102(b) as being anticipated by Van Lommen et al., U.S. Patent No. 4,654,362, is respectfully requested.

III. The Section 103 Rejection based upon Van Lommen and Van de Water et al.

It is first respectfully pointed out that the Van de Water et al. article does not significantly add to the teachings of the Van

Lommen patent, except for highlighting the Base Compound, which is referred to in the article as "nebivolol". While nebivolol is now known to be the presently claimed mixture of the RSSS isomer and its enantiomer the SRRR isomer, this is not disclosed in the article. In fact, the article contains no discussion of stereochemistry at all. However, it is not necessary to argue patentability over the teachings of Van de Water et al., because this article is not available as a reference against the claims of this application, as will be demonstrated below.

In the response to the previous Office Action, Applicants pointed out that Van de Water et al. was not a proper reference because the Van de Water et al. article was published in May, 1988 (see copy of FAXed transmission from *Information Research Services Inc.* enclosed with Applicants' previous response), whereas Applicants are entitled to the filing date of their parent application Serial No. 07/172,747, which was March 23, 1988. At the interview that was held on May 4, 1994, the Examiner pointed out that the reason that the rejection based upon Van de Water et al. was maintained was that Applicants' response did not specifically point out where in the parent application the presently claimed invention was supported. Such support is indicated below.

Claim 25, directed to the RSSS isomer, is supported by the disclosures at pages 11-12, Example 3(b), which specifically discloses the preparation of the subject claimed RSSS isomer as compound 1; and page 2, lines 33-34, which discloses that the subject claimed RSSS isomer is the most preferred compound;

Claim 26, which relates to a pharmaceutical composition containing the RSSS isomer and its enantiomer, the SRRR isomer, is supported by the passage on page 5, lines 20-23, which specifically discloses the SRRR enantiomers of the potentiating RSSS isomers as particular blood pressure reducing compounds for use in combination with the RSSS potentiating compounds of the invention, and by Claim 8 on page 15, which is specifically directed to a pharmaceutical composition containing said SRRR isomer in combination with the RSSS isomer of this invention;

Claim 21, which relate to a composition wherein the proportions of the RSSS and SRRR isomers are 1:1 is supported by Claim 10 on page 15 [the proportions of 1:5 to 5:1 recited in Claim 20 pending herein are not disclosed in the Van de Water et al. article, so support by the parent application in order to antedate Van de Water et al. is not an issue for Claim 20]; and

Claims 22-24, which relate to methods of treating hypertension in warm blooded animals, are supported throughout the disclosure of the parent application, for example, in the three paragraphs beginning at page 5, line 4.

For the reasons set forth above, it is respectfully urged that the presently pending claims are supported by the parent application, Serial No. 07/172,747, which was filed on March 23, 1988. Therefore, it is respectfully urged that the Van de Water et al. article, which was published in May, 1988, is not available as a reference against the claims herein. Accordingly, favorable

reconsideration and withdrawal of the rejection of all the claims as being unpatentable under 35 U.S.C. 103 over Van Lommen, in view of Van de Water et al., **Pharmacological and Hemodynamic Profile of Nebivolol, a Chemically Novel, Potent, and Selective B_1-Adrenergic Antagonist**, *Journal of Cardiovascular Pharmacology*, **11**, No. 5, 552-563 (1988), is respectfully requested.

IV. The Section 103 Rejection based upon Van Lommen

It is respectfully submitted that the subject claimed invention is patentable over Van Lommen because the cited patent fails to teach or suggest the unexpected properties exhibited by the subject claimed RSSS isomer. In the interview held on May 4, the Examiner stated that he felt that the showing that has been made by Applicants did not establish unexpected properties because it was his view that the difference over the prior art was one of degree rather than of kind, and the latter was required in order to establish patentability. Applicants respectfully submit that the facts in the present case establish a difference in kind, and that therefore the subject claimed invention is patentable over the cited art.

The unexpected property that is principally relied upon by Applicants herein resides in the fact that the subject RSSS isomer, which has quite low activity itself as a blood pressure reducing agent, nevertheless significantly and substantially potentiates the blood pressure reducing activity of its enantiomer, the SRRR isomer.

The Examiner's attention is respectfully directed to the Declaration of Raymond M. Xhonneux that was submitted with the PRELIMINARY AMENDMENT in this application. Please refer to Paragraph 4 on pages 2-4 of the declaration, which further explains the experiments described in the *European Journal of Pharmacology* article attached to the Declaration. In the experiment whose results are reported in Table 1 of the Declaration, the median % change in blood pressure ("BP") after administration of placebo (vehicle only - the vehicle was 20% polypropylene glycol) and various dosages of the RSSS isomer in spontaneously hypertensive rats ("SHR") is shown. [The changes reported are the % changes from the BP of the rats prior to treatment (i.e., before the rats have been given either placebo or RSSS isomer). It is noted that administration of the vehicle alone slightly increases the BP.] In this experiment, the vehicle was used as a control. That is, the data obtained wherein varying dosages of the RSSS isomer were employed were compared with the vehicle control. If a statistically significant change from the vehicle control was found in any given experiment, the data from that experiment is marked with an asterisk "*". The results are summarized in the table below.

RSSS Isomer mg/kg	Median % Change from Untreated SHR Systolic	Diastolic
0 (Vehicle control)	3.8	4.13
0.63	4.21	4.91
1.25	2.87	4.84
2.5	-1.93*	1.07
5	-0.012*	4.17

Mr. Xhonneux' conclusion (see page 4 of the Declaration) is that the RSSS compound, when administered alone, only minimally affects blood pressure.

In the experiment whose results are reported in Table 2 of the Declaration, the blood pressure reducing effectiveness of the SRRR isomer in SHR is compared with the results recorded after administration of vehicle alone in an experiment that otherwise parallels the procedure set forth above for the experiment in which the effectiveness of the RSSS isomer was tested. A summary of the results follows:

SRRR Isomer mg/kg	Median % Change from Untreated SHR Systolic	Diastolic
0 (Vehicle control)	3.8	4.13
0.63	-0.47*	4.13
1.25	-4.98*	2.06*
2.5	-7.36*	1.23*
5	-9.26*	-1.03*

In the experiment whose results are reported in Table 3 of the Declaration, the blood pressure reducing effectiveness of a dosage of 1.25 mg/kg of the SRRR isomer combined with varying dosages of RSSS isomer is evaluated. As is pointed out in the last sentence on page 2 of the Declaration, the experiment in which 1.25 mg/kg of SRRR isomer was administered alone was used as the control. Thus, those data that differ significantly from the control (in this case, 1.25 mg/kg of SRRR isomer used alone) are marked with an asterisk "*". The results are summarized as follows:

1.25 mg/kg of SRRR Isomer + indicated amount of RSSS Isomer mg/kg	Median % Change from Untreated SHR	
	Systolic	Diastolic
0 (Control - 1.25 mg/kg SRRR Isomer)	-4.98	2.06
0.16	-6.78*	1.36
0.31	-10.39*	-4.08*
0.63	-9.49*	-4.08*
1.25	-12.29*	-4.76*
2.5	-16.04*	-10.02*
5	-19.43*	-11.56*

It is noteworthy that, by itself, the RSSS isomer did not show any significant blood pressure reducing effectiveness until it was used in dosages of 2.5 and 5 mg/kg. That is, when used alone in dosages of 0.63 and 1.25 mg/kg, the effect on blood pressure did not differ significantly from the vehicle control. Thus, from the data presented in Table 1 of the Declaration, one would have expected that if the RSSS isomer were used in dosages of up to 1.25 mg/kg in combination with 1.25 mg/kg of the SRRR isomer, no significant difference, either positive or negative, from the control would be observed. But the expected is not what happened! Beginning with dosages as small as 0.16 mg/kg of the RSSS isomer, a significant potentiation of the (more) active SRRR isomer is observed. There is nothing in the prior art that would have led one skilled in the art to predict that this would happen.

It is clear that there is more than an additive effect resulting from the use of a combination of the two enantiomers. Accordingly, it is urged that this amounts to a difference in kind rather than one of degree, and as such overcomes any prima facie

case of obviousness over the cited Van Lommen patent, and establishes the patentability under Section 103 of the subject claimed invention.

During the interview held on May 4, the Examiner questioned why the blood pressure changes reported in Mr. Xhonneux' Declaration were reported as differences, rather than actual values. The reasons are the following:

The first reason is that the BP's of SHR's vary considerably from animal to animal. Consequently, taking the mean value of the BP's of all the SHR's before therapy will include a large margin of error. Since the same applies to the BP's measured after therapy, no useful information would be gained. The problem in essence is that the INDIVIDUAL response of each animal to therapy would be lost in averaging the initial and final conditions. Obviously, in finding out whether hypertensive therapy works, one should consider whether the average of all individual RESPONSES is significant. Response implies that for each animal tested one measures the change in BP caused by the therapy and one tests the significance of that change by accepted statistical analysis, in this case the Mann-Whitney U-test.

A secondary reason is based on the observation that what people experience as hypertension is very much an individual feeling. One person can feel uncomfortable at a BP with value "x", whereas another would feel perfectly fit at such value and only start to complain at value "x+y". In the second person it would suffice to

reduce the BP by an amount "y" to get back to value "x". In the first a reduction from value "x" would be required.

In conclusion, it is not the actual BP values before and after therapy that are significant, but the fact that the actual values are reduced by a significant amount so that the BP moves from an uncomfortable to a comfortable zone (which may be different from person to person).

For the reasons that are set forth above, it is respectfully urged that the rejection of all the claims as being unpatentable under 35 U.S.C. 103 over Van Lommen et al., U.S. Patent No. 4,654,362, is in error. Favorable reconsideration and withdrawal of this rejection is respectfully requested.

In view of the foregoing remarks, it is urged that this application is in condition for allowance. Early favorable action is respectfully requested.

Respectfully submitted,

Charles J. Metz
Attorney for Applicants
Registration #20,359

Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933

(908) 524-2814

June 27, 1994

AF/GP125

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JRP 8/11/94

JAB 775

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Raymond Mathieu Xhonneux et al.

Corres. and Mail BOX AF

Serial No.: 07/825,488 Art Unit: 125

Filed : January 24, 1992 Examiner: R. Travers

For : METHOD OF LOWERING THE BLOOD PRESSURE

I, Charles J. Metz, Reg. No. 20,359, certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231.

On: August 4, 1994 Charles J. Metz

Charles J. Metz, Reg. No. 20,359

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

NOTICE OF APPEAL

Applicants hereby appeal to the Board of Patent Appeals and Interferences from the decision of the Examiner dated February 15, 1994, finally rejecting Claims 20-26 of the above-identified application.

The item(s) checked below are appropriate:

1. [X] An extension of time to respond to the final rejection was granted on June 27, 1994, for two (2) months.

2. [X] A Petition for Extension of Time under 37 CFR 1.136 is attached hereto in triplicate.

3. [X] A timely response to the final rejection has been filed.

4. [X] Fee $270.00: for filing of Notice of Appeal

   [X] Charge to Deposit Account No. 10-0750/JAB 775/CJM. (Two additional copies of this Notice are enclosed)

   [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, in connection herewith to Deposit Account No. 10-0750/JAB 775/CJM.

Respectfully submitted,

Charles J. Metz

Charles J. Metz
Attorney for Applicant
Registration #20,359

SC13033 08/10/94 07825488 10-0750 130 119 270.00CH

Johnson & Johnson
One Johnson & Johnson Plaza
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(908) 524-2814
August 4, 1994

JAB 775

#21

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Raymond Mathieu Xhonneux et al.

Serial No.: 07/825,488 Art Unit: 125

Filed : January 24, 1992 Examiner: R. Travers

For : METHOD OF LOWERING THE BLOOD PRESSURE

10/27

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

I, Charles J. Metz, Reg. No. 20,359, certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231.

On: October 7, 1994

Charles J. Metz

Charles J. Metz, Reg. No. 20,359

Sir:

Transmitted herewith is an APPELLANTS' BRIEF (three copies) in the above-identified application.

[X] One stamped, self-addressed postcard for the PTO Mail Room date stamp.

[X] Charge $ 280.00 to Deposit Account No. 10-0750/JAB 755/CJM for filing the brief. Three copies of this sheet are enclosed.

[X] Please charge any additional fees in connection with the filing of this communication, or credit overpayment, to Deposit Account No. 10-0750/JAB 775/CJM. Three copies of this sheet are enclosed.

Respectfully submitted,

Charles J. Metz

Charles J. Metz
Attorney for Appellants
Registration #20,359

Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933

(908) 524-2814

October 7, 1994

125

JAB 775

#21
1 of 3
JRP
10/28/94

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Raymond Mathieu Xhonneux et al.

Serial No.: 07/825,488 Art Unit: 125

Filed : January 24, 1992 Examiner: R. Travers

For : METHOD OF LOWERING THE BLOOD PRESSURE

10/28

I, Charles J. Metz, Reg. No. 20,359, certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231.

On: October 7, 1994

Charles J. Metz

Charles J. Metz, Reg. No. 20,359

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

APPELLANTS' BRIEF

Status of the Claims

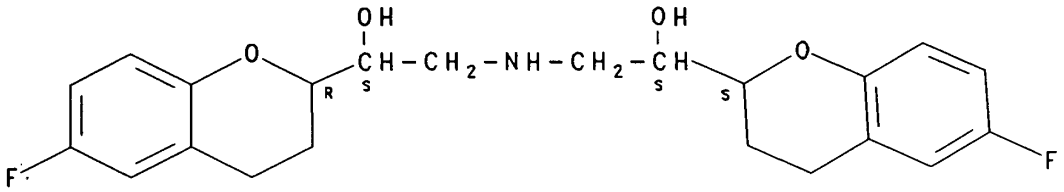
This is an appeal from the final rejection of Claims 20-26. No claims have been allowed. Original Claims 1-17 have been canceled, and Claims 18-19, added by Preliminary Amendment in this application, have also been canceled. A copy of the claims on appeal is appended hereto in APPENDIX I.

Status of Amendments

The claims were not amended after the final rejection. A response to the final rejection was considered, but did not result in allowance.

Summary of Invention

The invention relates to a composition consisting essentially of the compound [2R,αS,2'S,α'S]-α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol] having the formula:



or a pharmaceutically acceptable acid addition salt thereof, to a pharmaceutical composition comprising said compound and its enantiomer, and to a method of treating hypertension in warm blooded animals in need of such treatment which comprises administering to said warm blooded animals an effective amount of said pharmaceutical composition.

Issues

The following issues are presented for review:

1. All the claims in the application (Claims 20-26) are rejected under both 35 U.S.C. 102(a) and 35 U.S.C. 102(b) as being anticipated by Van Lommen et al., U.S. Patent No. 4,654,362 ("Van Lommen");

2. All the claims in the application are rejected under 35 U.S.C. 103 over Van Lommen, in view of Van de Water et al., **Pharmacological and Hemodynamic Profile of Nebivolol, a Chemically Novel, Potent, and Selective B_1-Adrenergic Antagonist**, *Journal of Cardiovascular Pharmacology*, **11**, No. 5, 552-563 (1988); and

3. All the claims in the application are rejected under 35 U.S.C. 103 over Van Lommen.

Grouping of Claims

The claims do not all stand or fall together. There is one argument for patentability that applies to Claim 25 that does not apply to the other pending claims.

Argument

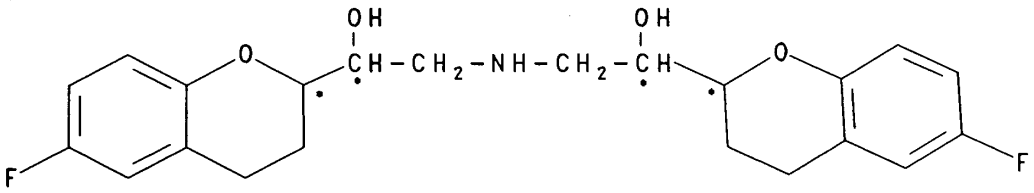
Appellants present below a background discussion, followed by a discussion of the above-identified three issues.

I. Background Discussion

The claimed invention relates to a composition consisting essentially of a particular stereochemically isomeric form (i.e., *stereoisomer*) of the compound α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol], to a pharmaceutical composition consisting essentially of said stereoisomer plus a

particular blood pressure reducing agent [the mirror image stereoisomer (or *enantiomer*) of the subject claimed stereoisomer], and to a method of treating hypertension in warm blooded animals which comprises administering to warm blooded animals in need of such treatment an effective amount of said pharmaceutical composition.

The compound α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol] has the following molecular structure:



This compound (which *per se*, without regard to its stereochemical configuration) will be referred to herein as the "Base Compound"). The Base Compound, which is disclosed by Van Lommen, has four chiral centers, which are indicated in the formula with asterisks ("*"). Each chiral center can have either of two absolute spatial configurations, designated by convention as "R" or "S". Theoretically, a compound having 4 chiral centers, each of which can have 2 absolute spatial configurations, would have sixteen [i.e., 2^4] possible stereoisomers. The present Base Compound, however, has only ten because the two moieties of the Base Compound that are bonded to the central -NH- group are geometrically identical (as distinguished from "stereochemically identical"). By virtue of having two geometrically identical moieties bonded to the central -NH- group, the formula used to calculate the number of

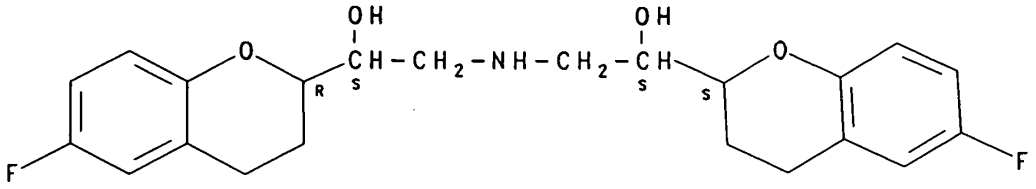
theoretically possible stereochemical configurations "degenerates" so that there are in fact fewer such configurations than the formula predicts because the members of certain pairs of the sixteen theoretically possible stereoisomers are identical to each other. I.e., they are the same stereoisomer but "written" forwards and backwards. The ten possible stereoisomers (and, where appropriate, their "written backwards" equivalents) are shown in Table I:

TABLE I

1.	SRRR	[same as RRRS]
2.	RSSS	[same as SSSR]
3.	SRRS	
4.	RSSR	
5.	SRSR	[same as RSRS]
6.	SRSS	[same as SSRS]
7.	RSRR	[same as RRSR]
8.	RRSS	[same as SSRR]
9.	SSSS	
10.	RRRR	

The present invention is based on the discovery that one of the ten possible stereoisomers, the RSSS isomer, possesses unexpected properties, which will be discussed in more detail below in the section relating to the Section 103 rejection over Van Lommen.

The specific stereoisomeric compound of the invention is represented by the formula:



It will be seen that the four chiral centers, reading from left to right in the formula, have, respectively, the R, S, S, and S absolute configurations. This stereoisomer of the Base Compound will be referred to as the "RSSS isomer", and its mirror image (enantiomer) will be referred to herein as the "SRRR isomer".

II. The Section 102 Rejections

Claim 25 on appeal relates to a composition consisting essentially of the compound [2R,αS,2'S,α'S]-α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol]. The limitation that distinguishes over the disclosure of the Base Compound in Van Lommen is "[2R,αS,2'S,α'S]", which is the nomenclature designation that specifies the subject RSSS isomer.

Appellants will discuss below exactly what it is that Van Lommen discloses and teaches the artisan, why that disclosure does not anticipate the presently claimed invention, and the applicability of a CCPA decision [*In re May et al.*, 197 USPQ 601 (CCPA 1978)] to the facts involved herein.

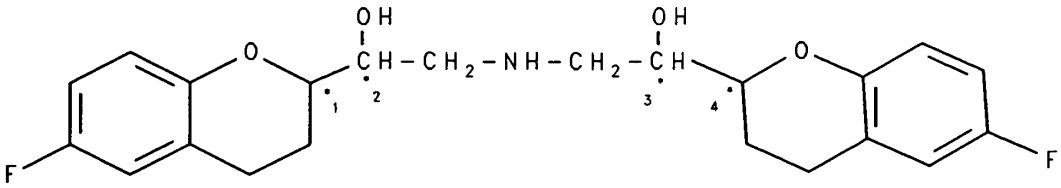
A. What Van Lommen Discloses and Teaches

Van Lommen discusses the stereochemical isomerism of the compounds disclosed in the patent at Col. 4, line 40, through Col. 5, line 10. The compounds of Van Lommen can be prepared by coupling two "halves" of the final compound (see Col. 3), each half of which can exist in stereochemical isomeric forms. For those compounds whose specific stereoisomeric configurations were not determined, by convention, it was agreed to designate the form (of each half) first isolated (as by chromatography) as "A" and the second as "B", without further reference to the actual stereochemical configuration (Col. 4, lines 59-65). It is pointed out at Col. 5, lines 1-4, of Van Lommen, that the "A" designation denotes the RS or the SR configuration at the chiral centers 1 and 2 or 3 and 4 (the designation "A" can be taken to denote a mixture of both the RS and the SR diastereomers) and the "B" designation denotes the RR or the SS configuration at the chiral centers 1 and 2 or 3 and 4 (the designation "B" can be taken to denote a mixture of both the SS and the RR stereoisomers).

B. Van Lommen Does Not Anticipate the Subject Invention

Stereoisomeric mixtures of the Base Compound are disclosed in Van Lommen as Compound Nos. 84 and 87, shown in the table in Col. 21 of the patent. The stereoisomeric configurations of Compound Nos. 84 and 87 of Van Lommen are designated as "AB" and "AA". The chiral centers 1, 2, 3 and 4, applied to the Base Compound, are

shown in the following formula (see Col. 5, lines 5-10, of Van Lommen):



The possible absolute configurations of Compounds 84 and 87 are therefore the following:

Compound 84, Designated "AB"

Since A = RS or SR and B = RR or SS then AB = RSRR or RSSS or SRRR or SRSS.

Thus, four possible diastereomers are possible from the AB designation.

Compound 87, Designated "AA"

Since A = RS or SR, then AA = RSRS or RSSR or SRRS.

Thus there are three possible absolute stereoisomeric configurations with the AA designation. [The SRSR configuration, which is formed by addition of SR + SR, is equivalent to the RSRS configuration because both right and left halves of the Base Compound

molecule (as one views the formula shown above) are identical, but just "written" either forwards or backwards - see TABLE I, above.]

The disclosure of Compound No. 84 is most relevant to the facts herein. There are four possible stereoisomeric configurations of Compound No. 84, that is, the RSRR, RSSS, SRRR, and SRSS (one of which is the presently claimed RSSS isomer). Because, in the disclosure of Van Lommen, Compound No. 84 was not resolved into a stereoisomer whose absolute stereoisomeric configuration was known, there is no way to determine from the disclosure of Van Lommen which stereoisomer was the one that was prepared. *A fortiori*, then, the artisan was not put in possession of the present invention, which relates to a composition consisting essentially of the RSSS isomer, a composition comprising a mixture of the RSSS isomer and its enantiomer, and the use of said composition to treat hypertension in mammals. For this reason, it is clear that Van Lommen does not anticipate the presently claimed invention.

C. The Decision in *In re May et al.* is Controlling

It is respectfully submitted that the Section 102 issues can be resolved by applying the reasoning of the decision in *In re May and Eddy*, 197 USPQ 601 (CCPA 1978) ["May et al."].

The point of law brought out by May et al. that is applicable to the facts of this case is that **"the novelty of optical isomers is not negated by the prior art disclosure of the racemate"** (May et

al., page 607). [In the present situation, the prior art discloses unresolved stereoisomers of the Base Compound, not a racemate.] *In re Williams*, 80 USPQ 150 (CCPA 1948), was cited by the CCPA in support of the decision in May et al. The Examiner has criticized *In re Williams* on the grounds that in the 1948 decision the court stated that there was "no evidence of record to show actual knowledge of the racemic nature of the ... [prior art compound]". Regardless of whether the state of the art in 1948 was such that the artisan would have known that the *In re Williams* prior art compound was a racemate that contained a levo and a dextro isomer, the facts in May et al. make it clear that the prior art in May et al. disclosed that the prior art racemates can be separated into optical isomers. Therefore, it is apparent that the May et el. holding quoted above did not depend upon lack of knowledge in the prior art that the racemate could be resolved into its isomers or that the prior art was unaware of the possible stereoisomeric configurations of the prior art compounds. In APPENDIX II, attached hereto, Appellants present a brief summary of the facts in the May et al. case to demonstrate that the facts in the present case are sufficiently analogous to those in May et al. that it is clear that the reasoning of May et al. is applicable to the issues herein.

It is believed that the facts and issues in May et al. (as summarized by Appellants in APPENDIX II, below) support the following rule of law from that decision:

> "... the disclosure in the prior art of a base compound that has stereoisomeric configurations is not an antici-

pation of particular stereoisomers of that base compound, even though the knowledge of the prior art is such that the artisan could deduce the specific stereoisomeric configurations from the disclosure of the base compound." (Quoting from the conclusion presented in APPENDIX II, below.)

The Examiner urges that:

"Reliance on ... [May et al.] in the instant case is ill advised. Applicants' attention is directed to *In re Adamson and Duffin*, 125 USPQ 233 (CCPA 1960) which would seem to be controlling in the instant case." (Quoting from page 6 of the Final Rejection of February 15, 1994.)

It is respectfully urged that *In re Adamson et al.* is not applicable to the facts here because the rejection in the Adamson case was a rejection under 35 U.S.C. 103 obviousness, not an anticipation rejection under 35 U.S.C. 102. In the Adamson et al. case, the Board had held that "... both the compounds and the broad method claims would have been **obvious** to one of ordinary skill in the art." (Page 234, second column - emphasis supplied.) This <u>obviousness</u> rejection, not an anticipation rejection, was the one that was affirmed by the Court. It is respectfully urged that since the Adamson et al. decision involved a rejection under 35 U.S.C. 103 obviousness, rather than 35 U.S.C. 102 anticipation, the reliance by the Examiner on this decision to support the present Section 102 anticipation rejection is in error.

It is urged that it is clear from the facts and the holding in May et al. that the disclosure in the prior art of a base compound,

per se, unresolved into isomers whose specific stereoisomeric configurations are known, is not an anticipation of specific stereoisomers of said base compound. For this reason, it is respectfully submitted that the rejection of all the claims under both 35 U.S.C. 102(a) and 35 U.S.C. 102(b) as being anticipated by Van Lommen et al., U.S. Patent No. 4,654,362, is in error. Reversal is respectfully requested.

III. The Section 103 Rejection based upon Van Lommen and Van de Water et al.

It is first respectfully pointed out that the Van de Water et al. article does not significantly add to the teachings of the Van Lommen patent, except for highlighting the Base Compound, which is referred to in the article as "nebivolol". While nebivolol is now known to be the presently claimed mixture of the RSSS isomer and its enantiomer the SRRR isomer, this is not disclosed in the article. In fact, the article contains no discussion of stereochemistry at all. However, it is not necessary to argue patentability over the teachings of Van de Water et al., because this article is not available as a reference against the claims of this application, as will be demonstrated below.

In the response to the Office Action of May 14, 1993, Appellants pointed out that Van de Water et al. was not a proper reference because the Van de Water et al. article was published in May, 1988 (see copy of FAXed transmission from *Information Research Services Inc.* enclosed with Appellants' response filed on August 30,

1993), whereas Appellants are entitled to the filing date of their parent application Serial No. 07/172,747, which was March 23, 1988. At the interview that was held on May 4, 1994, the Examiner pointed out that the reason that the rejection based upon Van de Water et al. was maintained was that Appellants' response did not specifically point out where in the parent application the presently claimed invention was supported. Such support is indicated below.

Claim 25, directed to a composition consisting essentially of the RSSS isomer, is supported by the disclosures at pages 11-12, Example 3(b) of Serial No. 07/172,747, which specifically discloses the preparation of the subject RSSS isomer as Compound 1; and page 2, lines 33-34, which discloses that the subject RSSS isomer is the most preferred compound;

Claim 26, which relates to a pharmaceutical composition containing the RSSS isomer and its enantiomer, the SRRR isomer, is supported by the passage on page 5, lines 20-23, of Serial No. 07/172,747, which specifically discloses the SRRR enantiomers of the potentiating RSSS isomers as particular blood pressure reducing compounds for use in combination with the RSSS potentiating compounds of the invention, and by Claim 8 on page 15, which is specifically directed to a pharmaceutical composition containing said SRRR isomer in combination with the RSSS isomer of this invention;

Claim 21, which relate to a composition wherein the proportions of the RSSS and SRRR isomers are 1:1 is supported by Claim 10 on page 15 of Serial No. 07/172,747, [the proportions of 1:5 to 5:1 recited in Claim 20 pending herein are not disclosed in the Van de Water et al. article, so support by the parent application in order to antedate Van de Water et al. is not an issue for Claim 20]; and

Claims 22-24, which relate to methods of treating hypertension in warm blooded animals, are supported throughout the disclosure of the parent application, for example, in the three paragraphs beginning at page 5, line 4, of Serial No. 07/172,747, in which blood pressure reducing activity is discussed.

For the reasons set forth above, it is respectfully urged that the presently pending claims are supported by the parent application, Serial No. 07/172,747, which was filed on March 23, 1988. Therefore, it is respectfully urged that the Van de Water et al. article, which was published in May, 1988, is not available as a reference against the claims herein. Accordingly, reversal of the rejection of all the claims as being unpatentable under 35 U.S.C. 103 over Van Lommen, in view of Van de Water et al., **Pharmacological and Hemodynamic Profile of Nebivolol, a Chemically Novel, Potent, and Selective B_1-Adrenergic Antagonist**, *Journal of Cardiovascular Pharmacology*, **11**, No. 5, 552-563 (1988), is respectfully requested.

IV. The Section 103 Rejection based upon Van Lommen

It is respectfully submitted that the subject claimed invention is patentable over Van Lommen because the cited patent fails to teach or suggest the unexpected properties exhibited by the subject claimed RSSS isomer. In an interview with the Examiner on May 4, 1994, the Examiner stated that he felt that the showing that has been made by Appellants did not establish unexpected properties because it was his view that the difference over the prior art was one of degree rather than of kind, and the latter was required in order to establish patentability. Appellants respectfully submit that the facts in the present case establish a difference in kind, and that therefore the subject claimed invention is patentable over the cited art.

The unexpected property that is principally relied upon by Appellants herein resides in the fact that the subject RSSS isomer, which has quite low activity itself as a blood pressure reducing agent, nevertheless significantly and substantially potentiates the blood pressure reducing activity of its enantiomer, the SRRR isomer.

The Board's attention is respectfully directed to the Declaration of Raymond M. Xhonneux that was submitted with the PRELIMINARY AMENDMENT in this application. Please refer to Paragraph 4 on pages 2-4 of the declaration, which further explains the experiments described in the *European Journal of Pharmacology* article attached to the Declaration. In the experiment whose results are reported

in Table 1 of the Declaration, the median % change in blood pressure ("BP") after administration of placebo (vehicle only - the vehicle was 20% polypropylene glycol) and various dosages of the RSSS isomer in spontaneously hypertensive rats ("SHR") is shown. [The changes reported are the % changes from the BP of the rats prior to treatment (i.e., before the rats have been given either placebo or RSSS isomer). It is noted that administration of the vehicle alone slightly increases the BP.] In this experiment, the vehicle was used as a control. That is, the data obtained wherein varying dosages of the RSSS isomer were employed were compared with the vehicle control. If a statistically significant change from the vehicle control was found in any given experiment, the data from that experiment is marked with an asterisk "*". The results are summarized in TABLE II, below.

TABLE II

RSSS Isomer mg/kg	Median % Change from Untreated SHR	
	Systolic	Diastolic
0 (Vehicle control)	3.8	4.13
0.63	4.21	4.91
1.25	2.87	4.84
2.5	-1.93*	1.07
5	-0.012*	4.17

Mr. Xhonneux' conclusion (see page 4 of the Declaration) is that "[t]he potentiating (RSSS)-compound only minimally affects blood pressure when administered alone ... [TABLE II];".

In the experiment whose results are reported in Table 2 of the Declaration, the blood pressure reducing effectiveness of the SRRR

isomer in SHR is compared with the results recorded after administration of vehicle alone in an experiment that otherwise parallels the procedure set forth above for the experiment in which the effectiveness of the RSSS isomer was tested. A summary of the results follows in TABLE III:

TABLE III

SRRR Isomer mg/kg	Median % Change from Untreated SHR Systolic	Diastolic
0 (Vehicle control)	3.8	4.13
0.63	-0.47*	4.13
1.25	-4.98*	2.06*
2.5	-7.36*	1.23*
5	-9.26*	-1.03*

Mr. Xhonneux' conclusion (see page 4 of the Declaration) is that "[t]he blood pressure reducing (SRRR)-compound is a potent blood pressure reducing agent when administered alone ... [TABLE III];".

In the experiment whose results are reported in Table 3 of the Declaration, the blood pressure reducing effectiveness of a dosage of 1.25 mg/kg of the SRRR isomer combined with varying dosages of RSSS isomer is evaluated. As is pointed out in the last sentence on page 2 of the Declaration, the experiment in which 1.25 mg/kg of SRRR isomer was administered alone was used as the control. Thus, those data that differ significantly from the control (in this case, 1.25 mg/kg of SRRR isomer used alone) are marked with an asterisk "*". The results are summarized as follows:

TABLE IV

1.25 mg/kg of SRRR Isomer + indicated amount of RSSS Isomer mg/kg	Median % Change from Untreated SHR	
	Systolic	Diastolic
0 (Control - 1.25 mg/kg SRRR Isomer)	-4.98	2.06
0.16	-6.78*	1.36
0.31	-10.39*	-4.08*
0.63	-9.49*	-4.08*
1.25	-12.29*	-4.76*
2.5	-16.04*	-10.02*
5	-19.43*	-11.56*

Mr. Xhonneux' conclusion (see page 4 of the Declaration) is that "[t]he blood pressure reducing effect of the (SRRR)-compound administered at a dose of 1.25 mg/kg i.p. is potentiated significantly when the potentiating (RSSS)-compound is administered concomitantly at a dose ranging from 0.16 to 5 mg/kg i.p."

It is noteworthy that, by itself, the RSSS isomer did not show any significant blood pressure reducing effectiveness until it was used in dosages of 2.5 and 5 mg/kg. That is, when used alone in dosages of 0.63 and 1.25 mg/kg, the effect on blood pressure did not differ significantly from the vehicle control. Thus, from the data presented in Table 1 of the Declaration, one would have expected that if the RSSS isomer were used in dosages of up to 1.25 mg/kg in combination with 1.25 mg/kg of the SRRR isomer, no significant difference, either positive or negative, from the control would be observed. But the expected is not what happened! Beginning with dosages as small as 0.16 mg/kg of the RSSS isomer, a significant

potentiation of the (more) active SRRR isomer is observed. There is nothing in the prior art that would have led one skilled in the art to predict that this would happen.

It is clear that there is more than an additive effect resulting from the use of a combination of the two enantiomers. Accordingly, it is urged that this amounts to a difference in kind rather than one of degree, and as such overcomes any prima facie case of obviousness over the cited Van Lommen patent, and establishes the patentability under Section 103 of the subject claimed invention.

During the interview held on May 4, the Examiner questioned why the blood pressure changes reported in Mr. Xhonneux' Declaration were reported as differences, rather than actual values. The reasons are the following:

The first reason is that the BP's of SHR's vary considerably from animal to animal. Consequently, taking the mean value of the BP's of all the SHR's before therapy will include a large margin of error. Since the same applies to the BP's measured after therapy, no useful information would be gained. The problem in essence is that the INDIVIDUAL response of each animal to therapy would be lost in averaging the initial and final conditions. Obviously, in finding out whether hypertensive therapy works, one should consider whether the average of all individual RESPONSES is significant. Response implies that for each animal tested one measures the change in BP caused by the therapy <u>in that animal</u> and one tests the

significance of that change by accepted statistical analysis, in this case the Mann-Whitney U-test.

A secondary reason is based on the observation that what people experience as hypertension is very much an individual feeling. One person can feel uncomfortable at a BP with value "x", whereas another would feel perfectly fit at such value and only start to complain at value "x+y". In the second person it would suffice to reduce the BP by an amount "y" to get back to value "x". In the first a reduction from value "x" would be required.

In conclusion, it is not the actual BP values before and after therapy that are significant, but the fact that the actual values are reduced by a significant amount so that the BP moves from an uncomfortable to a comfortable zone (which may be different from person to person).

One further point needs to be mentioned. In the Final Rejection, the Examiner contended that "[a]ny information proffered to demonstrate unexpected benefits residing in any isomer must be compared to the natural racemic mixture." It is urged that this is in error, since the nature of the "natural racemic mixture" is not known. Appellants respectfully inquire what is the natural racemic mixture of a compound that has ten possible stereoisomers?

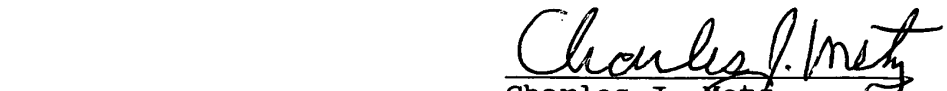
Appellants also wish to respectfully direct the Board's attention to the pharmacological examples that are presented in the subject application on page 14, line 35, through page 16, line 19.

It is there shown that the subject RSSS isomer significantly potentiates the blood pressure reducing effectiveness of seven different blood pressure reducing compounds. This demonstrates that the RSSS isomer is effective, generally, as a potentiator for blood pressure reducing agents. The effectiveness of the RSSS isomer in this regard is not limited to use with its enantiomer, the SRRR isomer. This property of the RSSS isomer is clearly not suggested by anything in the Van Lommen patent. Indeed, such a property is not suggested by Van Lommen with respect to any compound (including stereoisomers) disclosed in the Van Lommen patent.

For the reasons that are set forth above, it is respectfully urged that the rejection of all the claims as being unpatentable under 35 U.S.C. 103 over Van Lommen et al., U.S. Patent No. 4,654,362, is in error. Reversal is respectfully requested.

In view of the foregoing remarks, it is urged that each of the three rejections is in error. Reversal of said rejections and allowance of this application is respectfully requested.

Respectfully submitted,



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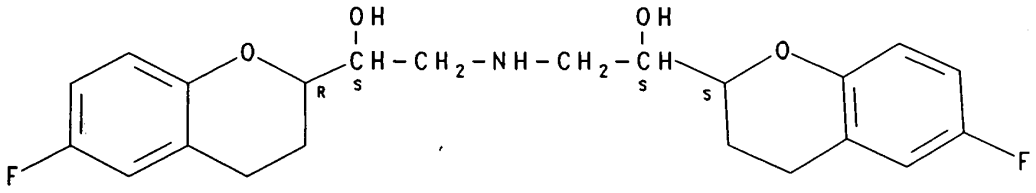
October 7, 1994

APPENDIX I

Claims on Appeal

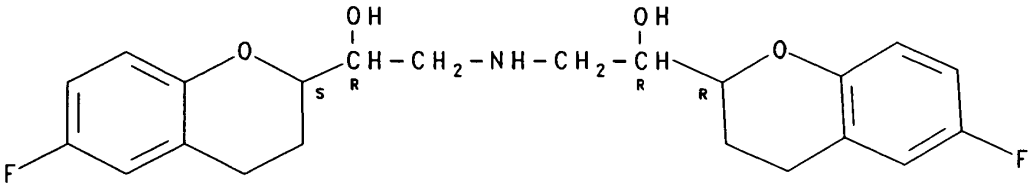
25. A composition consisting essentially of the compound [2R,αS,2'S,α'S]-α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol] having the formula:



or a pharmaceutically acceptable acid addition salt thereof.

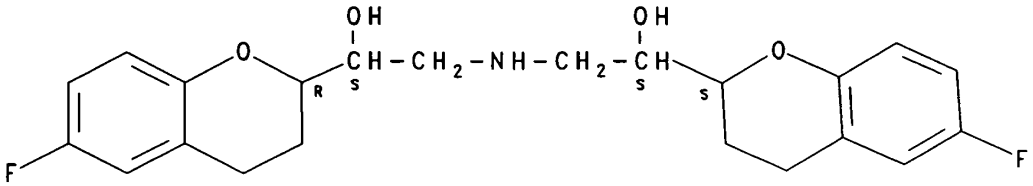
26. A pharmaceutical composition consisting essentially of a pharmaceutically acceptable carrier and, as active ingredients:

(a) the blood pressure reducing compound [2S,αR,2'R,α'R]-α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol] having the formula:



or a pharmaceutically acceptable acid addition salt thereof; and

(b) the compound [2R,αS,2'S,α'S]-α,α'-[iminobismethylene]-bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol] having the formula:



or a pharmaceutically acceptable acid addition salt thereof,

Compound (b) being present in an amount capable of potentiating the blood pressure lowering effect of compound (a), above.

20. A composition according to Claim 26 wherein the molar ratio of the compounds (a) and (b) is within the range of from about 5:1 to about 1:5.

21. A composition according to Claim 26 wherein the molar ratio of the compounds (a) and (b) is about 1:1.

22. A method of treating hypertension in warm blooded animals in need of such treatment which comprises administering to said warm blooded animals an effective amount of the pharmaceutical composition of Claim 26.

23. A method of treating hypertension in warm blooded animals in need of such treatment which comprises administering to said warm

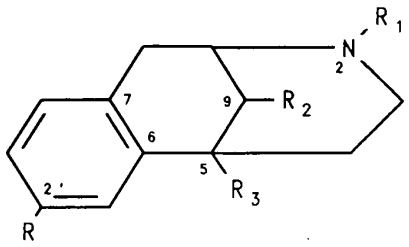
blooded animals an effective amount of the pharmaceutical composition of Claim 20.

24. A method of treating hypertension in warm blooded animals in need of such treatment which comprises administering to said warm blooded animals an effective amount of the pharmaceutical composition of Claim 21.

APPENDIX II

Discussion of In re May et al.

The prior art in May et al. showed compounds of the formula:



wherein:

R = hydrogen or **hydroxy**;

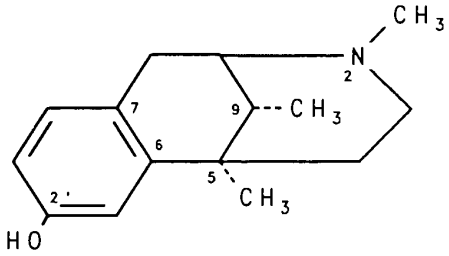
R_1 = hydrogen, **methyl**, straight chain alkyl or aralkyl;

R_2 = **hydrogen**, **alkyl**, methylene or substituted methylene; and

R_3 = hydrogen or **alkyl**.

[Variables that are particularly relevant to the subject matter sought to be patented by May et al. are shown in **bold faced type.**]

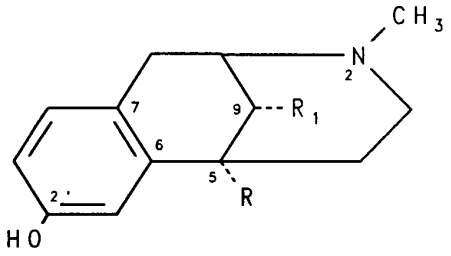
The prior art specifically disclosed the levo compound α-(-)-2'-hydroxy-2,5,9-trimethyl-6,7-benzomorphan, a compound of the formula:



The prior art also disclosed that "virtually all of the ... activity is due to the levo, as opposed to the dextro, isomer."

The following claim was found to be patentable to May et al. (a copy of the May et al. issued patent, No. 4,159,333, was enclosed with Appellants' RESPONSE UNDER 37 CFR 1.116, which was filed on July 6, 1994):

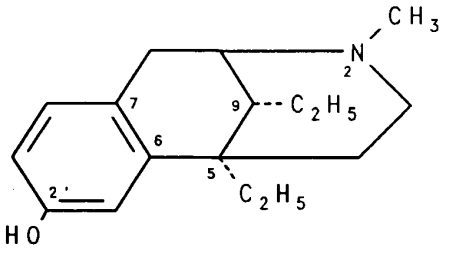
20. An acid addition salt of the levo isomer of a compound of the structure.



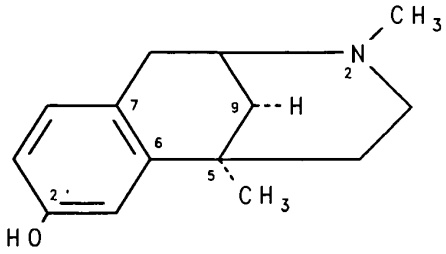
wherein R is a lower alkyl group and R_1 is hydrogen or a lower alkyl group, with the proviso that R and R_1 may not both be methyl.

The acid addition salts of the following specific compounds were also found to be patentable to May et al.:

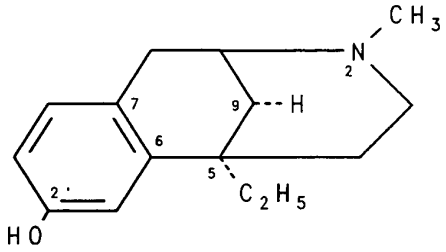
α-(-)-5,9-diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan:



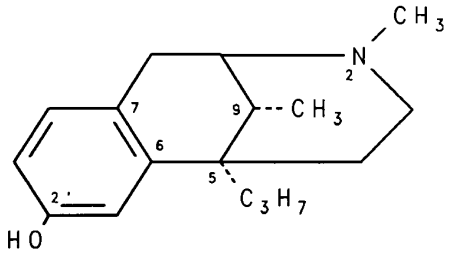
(-)-5-methyl-2'-hydroxy-2-methyl-6,7-benzomorphan:



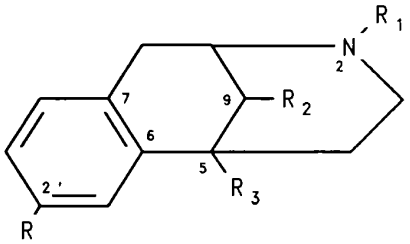
(-)-5-ethyl-2'-hydroxy-2-methyl-6,7-benzomorphan:



α-(-)-5-propyl-9-methyl-2'-hydroxy-2-methyl-6,7-benzomorphan:



Thus, the teaching in the prior art of compounds of the following formula:



wherein, inter alia:

R = **hydroxy;**

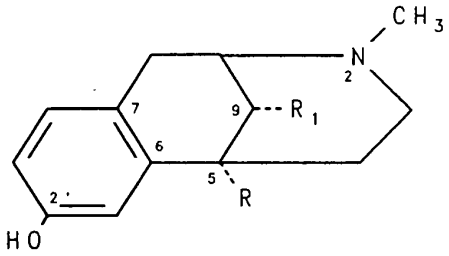
R_1 = **methyl;**

R_2 = **hydrogen, alkyl;** and

R_3 = **alkyl,**

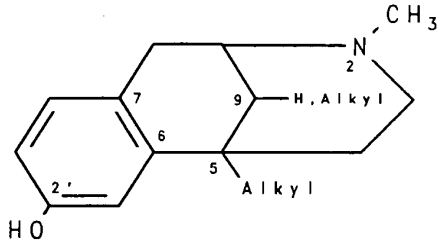
and the disclosure in the prior art that "virtually all of the ... activity is due to the levo, as opposed to the dextro, isomer ....",

was found not to anticipate levo compounds having the formula:

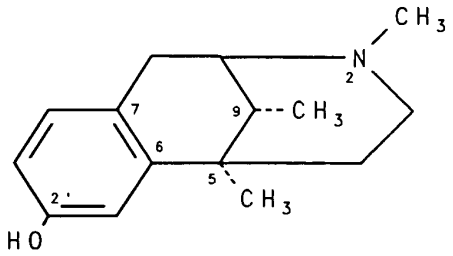


wherein R is a lower alkyl group and R_1 is hydrogen or a lower alkyl group, with the proviso that R and R_1 may not both be methyl.

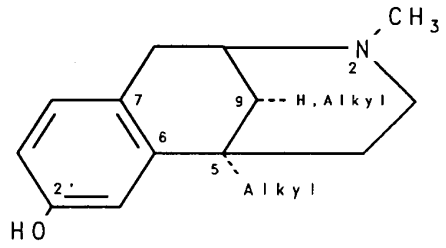
To summarize, the relevant prior art in May et al. (1) taught compounds of the formula:



(2) disclosed that "virtually all of the ... activity is due to the levo, as opposed to the dextro, isomer ....", and (3) further specifically disclosed a levo compound of the formula:



The Court found the following levo compounds not to be anticipated by the foregoing disclosures in the prior art (provided that the two "Alkyl" groups cannot both be methyl, so as not to "read on" the compound shown immediately above):



It is respectfully submitted that a reasonable interpretation of the holding in May et al. is that the disclosure in the prior art of a base compound that has stereoisomeric configurations is not an anticipation of particular stereoisomers of that base compound, even though the knowledge of the prior art is such that the artisan could deduce the specific stereoisomeric configurations from the disclosure of the base compound.

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Washington, D.C. 20231

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Paper No. 22

Serial Number: 07/825,488
Filing Date: 01/24/92
Appellant(s): RAYMOND MATHIEU XHONNEUX ET AL.

CHARLES J. METZ
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed October 11, 1994.

(1) *Status of claims.*

The statement of the status of claims contained in the brief is correct.

This appeal involves claims 20-26.

(2) *Status of Amendments After Final.*

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(3) *Summary of invention.*

The summary of invention contained in the brief is correct.

(4) *Issues.*

The appellant's statement of the issues in the brief is correct. Examiner finds compelling, Applicants' arguments with

regard to the rejection of claims 20-26 as anticipated by Van Lommen et al under 35 USC 102 (a) or 35 USC 102(b). Accordingly, rejection of claims 20-26 as anticipated by Van Lommen et al under 35 USC 102 (a) or 102(b) is no longer adhered to.

(5) *Grouping of claims.*

The brief includes a statement that claim 25 and claims 20-24 and 26 do not stand or fall together, but fails to present reasons in support thereof. Appellants mention claim 25 specifically, yet fail to patentably distinguish such claim from the other claims at appeal. Therefore, these claims are presumed to stand or fall together.

(6) *Claims appealed.*

The copy of the appealed claims contained in the Appendix to the brief is correct.

(7) *Prior Art of record.*

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

NUMBER	NAME	DATE
✓110CA:50943v	Van de Water	1988
✓4,654,362	Van Lommen et al	03/31/87

(8) *New prior art.*

No new prior art has been applied in this examiner's answer.

(9) *Grounds of rejection.*

The following ground(s) of rejection are applicable to the appealed claims.

Examiner finds compelling, Applicants' arguments with regard to the rejection of claims 20-26 as anticipated by Van Lommen et al under 35 USC 102 (a) or 35 USC 102(b). Accordingly, rejection of claims 20-26 as anticipated by Van Lommen et al under 35 USC 102 (a) or 102(b) is no longer adhered to.

Claims 20-26 are rejected under 35 U.S.C. § 103 as being unpatentable over Van Lommen et al in view of Van de Water, all of record, for reasons of record.

Van Lommen et al and Van de Water et al teach the claim designated compounds as old, well known and in combination with various carriers and excipients as useful for the claimed utility. This teaching includes all position isomers inherent in the claimed compound. The skilled artisan would have known that various isomers would exhibit biological activity at various levels. Absent information to the contrary, the skilled artisan would have seen optical isomer separation as a routine procedure leading to the compounds claimed herein. Biological testing for the claimed compounds would have been well within the skill of the artisan,a and such artisan would have expected the various biological activity levels set forth herein. It would follow therefore that the instant claims recite prima facie obvious subject matter and are properly rejected under 35 USC 103.

The declaration under 37 CFR 1.132 has been considered but is not deemed probative. It is well settled patent law that claimed compounds are deemed optical isomer mixtures, absent information to

the contrary. Additionally, the claimed compound is seen as an optical isomer mixture, wherein the individual isomers have various biological activity levels. Any information proffered to demonstrate unexpected benefits residing in any isomer must be compared to the natural racemic mixture. In the instant declaration applicants optical isomer comparison is devoid probative moment. Absent information to support unexpected benefits residing in the old and well known compositions and their methods of use, the instant claims are properly rejected under 35 USC 103.

Claims 20-26 are rejected under 35 U.S.C. § 103 as being unpatentable over Van Lommen et al.

Van Lommen et al teach the claim designated compounds as old, well known and in combination with various carriers and excipients as useful for the claimed utility. This teaching includes all position isomers inherent in the claimed compound. The skilled artisan would have known that various isomers would exhibit biological activity at various levels. Absent information to the contrary, the skilled artisan would have seen optical isomer separation as a routine procedure leading to the compounds claimed herein. Biological testing for the claimed compounds would have been well within the skill of the artisan, and such artisan would have expected the various biological activity levels set forth herein. It would follow therefore that the instant claims recite prima facie obvious subject matter and are properly rejected under 35 USC 103.

The instant claims are directed to effecting a biochemical pathway with an old and well known compound. Applicant's arguments that differential biological effects for rotational isomers are unexpected are not probative. Applicant's attention is directed to In re Swinehart, (169 USPQ 226 at 229) where the Court of Customs and Patent Appeals stated "is elementary that the mere recitation of a newly discovered function or property, inherently possessed by things in the prior art, does not cause a claim drawn to those things to distinguish over the prior art. Additionally, where the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to requires the applicant to prove that the subject matter shown to be in the prior art dose not posses the characteristic relied on. In the instant invention the claims are directed to the ultimate utility set forth in the prior art, abet distanced by various biochemical intermediates. The ultimate utility for the claimed compounds, to include all isomers for such compounds, is old and well known, rendering the claimed subject matter obvious to the skilled artisan. It would follow therefore that the instant claims are properly rejected under 35 USC 103.

Reliance on *In re May and Eddy*, 197 USPQ 601 (CCPA 1978) in the instant case is ill advised. Applicants' attention is

directed to *In re Adamson and Duffin*, 125 USPQ 233 (CCPA 1960) which would be seen as controlling in the instant case. *In re Williams*, 80 USPQ 150, quoted but not cited by Applicant, was differentiated by the Adamson court for reasons applicable in the instant case. Compounds at issue in the Williams case were not known to possess optical isomers, clearly a different situation than the instant case. The skilled artisan would have known the instant compounds contain asymmetric centers, rendering arguments based on *In re Williams*, supra, moot. It is well settled patent law that the skilled artisan possessing the racemate, possesses the optical isomers.

It is well settled patent law that the skilled artisan would have expected each isomer to exhibit biological activity at different levels. Applicants aver differences between optical isomers support patentability, this position is not well taken. In the instant case the stated differences are differences in degree, not patentably distinct differences in kind. Absent different biological activities for each isomer, patentability for optical isomers does not lie.

(10) *New ground of rejection.*

This Examiner's Answer does not contain any new ground of rejection.

(11) *Response to argument.*

Examiner finds compelling, Applicants' arguments with regard to the rejection of claims 20-26 as anticipated by Van Lommen et

al under 35 USC 102 (a) or 35 USC 102(b). Accordingly, rejection of claims 20-26 as anticipated by Van Lommen et al under 35 USC 102 (a) or 102(b) is no longer adhered to. Thus, arguments rebutting said rejection of claims 20-26 as anticipated by Van Lommen et al under 35 USC 102 (a) and 35 USC 102(b) are considered moot, and will not be considered.

The instant appeal involves two simple issues:

(1) is the instant invention placed in the skilled artisan's possession by Van Lommen (Examiner cited prior art), and

(2) do Appellants illustrate unexpected benefits residing in the instant compositions and methods of use; thereby overcoming the obvious nature of the instant invention.

Van Lommen places the skilled artisan in possession of the claimed invention, thereby anticipating the instant claims. Attention is directed to Van Lommen et al (column 4, at line 35) teaching "From formula (I) it is evident that the compounds of this invention may have several asymmetric carbon atoms in this structure. Each of these chiral centers may be present in a R- and a S- configuration, this R- and S- notation being in correspondence with the rules described in J. Org. Chem. 35 (9), 2849-2867 (1970). Pure stereochemically isomeric forms of the compounds of formula (I) may be obtained by the application of art-known procedures.". The claimed compounds are specifically encompassed by Van Lommen by the statement, "Stereochemically isomeric forms of the compounds of formula (I) are naturally

intended to be embraced within the scope of the (Van Lommen patent 4,654,362) invention.". Appellants' argument rests on the failure, by Van Lommen, to specifically illustrate the isomer herein claimed. This deficiency is cured by the information set forth in table I (column 25) illustrating biological activity for various stereochemically isomeric forms of the claimed medicament, thereby motivating the skilled artisan to possess the individual isomers. It is additionally noted that Van Lommen et al recite various stereochemically isomeric forms that encompass approximately half of the possible iterations. As set forth by Appellants, (page 5 of Appeal brief) the prior art compound possesses 4 chiral centers, thus, 16 theoretical stereochemically isomeric forms. Symmetry in the prior art compound yields only 10 stereochemically isomeric forms (Appellants' brief, page 5), and Van Lommen specifically illustrates 5 of the 10 possible stereochemically isomeric forms (see columns 4-5).

Appellants argue that *In re May and Eddy*, 197 USPQ 601 (CCPA 1978) is controlling; this argument is not convincing. Attention is directed to *In re May and Eddy*, supra at page 607, teaching "As recognized in *In re Williams*, 36 CCPA 756, 171 F.2d 319, 8-USPQ 150 (1948), the novelty of an optical isomer is not negated by the prior art disclosure of its racemate.". In the instant case, the Examiner cited prior art fully disclosed the 4 chiral centers, and the resultant stereochemically isomeric forms, thereby placing the various resultant stereochemically isomeric

forms in the skilled artisans possession, anticipating the instant claims. This rational is further reinforced by *In re Williams*, supra, at page 80, proposing the instant situation, "Accordingly, unless it can be shown that the Monatschefte product was actually known to be racemic, prior to appellant's original filing date, or unless it would have been obvious to one skilled in the art that the product was, in fact, racemic, the rejection on the ground of lack of invention cannot be sustained.". The *In re Williams* court failed to find evidence of racemic mixture residing in the claimed compound **at the time of invention**, in the instant case the stereochemically isomeric forms are fully disclosed in the Examiner cited prior art. It is noted that *In re Williams* court based the decision on a lack of knowledge regarding stereochemically isomeric forms at the time of filing. The *Williams* verbiage, at the very least, implicitly stands for anticipation of stereochemically isomeric forms if such isomers were known at time of publication. This anticipation of stereochemically isomeric forms, if such isomers were known at time of publication, analysis of *In re Williams*, supra is also set forth in *In re Adamson and Duffin*, 47 CCPA 841, 124 USPQ 233 (CCPA 1960), at 235.

In re Adamson and Duffin, supra was cited by Examiner to illustrate two points of law; one the explanation of *In re Williams*, supra and two, the evidence needed to illustrate unexpected benefits residing in various stereochemically isomeric

forms of old and well known medicaments.

The second issue at appeal is the obviousness of the composition and method of use claims. Van Lommen et al teach Applicants' compounds as a group of stereochemically isomeric forms possessing various levels of biological activity (Van Lommen patent 4,654,362, table I, column 25, compounds 84 and 87). Differences in biological activity between various stereochemically isomeric forms would have been expected by the skilled artisan. This phenomenon was discussed by the court in *In re Adamson and Duffin*, supra at page 234. The *Adamson and Duffin* court noted "that "the physiological properties of two antipodes [stereo-isomers] can differ considerably," giving as examples several pairs of optical isomers which differ substantially in their physiological effects. "The cause of the different physiological behavior," it is said, "lies in the fact that many constituents of cell within the organism with which the substances react are themselves asymmetric."" *In re Adamson and Duffin*, supra at 234.

SUMMARY

The references herein relied upon establish a strong prima facie case of obviousness as to applicants' invention. Hypotension treatments are old and well known in the art, and are administered with out regard to the underlying etiology. Possessing these teachings, the skilled artisan would have been motivated to employ Appellants old and well known medicaments for

treating hypotension. The claimed subject matter is of such a nature that the differences between said subject matter and the teachings of the prior art of record would have rendered applicants' subject matter as a whole obvious to those skilled in the art at the time of applicants' invention. The references clearly establish that the claim designated components were old, well known racemic mixtures and that one skilled in the art would have been motivated to employ the individual said components in the manner herein claimed to obtain the claimed, expected results. The claims are therefore properly rejected under 35 USC 103.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Travers:st
February 05, 1995

MARIANNE M. CINTINS
SUPERVISORY PATENT EXAMINER
GROUP 120

1205

JAB 775

#23
1 of 3
JRP
4/7/95

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Raymond Mathieu Xhonneux et al.

Serial No.: 07/825,488 Art Unit: 125

Filed : January 24, 1992 Examiner: R. Travers

For : METHOD OF LOWERING THE BLOOD PRESSURE

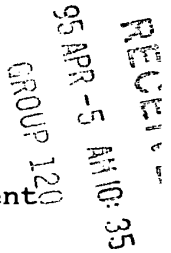
I, Charles J. Metz, Reg. No. 20,359, certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231.

On: March 16, 1995

Charles J. Metz

Charles J. Metz, Reg. No. 20,359

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231



Sir:

REPLY BRIEF AND REQUEST FOR CLARIFICATION

This REPLY BRIEF is addressed to certain new points of argument that are raised in the EXAMINER'S ANSWER.

1. There were three issues in this appeal. The first issue was a rejection of all the claims in the application under both 35 U.S.C. 102(a) and 35 U.S.C. 102(b) as being anticipated by Van Lommen et al., U.S. Patent No. 4,654,362 ("Van Lommen"). The Examiner has withdrawn this rejection.

2. The second issue in this appeal is a rejection of all the claims under 35 U.S.C. 103 over Van Lommen in view of Van de Water et al., **Pharmacological and Hemodynamic Profile of Nebivolol, a Chemically Novel, Potent, and Selective B_1-Adrenergic Antagonist,**

Journal of Cardiovascular Pharmacology, **11**, No. 5, 552-563 (1988). Beginning at the bottom of page 12 through page 14 of APPELLANTS' BRIEF, Appellants explained why the Van de Water et al. article is not a proper reference against this application because the claims herein are fully supported by Appellants' parent application, Serial No. 07/172,747, which was filed before the publication date of the Van de Water et al. article. Nowhere in the EXAMINER'S ANSWER is there a reply to any of the points made by Appellants. Nevertheless, the Examiner has maintained this rejection.

Clarification from the Examiner is respectfully requested on the reasons for maintaining this rejection. Absent such clarification, it is respectfully submitted that the record herein contains no rebuttal of Appellants' arguments with respect to this rejection.

3. The third issue is a rejection of all the claims under 35 U.S.C. 103 over Van Lommen. The Examiner's position is that Appellants' invention (relating to a particular stereoisomer of a compound disclosed by Van Lommen) is directed to the same ultimate utility (blood pressure reduction) as is disclosed in Van Lommen, thereby rendering the present claims obvious. Stated another way, it is the Examiner's position that the Van Lommen patent raises a prima facie case of obviousness, which Appellants have not overcome.

It is respectfully submitted that the Examiner has misunderstood Appellants' arguments with respect to this Section 103

rejection, which has led him into erroneously maintaining the rejection. Appellants' reasons are the following:

In Section IV of APPELLANTS' BRIEF, beginning at the top of page 15, Appellants presented arguments to support the proposition that the subject claimed invention is patentable over Van Lommen because of "unexpected results". Briefly, the unexpected results discovered by Appellants is that the subject RSSS compound, itself a rather weak anti-hypertensive agent, significantly and substantially potentiates the blood pressure reducing activity of its enantiomer, the SRRR isomer, as well as other blood pressure reducing agents. This is clearly not a property that is disclosed in the cited prior art.

Appellants' arguments with respect to this Section 103 rejection consisted almost entirely of a discussion and interpretation of the data of record herein. These arguments are presented on pages 15-21 of APPELLANTS' BRIEF.

The EXAMINER'S ANSWER contains no rebuttal to Appellants' factual arguments with respect to the sufficiency of the showing to overcome the prima facie case of obviousness over Van Lommen. Rather, the Examiner appears to have mixed up Appellants' arguments relating to the Section 102 rejection with Appellants' arguments with respect to the Section 103 rejection. Beginning on page 8 and continuing through page 10 of the EXAMINER'S ANSWER, in the section headed "*Response to [Appellants'] argument*", the Examiner discusses

the decisions in *In re May and Eddy*, 197 USPQ 601 (CCPA 1978), *In re Williams*, 80 USPQ 150 (CCPA 1948) and *In re Adamson and Duffin*, 125 USPQ 233 (CCPA 1960). This discussion is presented as a rebuttal to Appellants' position on the Section 103 rejection. For instance, the Examiner states the following:

> "Appellants argue that *In re May and Eddy*, 197 USPQ 601 (CCPA 1978) is controlling; this argument is not convincing." (EXAMINER'S ANSWER, page 8.)

It is respectfully, but urgently, pointed out that Appellants NEVER argued that *In re May* was controlling with respect to the Section 103 rejection. Rather, Appellants argued this decision only with respect to the Section 102 rejection (e.g., see pages 9 et seq. of APPELLANTS' BRIEF). In fact, Appellants never mentioned any case law at all in their arguments with respect to the Section 103 rejection. Appellants arguments were strictly limited to an argument based on the facts of the case (i.e., the adequacy of the showing to overcome a prima facie case of obviousness). Thus, the arguments presented in the EXAMINER'S ANSWER in connection with this Section 103 rejection seem to consist entirely of a rebuttal to arguments that Appellants never made. It seems apparent that the Examiner has misunderstood Appellants' position with respect to this rejection.

Clarification by the Examiner is respectfully requested. Absent such clarification, it is respectfully submitted that the record herein contains no rebuttal to Appellants' arguments with respect to this rejection.

4. It is respectfully submitted that the Examiner has not presented any rebuttal to Appellants' arguments relating to the two Section 103 rejections. This being the case, it is urged that the rejections are clearly in error, and reversal is respectfully requested.

Respectfully submitted,

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March 16, 1995

UNITED STATES DEPARTMENT OF COMMERCE
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Washington, D.C. 20231

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Paper No. 25

Serial Number: 07/825,488
Filing Date: 01/24/92
Appellant(s): RAYMOND MATHIEU XHONNEUX ET AL.

CHARLES J. METZ
For Appellant

SUPPLEMENTAL EXAMINER'S ANSWER

The reply brief filed March 20, 1995 has been entered and considered.

The Examiner's Answer, paper 22, is hereby incorporated by reference, and remains unchanged unless specifically superseded.

The following response is in reply to Appellant's arguments and request for clarification filed March 20, 1995.

1) Response to statement one (1) is not required.

2) Appellant's argument regarding the Van de Water prior art reference has been considered, but is not found convincing. Attention is directed to Paper 11, filed 5/14/93, (at page 3), where the rejection states "in view of Van de Water (newly cited).". In view of the FAX transmission filed February 20, 1993, Examiner renewed his search and issued a new rejection

utilizing a new reference. It is noted that Examiner did not make the rejection filed 5/14/93 final for this reason. A form PTO 892 was filed with paper 11 setting forth the new Van de Water cited prior art. Apparently, the subtle shift in Van de Water references eluded Appellant's attention. Examiner apologizes for any inconvenience caused by the newly cited Van de Water reference.

3) Appellant's argument at item 3 has been considered but this argument is not convincing. Arguments presented in Appellant's brief were fully rebutted in the Examiner's answer filed 2/7/95 (see pages 6-10). Examiner fully understands the instant invention and the rejections presented in the case; this fact being self evidenced by the various office actions filed in the instant application.

Appellant argues that the declaration under 37 CFR 1.132 illustrates unexpected benefits residing the subject matter, this argument is not well taken. Examiner has argued repeatedly that probative comparisons of optical isomeric forms must be made with the racemic mixture. Attention is directed to paper 6, filed 5/29/92, rebutting Appellant's declarations by stating, "Any information proffered to demonstrate unexpected benefits residing in any isomer must be compared to the natural racemic mixture. In the instant declaration applicants optical isomer comparison is devoid probative moment.". This objection was repeated in papers 8 (filed 11.10/92), 11 (filed 5/14/93), 14 (filed 2/15/94) and 22 (filed 2/7/95), yet Appellant has consistently ignored this objection and failed to respond to Examiners argument.

Applicant's argument with regard to the patentability of the claims **constructively** relies on *In re May and Eddy*, 197 USPQ 601 (CCPA 1987). Examiner explained the case law rational regarding optical isomers in his rejections. If Appellant places on reliance on *In re May and Eddy*, supra, then this dissertation is simply makeweight.

Appellant argues that Examiner failed to rebut Appellant's arguments; this argument is not correct. In the instant case, the Examiner cited prior art fully disclosed the 4 chiral centers, and the resultant stereochemically isomeric forms, thereby placing the various resultant stereochemically isomeric forms in the skilled artisans possession, anticipating the instant claims. This rational is further reinforced by *In re Williams*, supra, at page 80, proposing the instant situation, "Accordingly, unless it can be shown that the Monatschefte product was actually known to be racemic, prior to appellant's original filing date, or unless it would have been obvious to one skilled in the art that the product was, in fact, racemic, the rejection on the ground of lack of invention cannot be sustained.". The *In re Williams* court failed to find evidence of racemic mixture residing in the claimed compound **at the time of invention**, in the instant case the stereochemically isomeric forms are fully disclosed in the Examiner cited prior art. It is noted that *In re Williams* court based the decision on a lack of knowledge regarding stereochemically isomeric forms at the time of filing. The *Williams* verbiage, at the very least, implicitly stands for anticipation of stereochemically isomeric forms if

such isomers were known at time of publication. This anticipation of stereochemically isomeric forms, if such isomers were known at time of publication, analysis of *In re Williams*, supra is also set forth in *In re Adamson and Duffin*, 47 CCPA 841, 124 USPQ 233 (CCPA 1960), at 235.

In re Adamson and Duffin, supra was cited by Examiner to illustrate two points of law; one the explanation of *In re Williams*, supra and two, the evidence needed to illustrate unexpected benefits residing in various stereochemically isomeric forms of old and well known medicaments.

The second issue at appeal is the obviousness of the composition and method of use claims. Van Lommen et al teach Applicants' compounds as a group of stereochemically isomeric forms possessing various levels of biological activity (Van Lommen patent 4,654,362, table I, column 25, compounds 84 and 87). Differences in biological activity between various stereochemically isomeric forms would have been expected by the skilled artisan. This phenomenon was discussed by the court in *In re Adamson and Duffin*, supra at page 234. The *Adamson and Duffin* court noted "that "the physiological properties of two antipodes [stereo-isomers] can differ considerably," giving as examples several pairs of optical isomers which differ substantially in their physiological effects. "The cause of the different physiological behavior," it is said, "lies in the fact that many constituents of cell within the organism with which the substances react are themselves asymmetric."" *In re Adamson and Duffin*, supra at 234. At the time of invention, the instant

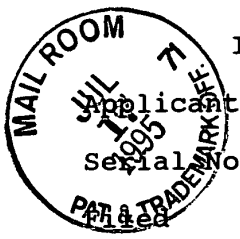
claims would have been *prima facie* obvious to the skilled artisan in view of the Examiner cited prior art. The presence of optical isomers, with the physiological activity claimed by Appellant exhibited at various levels, were known to the skilled artisan at the time of the instant invention. Thus, that various optical isomers would possess differing physiological activities would have been *prima facie* obvious to the skilled artisan, and properly rejected under 35 USC 103.

Any inquiry concerning this communication should be directed to Russell Travers at telephone number (703) 308-4603.

Russell Travers
Primary Examiner
Art Unit 1205

JAB 775

#26
JRT
8/2/95



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Raymond Mathieu Xhonneux et al.

Serial No.: 07/825,488 Art Unit: 125

Filed : January 24, 1992 Examiner: R. Travers

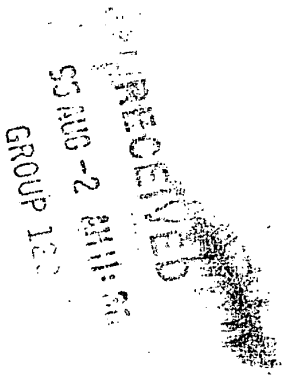
For : METHOD OF LOWERING THE BLOOD PRESSURE

I, Charles J. Metz, Reg. No. 20,359, certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231.

On: July 14, 1995

Charles J. Metz

Charles J. Metz, Reg. No. 20,359



Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

REPLY BRIEF TO SUPPLEMENTAL EXAMINER'S ANSWER

This REPLY BRIEF is addressed to certain new points of argument that are raised in the SUPPLEMENTAL EXAMINER'S ANSWER dated June 14, 1995. The numbering below corresponds to the numbered sections in the SUPPLEMENTAL EXAMINER'S ANSWER.

2. The Van de Water et al. references

The Van de Water et al. reference abstracted at CA, 109:16771g, namely, Van de Water et al., **Pharmacological and Hemodynamic Profile of Nebivolol, a Chemically Novel, Potent, and**

Selective B_1-Adrenergic Antagonist, *Journal of Cardiovascular Pharmacology*, **11**, No. 5, 552-563 (1988) ["Van de Water (I)"], was first cited by the Examiner in an Office Action dated November 10, 1992. In Appellants' response to this Office Action, dated February 17, 1993, and filed in the PTO on February 22, 1993, Appellants submitted a FAXed memo from Information Research Services Inc., which stated that the publication date of this reference was May, 1988, which is the date that appears on the Journal. A copy of a page from the Journal of Cardiovascular Pharmacology, Vol. 11, No. 5, which shows the publication date, is attached hereto for the convenience of the Board. The undersigned Attorney for Appellants has just learned of a letter from the publisher, Raven Press, that states that the official publication date of this issue was April 14, 1988. A copy of this letter is also attached for the convenience of the Board. In any case, these dates are later than the filing date to which the present application is entitled, namely, the filing date of Appellants' parent application, Serial No. 07/172,747, which was March 23, 1988.

In response to Appellants' February 22, 1993, response, in the Office Action dated May 14, 1993, the Examiner then cited the Van de Water et al. reference abstracted at CA, 110:50943v, namely, *Eur. J. Pharmacol.*, **1988**, Vol. 156(1), 95-103 ["Van de Water (II)"]. In their response dated August 26, 1993, and filed in the PTO on August 30, 1993, Appellants' submitted a FAXed memo from

Information Research Services Inc. that stated that the publication date of Vol. 156, No. 1, of this journal was November 2, 1993. In the Final Rejection of February 15, 1994, the Examiner repeated the rejection based on Van de Water (II). In an interview held with the Examiner on May 4, 1994, the Examiner informed the undersigned Attorney for Appellants that the reason the rejection based on Van de Water (II) was maintained was that Appellants had not specifically pointed out where in the parent application, Serial No. 07/172,747, the pending claims were supported. In Appellants' Rule 116 response, dated June 27, 1994, and filed in the PTO on July 6, 1994, Appellants pointed out where in the parent application, Serial No. 07/172,747, support for the pending claims was found. This discussion is found in Section III, pages 8-11, of the Rule 116 response. It is noted that in this discussion, Van de Water (I) was inadvertently referred to, rather than Van de Water (II), and this mis-citation has been carried through on the record until the Examiner pointed out the error in the SUPPLEMENTAL EXAMINER'S ANSWER.

The confusion caused by this mis-citation of Van de Water (II) is regretted. It is respectfully pointed out, however, that Appellants have submitted evidence on the record establishing that the publication dates of both Van de Water (I) and (II) are later than the filing date of the parent case, Serial No. 07/172,747, and also have pointed out where the claims on appeal are supported in the

parent case, Serial No. 07/172,747. It would be useful for the Board to have the Examiner's views on whether or not Appellants' have satisfied the burden of demonstrating that neither Van de Water et al. publication is available as a reference against the claims on appeal, in order to reduce the issues involved.

3. The Section 103 Rejection

a. The Comparative Data

The Examiner has consistently urged that the evidence of record is not sufficient to establish unexpected benefits because "probative comparisons of optical isomeric forms must be made with the racemic mixture." It is respectfully urged that this position is in error.

Patentability of the subject claimed RSSS stereoisomer is predicated upon its unexpected ability to potentiate the blood pressure reducing activity of other hypertensive drugs, including its enantiomer, the SRRR isomer. Comparison with "the racemic mixture" is inappropriate here. First, it is respectfully pointed out that the racemic mixture of the RSSS and SRRR isomers is claimed herein in Claims 20, 21 and 26, so this racemic mixture cannot be used as a control with which to compare the invention, since it is itself part of the claimed subject matter. If the

RSSS/SRRR racemate cannot be used as a control, in this situation where there are 10 stereoisomers of the Base Compound, what mixture of these stereoisomers should be used as the control? The Examiner has at times urged that the "natural racemate" should be used as a control. But the prior art does not teach what a natural racemate would be.

Even if one could identify a natural racemate, how would one use it in a comparison with the claimed invention? As stated above, it is the ability of the RSSS isomer to potentiate other anti-hypertensive agents that comprises the unexpected benefits, not its own anti-hypertensive ability, which is actually not very strong. Thus, to compare the anti-hypertensive strength of the RSSS isomer with the hypothetical natural racemate would not be informative because that is not where the unexpected benefits reside. Rather, the unexpected benefits reside in the fact that when the RSSS isomer is used with another anti-hypertensive agent, the resulting mixture shows much more effective anti-hypertensive action than would be expected from the strengths of the two materials alone.

b. <u>In re May et al.</u>

Appellants relied upon In re May et al. solely for its affirmation of the rule of law that the novelty of an optical

isomer is not negated by the prior art disclosure of its racemate (197 USPQ 601, at 607). This decision is not relevant to the issues involved in the Section 103 rejection.

For the reasons set forth hereinabove, and in Appellants' earlier Briefs, it is urged that the rejections of the claims on appeal are in error. Reversal is respectfully requested.

Respectfully submitted,

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July 14, 1995

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER OF
PATENTS AND TRADEMARKS
Washington, D.C. 20231

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Paper No. 27

Serial Number: 07/825,488
Filing Date: 01/24/92
Appellant(s): RAYMOND MATHIEU XHONNEUX ET AL.

Mail
OCT 23 1995
Group 1200

CHARLES J. METZ
For Appellant

SUPPLEMENTAL EXAMINER'S ANSWER

This is in response to appellant's reply brief on appeal filed July 17, 1995.

The reply briefs filed March 20, 1995 and July 17, 1995 have been entered and considered.

The Examiner's answer and the supplemental Examiner's answer papers 22 and 25 respectively are hereby incorporated by reference, and remain unchanged unless specifically superseded.

The following response is in reply to Appellants' information regarding the Van de Water et al reference (109 CA:16771g); item 2.

Appellant has provided information indicating the Van de Water et al publication was issued after the effective date of the parent application, of which the instant application is a continuation-in-part.

The Van de Water et al teaching, although a powerful

motivation to practice the claimed invention, is not required to obviate the presented claims. Van Lommen et al, cited as prior art by Examiner, provides powerful motivation for the skilled artisan to employ one or another isomeric form of the claimed compound to treat the claimed hypertensive condition. That the compound possesses optical isomers, which are resolvable into the various forms is taught by Van Lommen et al reference (column 4-5, lines 34-65 and 1-16). It is noted that the preferred embodiment sets forth specific chiral center configurations. Van Lommen additionally teaches that the prior art compounds are effective in treating the hypertensive conditions herein claimed (column 5, lines 58-63). The inclusion of optical isomers in the Van Lommen et al teaching is reflected in the verbiage at column 4, lines 56-58 stating; "Steriochemically isomeric forms of the compounds of the formula (I) are naturally intended to be embraced within the scop;e of the invention.". Thus, the skilled artisan would see the use of one or another isomer to treat the conditions taught by Van Lommen et al as having been obvious to one of normal skill in the art at the time of Appellants' invention. It would follow therefor that the instant claimed recite obvious subject matter and are properly rejected under 35 USC 103.

The references herein relied upon establish a strong prima facie case of obviousness as to applicants' invention. Hypotension treatments are old and well known in the art, and are administered with out regard to the underlying etiology. Possessing these

teachings, the skilled artisan would have been motivated to employ Appellants old and well known medicaments for treating hypotension. The claimed subject matter is of such a nature that the differences between said subject matter and the teachings of the prior art of record would have rendered applicants' subject matter as a whole obvious to those skilled in the art at the time of applicants' invention. The references clearly establish that the claim designated components were old, well known racemic mixtures and that one skilled in the art would have been motivated to employ the individual said components in the manner herein claimed to obtain the claimed, expected results. The claims are therefore properly rejected under 35 USC 103.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Travers:st
October 14, 1995

Russell Travers
Patent Examiner
Art Unit 1205

THIS OPINION WAS NOT WRITTEN FOR PUBLICATION

The opinion in support of the decision being entered today (1) was not written for publication in a law journal and (2) is not binding precedent of the Board.

Paper No. 39

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte RAYMOND M. XHONNEUX and GUY R.E. VAN LOMMEN

Appeal No. 1996-2910
Application 07/825,488

HEARD: January 13, 2000

Before WINTERS, GRON and ROBINSON, Administrative Patent Judges.

WINTERS, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 21, 22, 24, 25 and 26, appeal having been withdrawn with respect to claims 20 and 23.

Claims 25, 26 and 22 are representative and a copy of same is appended to this decision.

The reference relied on by the examiner is:

Van Lommen et al. (Van Lommen) 4,654,362 March 31, 1987

PRELIMINARY MATTERS

Claims 20 through 26 were finally rejected under 35 U.S.C. §§ 102 (a) and (b) as described by Van Lommen (Paper no. 14, February 15, 1994), but both rejections were expressly withdrawn in the Examiner's Answer (page 3).

In the final rejection, claims 20 through 26 were also rejected under 35 U.S.C. § 103 as unpatentable over Van Lommen together with Van de Water.[1] In their Brief, appellants argued that Van de Water "was not a proper reference because the Van de Water et al. article was published [after] . . . the filing date of their parent application Serial No. 07/172,747" and pointed to portions of the parent disclosure that supported the claims on appeal (Brief, pages 12 through 14). The examiner continued the rejection in the Examiner's Answer without addressing appellant's argument. Following an exchange of Reply Briefs (paper nos. 23 and 26) and Supplemental Examiner's Answers (paper nos. 25 and 27), the examiner apparently conceded the issue ("Appellant has provided information indicating the Van de Water et al publication was

[1] Van de Water et al., Chem Abstracts No. 110:50943v (1989).

issued after the effective date of the parent application . . . The Van de Water et al teaching . . . is not required to obviate the presented claims"). See the Supplemental Examiner's Answer, paper no. 27. Therefore, we shall treat this rejection as having been withdrawn.

During oral argument counsel for appellants, Ellen Ciambrone Coletti, withdrew the appeal with respect to claim 20. Appeal was also withdrawn with respect to claim 23 (which depends from claim 20) pursuant to a telephone conversation with counsel on February 16, 2000.

Accordingly, the appeal with respect to claims 20 and 23 is dismissed, and the only rejection remaining for our consideration is that of claims 21, 22, 24, 25 and 26 under 35 U.S.C. § 103 as unpatentable over Van Lommen (Examiner's Answer, page 4). For the reasons set forth below, we reverse the rejection. In addition, we raise several issues for consideration on return of the application to the examining group.

DISCUSSION

Van Lommen discloses unresolved stereoisomeric mixtures of the antihypertensive compound α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol] (compounds 84 and 87, column 21). The compound has four chiral carbons, and ten possible stereoisomers. As acknowledged in the Brief (page 7) and oral argument, compound 84 is an unresolved mixture of four of the ten isomers,

designated RSSS, SRRR, RSRR and SRSS. At column 4, lines 40-58, Van Lommen states that "[p]ure stereochemically isomeric forms of the compounds . . . may be obtained by the application of art-known procedures" and "[s]tereochemically isomeric forms of the compounds . . . are naturally intended to be embraced within the scope of the invention."

Claim 25 is directed to "[a] composition consisting essentially of" the RSSS stereoisomer of α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol], while claim 26 is directed to "[a] pharmaceutical composition consisting essentially of" a combination of the RSSS stereoisomer and its enantiomer, SRRR.

The examiner's statement of the rejection is as follows:

> Van Lommen et al teach the claim designated compounds as old, well known and in combination with various carriers and excipients as useful for the claimed utility. This teaching includes all position isomers inherent in the claimed compound. The skilled artisan would have known that various isomers would exhibit biological activity at various levels. . . [T]he skilled artisan would have seen optical isomer separation as a routine procedure leading to the compounds claimed herein . . . such artisan would have expected the various biological activity levels set forth herein. It would follow therefore that the instant claims recite prima facie obvious subject matter and are properly rejected under 35 USC 103. (Examiner's Answer, page 4.)

For purposes of this appeal we accept, without deciding, that the examiner has established a prima facie case of obviousness against claims 21, 22 and 24 through 26. Nevertheless, a conclusion of prima facie obviousness does not end a patentability

determination under 35 U.S.C. § 103. As stated in In re Hedges, 783 F.2d 1038, 1039, 228 USPQ 685, 686 (Fed. Cir. 1986):

> If a prima facie case is made in the first instance, and if the applicant comes forward with reasonable rebuttal, whether buttressed by experiment, prior art references, or argument, the entire merits of the matter are to be reweighed. (Citations omitted).

The Declaration of Raymond Xhonneux, filed January 24, 1992 under the provisions of 37 CFR § 1.132, presents evidence supporting a conclusion that the RSSS stereoisomer, unlike its enantiomer, SRRR, "only minimally affects blood pressure when administered alone" but significantly "potentiates the antihypertensive effects of the (SRRR)-compound, but not the bradycardiac affects [sic] of the (SRRR)-compound." See page 4 of the Declaration. The examiner does not propose any reason why a person having ordinary skill in the art would have expected the RSSS stereoisomer to have such properties. Nor does the examiner contend that the potentiating property, described in the declaration, is insignificant. Therefore, we reverse the rejection of the claims under 35 U.S.C. § 103 on the strength of appellants' rebuttal evidence establishing that the claimed subject matter possesses unexpectedly superior results.

OTHER ISSUES

As stated previously, the appealed claims were finally rejected under 35 U.S.C. §§ 102 (a) and (b) (Paper no. 14, February 15, 1994). The claims were said to be

described by Van Lommen, without clarification or explanation. On pages 6 through 9 of their Brief, appellants argue that Van Lommen discloses only unresolved mixtures of stereoisomers, and so does not anticipate the RSSS stereoisomer alone (claim 25), or in combination with its enantiomer, SRRR (claim 26). The examiner was persuaded by that argument, and both rejections were expressly withdrawn in the Examiner's Answer (page 3).

Inasmuch as the rejections under 35 U.S.C. §§ 102 (a) and (b) were entered and withdrawn without meaningful explanation from the examiner, it is unclear on the record (1) whether independent claim 25 was evaluated under the appropriate legal standards; or (2) whether the scope of independent claim 26 was properly interpreted.

(1) Claim 25 is directed to a composition consisting essentially of the RSSS stereoisomer of α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol] or a pharmaceutically acceptable acid addition salt thereof. Van Lommen discloses compound 84, which has a bilaterally symmetrical structure identical to the compound of claim 25, but has the isomeric designation "AB" (column 21). As explained in the paragraph bridging columns 4 and 5 of Van Lommen, "A" and "B" specify the stereochemical configuration at the compound's four chiral centers. Because "A" corresponds to the RS or SR configuration, and "B" corresponds to the SS or RR configuration, the "AB" designation indicates that compound 84 is an unresolved mixture of four stereoisomers: RSSS, SRRR, RSRR and SRSS. Appellants' argument

at pages 7 through 9 of the Brief is consistent with this. Moreover, at column 4, lines 40-58, Van Lommen states that "[p]ure stereochemically isomeric forms of the compounds . . . may be obtained by the application of art-known procedures" and "are naturally intended to be embraced within the scope of the invention."

As stated in In re Schaumann, 572 F.2d 312, 315, 197 USPQ 5, 8 (CCPA 1978), a "fundamental question presented by this appeal is whether the disclosure of a chemical genus may ever constitute a description of a specific compound falling within the ambit of the genus." That case involved a generic prior art disclosure embracing seven compounds. The court held that the genus "embrace[d] a very limited number of compounds closely related to one another in structure" and "led inevitably to the conclusion that the reference provide[d] a description of those compounds just as surely as if they were identified in the reference by name." In re Schaumann, 572 F.2d at 1316-17, 197 USPQ at 9. Under this reasoning, Van Lommen's disclosure of compound 84, together with its designation "AB," appears to describe the individual RSSS, SRRR, RSRR and SRSS stereoisomers "just as surely as if they were identified in the reference by name." On return of this application, the examiner should consider whether a person having ordinary skill in the art would have envisioned each individual stereoisomer (RSSS, SRRR, RSRR, SRSS) in light of Van Lommen's disclosure of compound 84; and whether Van Lommen constitutes an enabling disclosure, i.e., puts a person having ordinary skill in possession of each stereoisomer.

Appellants, on the other hand, cite In re May, 574 F.2d 1082, 1090, 197 USPQ 601, 607 (CCPA 1978) for the proposition that "the novelty of an optical isomer is not negated by the prior art disclosure of its racemate." According to appellants, "a reasonable interpretation of the holding in May et al. is that the disclosure in the prior art of a base compound that has stereoisomeric configurations is not an anticipation of particular stereoisomers of that base compound." See Appendix II, accompanying appellants' main Brief, page 29, last paragraph.

On return of this application, we recommend that the examiner reevaluate the patentability of claim 25 under 35 U.S.C. § 102 in light of the Van Lommen reference, the decisions in Schaumann and May, and the foregoing remarks.

(2) In making a patentability determination, "[a]nalysis begins with a key legal question -- what is the invention claimed?" since "[c]laim interpretation . . . will normally control the remainder of the decisional process," Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1567-68, 1 USPQ2d 1593, 1597 (Fed. Cir. 1987), cert. denied, 481 U.S. 1052 (1987).

Claim 26 is directed to a pharmaceutical composition "consisting essentially of" a pharmaceutically acceptable carrier and, as active ingredients, (a) the blood pressure reducing SRRR stereoisomer of α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol] or a pharmaceutically acceptable acid addition salt thereof and (b) its enantiomer, RSSS, or a pharmaceutically acceptable acid addition salt

thereof; the RSSS stereoisomer being present in an amount capable of potentiating the blood pressure lowering effect of the SRRR stereoisomer. It is well settled that "the phrase 'consisting essentially of' limits the scope of a claim to the specified ingredients and those that do not materially affect the basic and novel characteristic(s) of a composition." In re Herz, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976). Here, a basic and novel characteristic of the pharmaceutical composition of claim 26 is its blood pressure reducing or antihypertensive effect. Thus, claim 26 is open to ingredients that do not materially affect its antihypertensive activity.

Van Lommen's antihypertensive compound 84 is a mixture of four stereoisomers: RSSS, SRRR, RSRR and SRSS. Because the RSRR and SRSS stereoisomers do not materially affect blood pressure reducing or antihypertensive activity, it appears that they are not excluded from the composition of claim 26. On return of the application, we recommend that the examiner reevaluate the patentability of claim 26, and any claims depending therefrom, under 35 U.S.C. § 102 in light of Van Lommen. Specifically, the examiner should consider whether claim 26 "reads on" Van Lommen's compound 84 taking into account the appropriate principles of claim interpretation and the foregoing remarks.

It is axiomatic that one cannot patent what is old. If, on return of this application to the examining group, the examiner determines that any claim or claims are described by Van Lommen within the meaning of 35 U.S.C. § 102, we emphasize that "[t]he discovery of a new property or use of a previously known composition, even when that property and use are unobvious from the prior art, can not impart patentability to claims to the known composition." In re Spada, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990) (citations omitted). In other words, if the examiner determines that the claimed subject matter is described by Van Lommen under 35 U.S.C. § 102, declaration evidence establishing unexpectedly superior results would be unavailing to the appellants. See In re Petering, 301 F.2d 676, 682, 133 USPQ 275, 280 (CCPA 1962) (Even though appellants' claimed compound may exhibit antivitamin activity, a property not disclosed by Karrer, this fact is not significant here because appellants' invention *as defined in these claims* is *described* in the Karrer patent.). Emphasis original. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) (Without novelty, evidence of unobviousness is superfluous.)

CONCLUSION

In conclusion, for the reasons set forth in the body of this opinion, the appeal with respect to claims 20 and 23 is dismissed. The rejection of claims 21, 22 and 24

through 26 under 35 U.S.C. § 103 as unpatentable over Van Lommen is reversed. In addition, we raise several issues for consideration on return of this application to the examining group.

REVERSED

SHERMAN D. WINTERS)
Administrative Patent Judge)
)
)
) BOARD OF PATENT
TEDDY S. GRON)
Administrative Patent Judge) APPEALS AND
)
) INTERFERENCES
DOUGLAS W. ROBINSON)
Administrative Patent Judge)

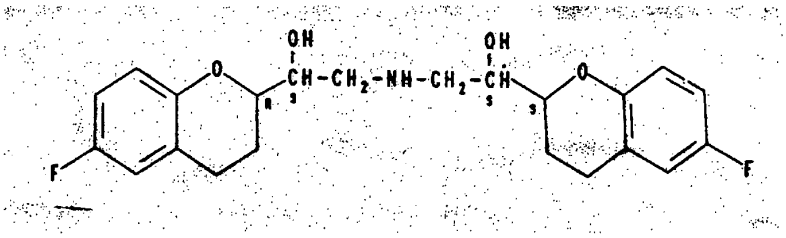
vsh

Appeal No. 1996-2910
Application 07/825,488

Robert L. Minier
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003

APPENDIX A

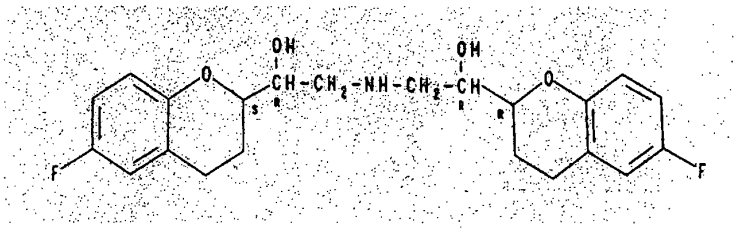
25. A composition consisting essentially of the compound [2R,αS,2'S,α'S]-α,αl- [iminobismethylene]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol] having the formula:



or a pharmaceutically acceptable acid addition salt thereof.

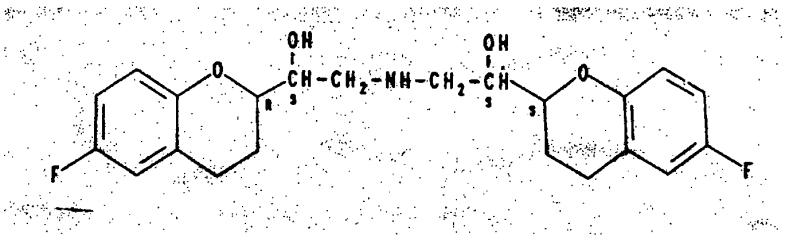
26. A pharmaceutical composition consisting essentially of a pharmaceutically acceptable carrier and, as active ingredients:

(a) the blood pressure reducing compound [2S,αR,2'R,α'R]-α,αl-[iminobismethylene]bis[6-fluoro-3,4- dihydro-2*H*-1-benzopyran-2-methanol] having the formula:



or a pharmaceutically acceptable acid addition salt thereof; and

(b) the compound [2R,αS,2'S,α'S]-α,α'-[iminobismethylene]bis [6-fluoro -3,4-dihydro-*2H*- 1-benzopyran-2-methanol] having the formula:



or a pharmaceutically acceptable acid addition salt thereof,,

Compound (b) being present in an amount capable of potentiating the blood pressure lowering effect of compound (a), above.

22. A method of treating hypertension in warm blooded animals in need of such treatment which comprises administering to said warm blooded animals an effective amount of the pharmaceutical composition of Claim 26.

#40 8/01/01

Docket No. JAB-775

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Raymond M. Xhonneux et al.
Serial No.	:	07/825,488
Filed	:	January 24, 1992
Title	:	METHOD OF LOWERING THE BLOOD PRESSURE
Art Unit	:	1205
Examiner	:	R. Travers

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents, Washington, D.C. 20231 on

July 20, 2001
(Date of Deposit)

Ellen Ciambrone Coletti
(Name of applicant, assignee, or Registered Representative)

(Signature)

July 20, 2001
(Date of Signature)

Honorable Commissioner of Patents
Washington, D.C. 20231

AMENDMENT

Dear Sir:

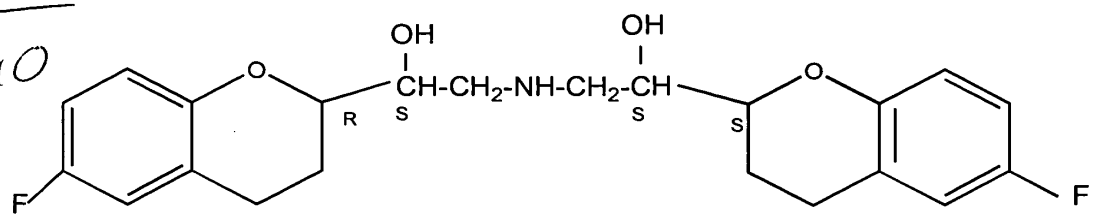
Please amend the above-identified application as follows:

In the Claims:

Please cancel claims 20, 23, 25 and 26.

Please add the following new claims:

--27. (New) A composition consisting of the compound [2R,αS,2'S,α'S]-α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol] having the formula:



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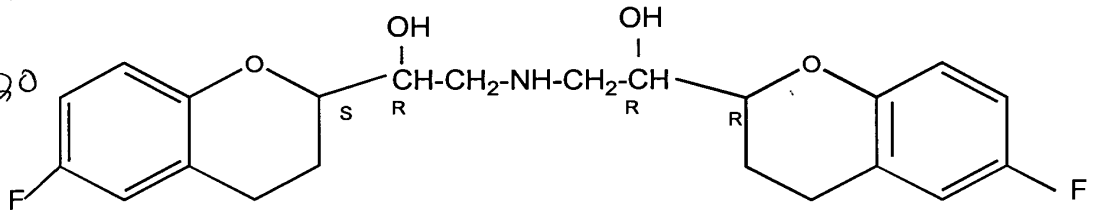
or a pharmaceutically acceptable acid addition salt thereof.

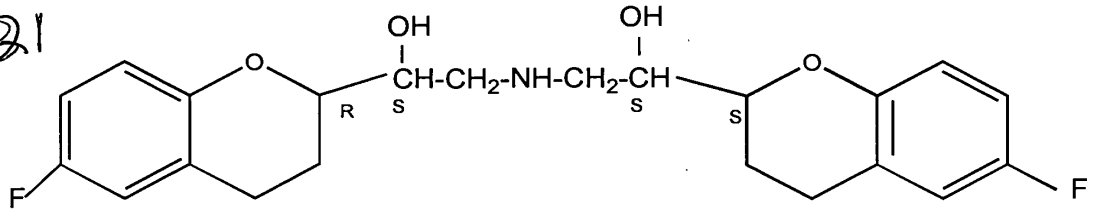
28. (New) A pharmaceutical composition consisting of a pharmaceutically acceptable carrier and, as active ingredients:

(a) the blood pressure reducing compound [2S,αR, 2'R,α'R]-α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol] having the formula:



or a pharmaceutically acceptable acid addition salt thereof; and

(b) the compound [2R,αS,2'S,α'S]-α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol] having the formula:



or a pharmaceutically acceptable acid addition salt thereof.

29. (New) A composition according to claim 28 wherein compound (b) is present in an amount capable of potentiating the activity of the blood pressure reducing compound (a). -

---

The following claims have been amended:

4 21. A composition according to claim 29 wherein the molar ratio of the compounds (a) and (b) is about 1:1.

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5 22. A method of treating hypertension in warm blooded animals in need of such treatment which comprises administering to said warm blooded animals an effective amount of the pharmaceutical composition of claim 28.

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REMARKS/ARGUMENTS

Applicants hereby request that claims 20, 23, 25 and 26 be canceled, claims 21 and 22 be amended and new claims 27-29 be added. Upon entry of this Amendment, the claims pending and under consideration are claims 21-22, 24 and 27-29.

Applicants respectfully submit that new claims 27, 28 and 29 do not introduce new matter. Support for new claims 27, 28 and 29 can be found throughout the specification, for example, at page 1, lines 24-25 and page 5, lines 27-30 and at original claim 4.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page(s) is/are captioned "Version with markings to show changes made".

Applicants' attorney wishes to thank the Examiner for the courtesies extended during an interview in the captioned application held on July 17, 2001 in which Ms. Barbara Ernst and Ms. Shelly Monteleone (attorneys representing Mylan Labs) attended. During the interview, this Amendment as well as accompanying Declaration of Alain Dupont[1] were discussed.

A Decision on Appeal was rendered in the captioned application and mailed March 14, 2000 ("Decision") in which the appeal with respect to claims 20 and 23 is dismissed and the rejection of claims 21, 22 and 24 through 26 under 35 U.S.C. § 103 as unpatentable over Van Lommen is reversed.

With respect to the reversal of the rejection of the claims under 35 U.S.C. § 103, the Decision reads in part :

> The Declaration of Raymond Xhonneux, filed January 24, 1992 under the provisions of 37 CFR § 1.132, presents evidence supporting a conclusion that the RSSS stereoisomer, unlike its enantiomer, SRRR, "only minimally affects blood pressure when administered alone" but significantly "potentiates the

[1] A faxed executed copy is attached. The original will be filed upon receipt of same.

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> antihypertensive effects of the (SRRR)-compound, but not the bradycardiac affects [sic] of the (SRRR)-compound." See page 4 of the Declaration. The examiner does not propose any reason why a person having ordinary skill in the art would have expected the RSSS stereoisomer to have such properties. Nor does the examiner contend that the potentiating property, described in the declaration, is insignificant. Therefore, we reverse the rejection of the claims under 35 U.S.C. § 103 on the strength of appellants' rebuttal evidence establishing that the claimed subject matter possesses unexpectedly superior results.

Subsequent to the Decision, Applicants attorney became aware of two articles (Lacourciére et al., J. Cardiovasc. Pharmacol. 25 (4):619-624 (1995) and Van Nueten & De Cree, Cardiovasc. Drugs Ther. 12:339-344 (1998) relating to blood pressure lowering effects in man of nebivolol (racemic mixture of the d-(or SRRR) enantiomer and the l- (or RSSS) enantiomer) and its d-and l- enantiomers.

These articles are summarized in the Declaration of Alain Gilbert Dupont dated July 20, 2001, ("Dupont Declaration") (copies of articles referred to in the Dupont Declaration are attached thereto) as follows:

> Lacourcière et al. (J. Cardiovasc. Pharmacol. 25 (4):619-624; 1995) assessed the comparative antihypertensive efficacy of 4 weeks of treatment with 5 mg nebivolol and 2.5 mg of the d-enantiomer in 30 patients with mild to moderate hypertension following a double-blind cross-over design. Unlike the animal studies with SHRs [spontaneously hypertensive rats] referred to in the Xhonneux Declaration, the results showed similar reductions in blood pressure with the two treatments.
>
> Van Nueten & De Cree, Cardiovasc. Drugs Ther. 12:339-344; (1998) it was shown that the beta-blocking activity of nebivolol resides in the d-enantiomer and that the l-enantiomer did not differ from placebo in its lack of effect on exercise-induced tachycardia and increases in systolic blood pressure. Nebivolol tended to reduce exercise-induced systolic blood pressure at peak plasma levels more than the d-enantiomer alone (mean values : -13.6 versus –9.7 mmHg) but the difference was not significant.
>
> With respect to the data presented in these articles and the Xhonneux Declaration, the Dupont Declaration states:
>
> > The failure to show superiority with respect to reduction in blood pressure of nebivolol over the d-enantiomer in this small short term trial [reported in Lacourciere] does not however mean that the two treatments are equivalent.

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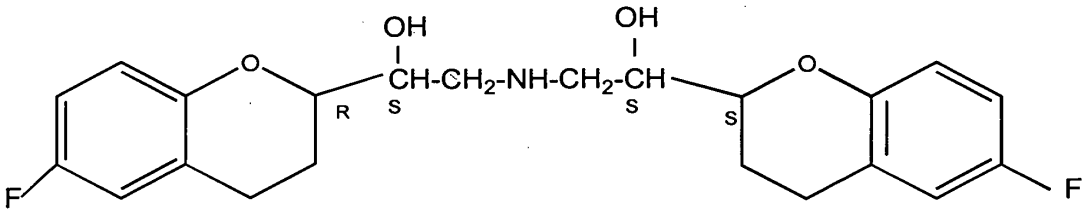
Although different from the results obtained with nebivolol in spontaneously hypertensive rats as presented in the Xhonneux Declaration, this small trial [reported in Van Nueten & DeCree] in healthy normotensive volunteers was not designed to answer questions regarding the possible potentiation of the blood pressure lowering effect of the l-enantiomer on the d-enantiomer.

The Dupont Declaration also states that on the basis of other studies, the l-enantiomer possesses unique properties, alone and in combination with the d-enantiomer.

Claims 25 and 26 under appeal are directed to:

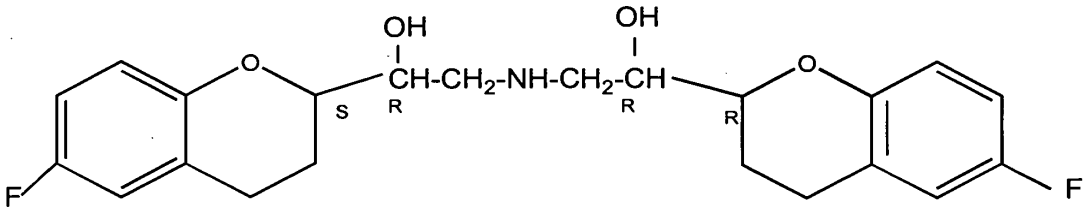
25. A composition consisting essentially of the compound [2R,αS,2'S, α'S]- α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol] having the formula:



or a pharmaceutically acceptable acid addition salt thereof.

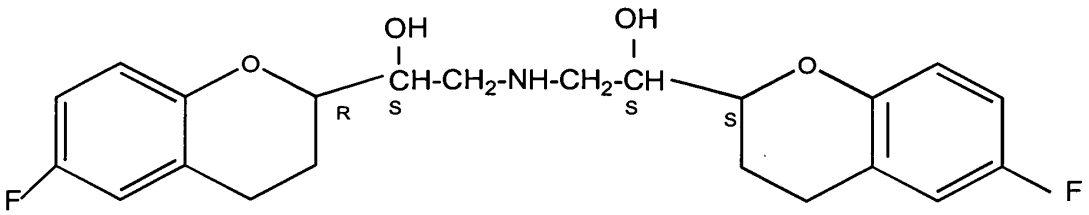
26. A pharmaceutical composition consisting essentially of a pharmaceutically acceptable carrier and, as active ingredients:

(a) the blood pressure reducing compound [2S, αR,2'R, α'R]]- α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol] having the formula:



or a pharmaceutically acceptable acid addition salt thereof; and

(b) the compound [2R, αS,2'S, α'S]]- α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihyro-2*H*-1-benzopyran-2-methanol] having the formula:



or a pharmaceutically acceptable acid addition salt thereof,

Compound (b) being present in an amount capable of potentiating the blood pressure lowering effect of compound (a), above.

Applicants note that compound (a) in the pending claims refers to the SRRR (or d-) enantiomer referred to in the Dupont Declaration and compound (b) of the pending claims refers to the RSSS (or l-) enantiomer in the Dupont Declaration.

Applicants request that claims 25 and 26 be canceled and replaced with new claims 27, 28 and 29, which do not recite with respect to "previous" claim 26 that compound (b) is " present in an amount capable of potentiating the blood pressure lowering effect of compound (a), above." In addition, applicants note that new claims 27, 28 and 29 are directed to compositions "consisting of" , as active ingredients, the identified compounds and do not recite the term "consisting essentially of" which is present in claims 25 and 26.

Claims 25 and 26 (and claims dependent thereon) were rejected under 35 USC § 103 as unpatentable over Van Lommen. As set forth above, the Decision of the Board reversed the rejection under 35 USC 103"on the strength of appellants' rebuttal evidence establishing that the claimed subject matter possesses unexpectedly superior results."

Applicants respectfully submit that the claims, as amended, are patentable over Van Lommen.

Applicants submit that neither a composition consisting of the RSSS enantiomer, nor a composition consisting of the RSSS enantiomer and its enantiomer the SRRR enantiomer, are disclosed in Van Lommen et al. Van Lommen discloses the base compound, as an undefined

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mixture of stereoisomers, as compound Nos. 84 (designated as "AB") and 87 (designated as "AA"), shown in the table in Col. 21 of the patent. There is no way that one can determine from the teachings of the patent the specific stereoisomeric configurations of Van Lommen et al's compound Nos. 84 and 87, as will be explained below.

At col. 4, lines 59 et seq., in referring to the two intermediates used to prepare the final compounds, each [intermediate] of which forms half the final compound, the patentees disclose that "...it is conventionally agreed to designate the stereochemically isomeric form [of the intermediate] which is first isolated as 'A' and the second as 'B', without further reference to the actual stereochemical configuration." With respect to Van Lommen's preferred compound, α,α'-[iminobismethylene]bis[3,4-dihydro-2*H*-1-benzopyran-2-methanol], the patentees disclose that "... it has experimentally been determined that the "A" form corresponds with the RS or SR configuration at the chiral centers 1 and 2 or 3 and 4 while the 'B' form corresponds with the SS or RR configuration at the said chiral centers." Thus "A" means RS or SR or both RS and SR, and "B" means SS or RR or both SS and RR.

Employing these definitions wherein A = RS or SR or both, and B = SS or RR or both, Van Lommen's Compound 84, designated as "AB", is an undefined mixture of the RSRR, RSSS, SRSS and SRRR isomers, and Compound 87, designated as "AA", is an undefined mixture of the RSRS, RSSR, and SRRS isomers.

From the above discussion, it is clear that the cited Van Lommen et al. patent discloses neither a composition consisting of the RSSS enantiomer of the base compound, nor a composition consisting of the RSSS and SRRR enantiomers.

Attention is directed to the Dupont Declaration, a copy of which is enclosed herewith in which the declarant concludes that:

Nebivolol is the racemic mixture of two enantomers and can be classified as a "third generation" or "vasodilating" beta blocker with beneficial effects on systolic and diastolic cardiac performance. The drug combines highly selective beta –1 receptor blockade, mediated by the d-enantiomer, with vasodilation via stimulation of endothelial NO release which is mediated in part by the d-enantiomer but mainly by the l-enantiomer. Overall the data indicate,

as clearly shown in some of the studies (e.g.Stoleru et al), that the combination of both enantiomers is required to produce nebivolol's unique pharmacodynamic profile.

Applicants submit that the Dupont Declaration evidences the unexpected properties of the claimed subject matter, that is the composition of claims 27 and 28.

In further support of the patentability of the claimed subject matter over VanLommen, Applicants direct attention to the declaration of Petrus Pauwels, dated January 17,1992, ("Pauwels Declaration") of record in the captioned application. In the Pauwels Declaration the declarant states that

"research results not reported in the present article show that the unusual pharmacological profile of nebivolol which differs from other classical B-adrenergic blockers, cannot be attributed to the d-enantiomer(SRRR) alone. The peculiar, advantageous properties of nebivolol such as improved left ventricular function, reduction in systemic vascular resistance and related increased cardiac output (i.e. positive inotropy) and the immediate reduction in blood pressure which are obtained after administration of nebivolol are mediated by the l-enantiomer"

For the foregoing reasons, Applicants respectfully submit that new claims 27, 28 and 29 (and claims dependent thereon) are patentable over Van Lommen.

Applicants respectfully request that the proposed amendments be entered and that a timely Notice of Allowance be issued in this case.

Respectfully submitted,

By: _____

Ellen Ciambrone Coletti
Reg. No. 34,140

Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003
(732) 524-2359
Dated: July 20, 2001

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#41

US JAB 7/16

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	)	
Raymond Mathieu Xhonneux et al.	)	Examiner Russell Travers
Serial No. 07/825488	)	
filed January 24, 1992	)	Group 120-Art Unit 1205
for METHOD OF LOWERING THE BLOOD PRESSURE	)	

DECLARATION

I, Alain Gilbert Dupont, a citizen of Belgium residing at Boslaan 14A, 2820 Bonheiden,Belgium, make the following declaration :

1. I am a medical doctor, specialist in internal medicine, Ph.D. in Pharmacology , professor and Head of Clinical Pharmacology and Pharmacotherapy at the Vrije Universiteit Brussel, and also responsible for the Hypertension Unit at the University Hospital; I was at Janssen Research Foundation (in combination with a part-time activity at the Vrije Universiteit Brussel) from November 1991 till end February 2000, as Director of Clinical Scientific Affairs.

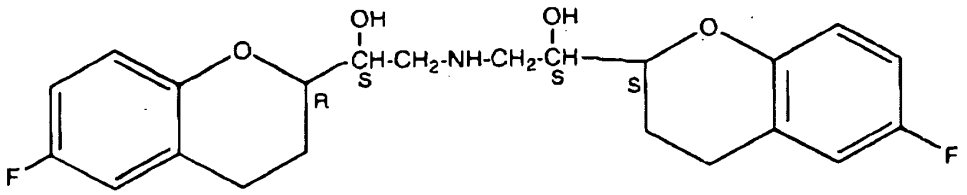
2. I am the author or co-author of many publications in the fields of pharmacology, clinical pharmacology and hypertension.

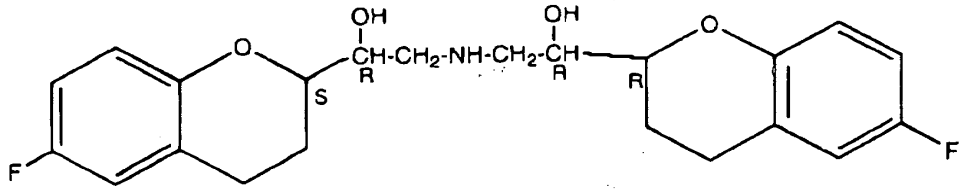
3. I have read the above-mentioned patent application, the declaration by P. Pauwels of January 17, 1992 and the declaration of R. Xhonneux of January 16, 1992 and I fully understand the contents thereof.

4. In the following sections, I will review the published literature concerning nebivolol and its d- and l-enantiomers in addition to some hitherto unpublished reports.

5. *In-vitro* Pharmacology

- Nebivolol is a racemic mixture of two enantiomers of the following formula:





The d-enantiomer is a potent and highly selective beta-1 receptor antagonist, whilst the l-enantiomer has much less (about 100 times less) affinity for the beta-1 receptor (Pauwels et al., Molecular Pharmacology 34:843-851;1988).

A number of features discriminates nebivolol from "classical" beta-blockers.

As is mentioned on page 849, second column in the paragraph entitled "Mode of action of nebivolol as antihypertensive agent" : "Recent observations have revealed that the particular haemodynamic profile is specifically obtained with nebivolol, whereas the β1-adrenergic active [d-]enantiomer R 67 138 (S, R, R, R) showed the activities of a typical β-adrenergic blocker. Hence, the properties of nebivolol apparently resulted from the combined activities of the two enantiomers".

- In the Declaration of January 17, 1992, P. Pauwels further clarifies this point as follows : "Indeed, research results not reported in the present article show that the unusual pharmacological profile of nebivolol which differs from other classical β-adrenergic blockers, cannot be attributed to the d-enantiomer (SRRR) alone. The peculiar, advantageous properties of nebivolol such as improved left ventricular function, reduction in systemic vascular resistance, and related increased cardiac output (i.e. positive inotropy) and the immediate reduction in blood pressure which are obtained after administration of nebivolol are mediated by the l-enantiomer".

6. Non-clinical Pharmacology

- An *in vivo* study in anesthetized dogs showed that the d-enantiomer has a similar cardiovascular profile to atenolol, i.e. reduction in stroke volume and in cardiac output. Whilst atenolol negatively influenced the variables related to left ventricular performance, nebivolol did not affect these variables, except at the two highest doses administered (0.16 and 0.63 $mg.kg^{-1}$ i.v.). However, at the lower to median doses (0.0025-0.04 $mg.kg^{-1}$ i.v.) nebivolol unexpectedly did not reduce cardiac output, and did not increase systemic resistance. These effects can be explained by the presence of the l-enantiomer, as this alone improved cardiac output and reduced systemic vascular resistance (Van de Water et al., Eur. J. Pharmacol. 156: 95-103; 1988).

- In contrast to "classical" beta-blockers, nebivolol reduced both systolic (- 26.9%) and diastolic (- 20%) blood pressure acutely in spontaneously

hypertensive rats (SHRs). These effects were more prominent than those observed with atenolol and pindolol which did not reduce diastolic blood pressure but caused only a slight, significant, and consistent decrease in systolic blood pressure (- 8.7% and - 6%, respectively) (Van de Water et al., J. Cardiovasc. Pharmacol. 11:552; 1988).

The d-enantiomer reduced heart rate (a measure of beta-1 antagonism) to the same extent as nebivolol but its blood pressure lowering potential was less. The l-enantiomer alone had no major effect on diastolic blood pressure in the lower dose range (0.63 – 5 $mg.kg^{-1}$). At 2.5 and 5 $mg.kg^{-1}$ l-nebivolol slightly but significantly decreased the systolic blood pressure, whereas the heart rate was significantly reduced after 5 $mg.kg^{-1}$. These results can be explained by postulating a potentiating effect by the l-enantiomer on the blood pressure lowering effect of the d-enantiomer (Xhonneux et al., Eur. J. Pharmacol. 181: 261-265; 1990).

The results shown graphically in Figures 3A and C on page 264, were represented numerically (median values and 95% confidence limits) in Tables 1 and 2 of paragraph 4 in the Declaration of R. M. Xhonneux of January 16, 1992 ("Xhonneux Declaration").

- The observation that nebivolol can reduce blood pressure acutely without compromising heart function differentiates it from "classical" beta-blockers and suggests that the l-enantiomer, which appears to be necessary for this profile, may have a vasodilator activity. This hypothesis was confirmed by Prof. Vanhoutte's group (Gao et al., J. Cardiovasc. Pharmacol. 17:964-969; 1991). These authors

observed in an *in vitro* study that nebivolol induced a dose-dependent relaxation of pre-contracted canine coronary arteries. The effect was inhibited by either removal of the endothelium or addition of nitro-L-arginine, an inhibitor of nitric oxide synthase, suggesting that this vasodilator response was mediated via the L-arginine-NO pathway. Further experiments with the two enantiomers separately indicated that the l-enantiomer was more potent than the d-enantiomer, and as potent as nebivolol, in inducing and potentiating endothelium-dependent vascular relaxation (Gao et al., J. Cardiovasc. Pharmacol. 17:964-969; 1991).
Taken together, these studies strongly suggest that in addition to being a selective beta 1-blocker, which is related to the presence of the d-enantiomer, nebivolol also reduces peripheral vascular resistance.

7. Blood pressure lowering effects in man

- Lacourcière et al. (J. Cardiovasc. Pharmacol. 25 (4):619-624; 1995) assessed the comparative antihypertensive efficacy of 4 weeks of treatment with 5 mg nebivolol and 2.5 mg of the d-enantiomer in 30 patients with mild to moderate hypertension following a double-blind cross-over design. Unlike the animal studies with SHRs referred to in Xhonneux, the results showed similar reductions in blood pressure with the two treatments. The failure to show superiority with (1) respect to reduction in blood pressure of nebivolol over the d-enantiomer in this small short term trial does not however mean that the two treatments are equivalent. Although cardiac function has not been assessed in the study, in the authors' opinion, (2) the possibility that cardiac function may have improved by nebivolol is not excluded. Additionally, they think (2) that their "results cast doubt on

the clinical relevance of findings made in anesthesized animals [however, note that Van de Water studied *awake* SHRs], *in vitro* with ring preparations of dog coronary arteries and in hemodynamic studies in human volunteers".

It is likely that the trial had insufficient assay sensitivity, that is, the trial had not enough power due to the limited number of patients to detect a potentiating effect of the l-enantiomer as observed in the animal studies mentioned above.

Other available trials in hypertensive patients beside the study discussed above in this section, for example, Breuel, Report – Double-blind placebo controlled phase II study of dl-nebivolol and its d- and l-enantiomers in patients with mild to moderate hypertension (AFB Study no 05/0454-90, dated February 2, 1993) and Van Bortel, Effect of nebivolol and its enantiomers in hypertensive patients. Comparison with placebo and atenolol. (Clinical research report, NEB-INT-4) did not show a difference between nebivolol and the d-enantiomer on blood pressure reduction. These pilot studies lacked sufficient trial sensitivity to answer that question.

- In a small trial in healthy volunteers (Van Nueten & De Cree, Cardiovasc. Drugs Ther. 12:339-344; 1998) it was shown that the beta-blocking activity of nebivolol resides in the d-enantiomer and that the l-enantiomer did not differ from placebo in its lack of effect on exercise-induced tachycardia and increases in systolic blood pressure. Nebivolol tended to reduce exercise-induced systolic blood pressure at peak plasma levels more than the d-enantiomer alone (mean values : -13.6 versus –9.7 mmHg) but the difference was not significant. Although different from the results obtained with nebivolol in spontaneously hypertensive rats as presented in the Xhonneux Declaration, this small trial in healthy normotensive volunteers was

not designed to answer questions regarding the possible potentiation of the blood pressure lowering effect of the l-enantiomer on the d-enantiomer.

- Another study in healthy male volunteers (De Meirleir, Cardiovascular and metabolic effect of d-, l- and dl-nebivolol) also did not show a difference between nebivolol and the d-enantiomer on exercise induced tachycardia (a measure of beta-1 antagonism).

In summary, there are no adequate clinical trials available that address the question whether the presence of the l-enantiomer can potentiate the blood pressure lowering effect of the d-enantiomer in patients with hypertension as can be expected based on the animal data.

8. Clinical Pharmacology/ Haemodynamic studies

Several human pharmacology studies confirm that nebivolol in addition to being a highly selective beta-1 receptor antagonist also displays endothelium-dependent vasorelaxant effects and beneficial effects on cardiac performance.

- Studies using venous occlusion plethysmography during brachial artery infusion in healthy volunteers have clearly shown that nebivolol dilates the human forearm vasculature via an L-arginine/NO dependent mechanism, an effect which was not seen with atenolol (Cockcroft et al., J. Pharmac. Exp. Ther. 274:1067-1071; 1995). This vasodilator response was also observed with the individual enantiomers (the l-enantiomer was slightly more potent than the d-enantiomer). In a further trial with nebivolol only, the same group also confirmed this NO

dependent vasodilator response in hypertensive patients (Dawes et al., Br. J. Clin. Pharmacol. 48:460-463; 1999).

- Bowman et al (Br. J. Clin. Pharm. 38:199-204; 1994) further demonstrated that nebivolol had NO dependent and dose-dependent venodilator effects after local infusion into a superficial hand vein in healthy volunteers.

- Himmelmann et al. (Eur. J. Clin. Pharmacol. 51:259-264; 1996) observed in a venous plethysmography study that oral nebivolol (5 mg) reduced total peripheral resistance at steady state in patients with hypertension.

- Stoleru et al. (J. Cardiovasc. Pharmacol. 22:183-190; 1993) studied the effect of the d- and l-enantiomers by means of left ventricular angiography and compared the effects of these enantiomers with those of intravenously administered nebivolol and of atenolol of a previously conducted study. Both studies were double blind and had identical design, inclusion criteria and methods. This invasive study was carried out in patients with ischemic heart disease who had to undergo heart catheterisation for diagnostic reasons. Atenolol -as expected from a beta-blocker- reduced ejection fraction and cardiac output, whilst with nebivolol the ejection fraction increased and the cardiac output remained unchanged despite the decrease in heart rate, reflecting an improved cardiac performance. Moreover, nebivolol -but not atenolol- resulted in a significant downward shift of the left ventricular pressure-volume curve. This reflects an improved left ventricular distensibility and an improvement in left ventricular diastolic function. These studies indicated that both the d- and the l-enantiomers must be given in combination in order to observe this marked improvements in left ventricular

systolic and diastolic function and cardiac performance. The authors hypothesize that the effects of nebivolol are the result of three actions: beta-blockade, effect on vascular endothelium and perhaps some effect on cardiac endothelium (see page 189). This beneficial effect on cardiac function of nebivolol is likely to be due not only to its peripheral vascular (arterial and venous dilator) effects, but also to more direct effects on heart function via stimulation of endocardial NO production.

- In a comparative trial in patients with ischemic left ventricular dysfunction, nebivolol and atenolol improved left ventricular systolic function, but only nebivolol produced a downward shift of the pressure-volume relationship during early diastolic filling, indicative of an improvement in diastolic distensibility (Rousseau et al., J. Card. Fail 2:15-23, 1996).

- In a comparative study with invasive monitoring of cardiac haemodynamics (Swan-Ganz catheter) in patients who had undergone cardiac bypass surgery, atenolol reduced stroke volume, slowed heart rate and reduced cardiac output and ejection fraction, as expected, and increased peripheral resistance. With nebivolol these parameters were not adversely affected : despite a reduction in heart rate, the cardiac output remained unchanged, stroke index and ejection fraction increased and the systemic vascular resistance index decreased. Right Ventricular Ejection Fraction decreased significantly versus baseline in the atenolol group but not in the nebivolol group. Differences between the two treatment groups at end point were not significant. (Goldstein et al., J. Cardiovasc. Pharmacol. 22:253-258; 1993). In a subsequent similar study in a limited number of patients, the same authors compared nebivolol with the l- and d-enantiomers (Goldstein,

Postoperative haemodynamic effects of racemic nebivolol compared to d- and l-nebivolol in patients with coronary artery bypass grafting. Trial No NEB-BEL-42) following a parallel group design. Except for stroke index, which was significantly higher after 6 hours with nebivolol than with the d-enantiomer, changes from baseline did not statistically differ between groups for most haemodynamic parameters (cardiac output, peripheral resistance); this could be related to the pronounced differences between groups observed at baseline.

- Wisenbaugh et al. (J. Am. Coll. Cardiol. 21:1094-1100; 1993) examined the long-term (3 month) effects of nebivolol on cardiac performance in patients with dilated cardiomyopathy using invasive haemodynamic measurements. They concluded that nebivolol improved stroke volume, ejection fraction and left ventricular end-diastolic pressure by improving systolic contractile performance.

- The favourable effects on cardiac performance of nebivolol which were clearly demonstrated in the invasive haemodynamic studies discussed above, had been suggested in a series of earlier studies using systolic time intervals and equilibrium radionuclide angiocardiography, as reviewed by De Cree et al. (Acta Antwerpiensa 6:2-21; 1989). Although the technique of systolic time intervals has a number of limitations compared to the invasive, "gold standard" methods used later on by Stoleru et al., Goldstein et al., Rousseau et al., and Wisenbaugh et al. (see above), the results of these systolic time interval studies were very reproducible and lent support to the invasive data generated in later studies. The results of the systolic time interval studies were validated in the same trial by equilibrium radionuclide angiocardiography studies.

In summary, the clinical pharmacology studies have confirmed that nebivolol is a selective beta-1 blocker also in man. This effect is mediated by the d-enantiomer since the l-enantiomer does not display any relevant beta-blocking activity. In addition, nebivolol clearly displays arterial and venous vasodilating properties, which are mediated by the L-arginine-NO pathway, and has beneficial effects on cardiac performance differentiating it from "classical" beta-blockers such as atenolol.

9. Conclusion

Nebivolol is the racemic mixture of two enantiomers and can be classified as a "third generation"or "vasodilating" beta blocker with beneficial effects on systolic and diastolic cardiac performance. The drug combines highly selective beta-1 receptor blockade, mediated by the d-enantiomer, with vasodilation via activation of the L-arginine-NO pathway ~~stimulation of endothelial NG release~~ which is mediated in part by the d-enantiomer but mainly by the l-enantiomer. Overall the data indicate, as clearly shown in some of the studies (e.g. Stolen et al.), that the combination of both enantiomers is required to produce nebivolol's unique pharmacodynamic profile.

20/07/10

10. I finally declare that all statements herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both.

under section 1001 of Title 18 of the United States Code and such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed, this 20th day of July 2001.

Alain G. Dupont

Docket No. JAB-775

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Raymond M. Xhonneux et al.

Serial No. : 07/825,488 Art Unit: 1205

Filed : January 24, 1992 Examiner: R. Travers

For : METHOD OF LOWERING BLOOD PRESSURE

Gp #1205 16/4

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231 on

November 14, 2001

(Date)

Ellen Ciambrone Coletti

Name of applicant, assignee, or Registered Representative

(Signature)

November 14, 2001

(Date of Signature)

Commissioner for Patents
Washington, D.C. 20231

COMMUNICATION

Dear Sir:

Further to the Amendment filed July 20, 2001, attached is the original executed Declaration of Alain Gilbert Dupont.

Respectfully submitted,

Ellen Ciambrone Coletti
Reg. No. 34,140
Attorney for Applicant(s)

Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003
(732) 524-2359
Dated: November 14, 2001

US JAB 775

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	)	
Raymond Mathieu Xhonneux et al.	)	Examiner Russell Travers
Serial No. 07/825488	)	
filed January 24, 1992	)	Group 120-Art Unit 1205
for METHOD OF LOWERING THE BLOOD PRESSURE	)	

DECLARATION

I, Alain Gilbert Dupont, a citizen of Belgium residing at Boslaan 14A, 2820 Bonheiden,Belgium, make the following declaration :

1. I am a medical doctor, specialist in internal medicine, Ph.D. in Pharmacology , professor and Head of Clinical Pharmacology and Pharmacotherapy at the Vrije Universiteit Brussel, and also responsible for the Hypertension Unit at the University Hospital; I was at Janssen Research Foundation (in combination with a part-time activity at the Vrije Universiteit Brussel) from November 1991 till end February 2000, as Director of Clinical Scientific Affairs.

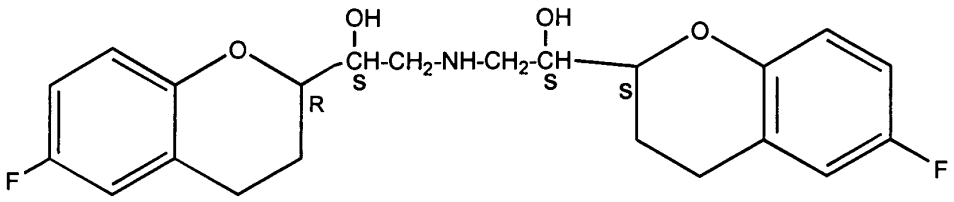
2. I am the author or co-author of many publications in the fields of pharmacology, clinical pharmacology and hypertension.

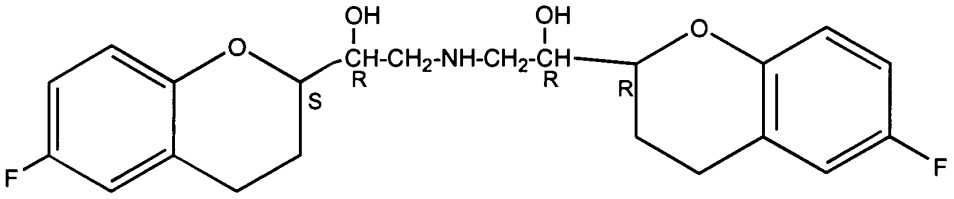
3. I have read the above-mentioned patent application, the declaration by P. Pauwels of January 17, 1992 and the declaration of R. Xhonneux of January 16, 1992 and I fully understand the contents thereof.

4. In the following sections, I will review the published literature concerning nebivolol and its d- and l-enantiomers in addition to some hitherto unpublished reports.

5. *In-vitro* Pharmacology

- Nebivolol is a racemic mixture of two enantiomers of the following formula:





The d-enantiomer is a potent and highly selective beta-1 receptor antagonist, whilst the l-enantiomer has much less (about 100 times less) affinity for the beta-1 receptor (Pauwels et al., Molecular Pharmacology 34:843-851;1988).

A number of features discriminates nebivolol from "classical" beta-blockers.

As is mentioned on page 849, second column in the paragraph entitled "Mode of action of nebivolol as antihypertensive agent" : "Recent observations have revealed that the particular haemodynamic profile is specifically obtained with nebivolol, whereas the β1-adrenergic active [d-]enantiomer R 67 138 (S, R, R, R) showed the activities of a typical β-adrenergic blocker. Hence, the properties of nebivolol apparently resulted from the combined activities of the two enantiomers".

- In the Declaration of January 17, 1992, P. Pauwels further clarifies this point as follows : "Indeed, research results not reported in the present article show that the unusual pharmacological profile of nebivolol which differs from other classical β-adrenergic blockers, cannot be attributed to the d-enantiomer (SRRR) alone. The peculiar, advantageous properties of nebivolol such as improved left ventricular function, reduction in systemic vascular resistance, and related increased cardiac output (i.e. positive inotropy) and the immediate reduction in blood pressure which are obtained after administration of nebivolol are mediated by the l-enantiomer".

6. Non-clinical Pharmacology

- An *in vivo* study in anesthetized dogs showed that the d-enantiomer has a similar cardiovascular profile to atenolol, i.e. reduction in stroke volume and in cardiac output. Whilst atenolol negatively influenced the variables related to left ventricular performance, nebivolol did not affect these variables, except at the two highest doses administered (0.16 and 0.63 $mg.kg^{-1}$ i.v.). However, at the lower to median doses (0.0025-0.04 $mg.kg^{-1}$ i.v.) nebivolol unexpectedly did not reduce cardiac output, and did not increase systemic resistance. These effects can be explained by the presence of the l-enantiomer, as this alone improved cardiac output and reduced systemic vascular resistance (Van de Water et al., Eur. J. Pharmacol. 156: 95-103; 1988).

- In contrast to "classical" beta-blockers, nebivolol reduced both systolic (- 26.9%) and diastolic (- 20%) blood pressure acutely in spontaneously hypertensive rats (SHRs). These effects were more prominent than those observed

with atenolol and pindolol which did not reduce diastolic blood pressure but caused only a slight, significant, and consistent decrease in systolic blood pressure (- 8.7% and - 6%, respectively) (Van de Water et al., J. Cardiovasc. Pharmacol. 11:552; 1988).

The d-enantiomer reduced heart rate (a measure of beta-1 antagonism) to the same extent as nebivolol but its blood pressure lowering potential was less. The l-enantiomer alone had no major effect on diastolic blood pressure in the lower dose range (0.63 – 5 $mg.kg^{-1}$). At 2.5 and 5 $mg.kg^{-1}$ l-nebivolol slightly but significantly decreased the systolic blood pressure, whereas the heart rate was significantly reduced after 5 $mg.kg^{-1}$. These results can be explained by postulating a potentiating effect by the l-enantiomer on the blood pressure lowering effect of the d-enantiomer (Xhonneux et al., Eur. J. Pharmacol. 181: 261-265; 1990).

The results shown graphically in Figures 3A and C on page 264, were represented numerically (median values and 95% confidence limits) in Tables 1 and 2 of paragraph 4 in the Declaration of R. M. Xhonneux of January 16, 1992 ("Xhonneux Declaration").

- The observation that nebivolol can reduce blood pressure acutely without compromising heart function differentiates it from "classical" beta-blockers and suggests that the l-enantiomer, which appears to be necessary for this profile, may have a vasodilator activity. This hypothesis was confirmed by Prof. Vanhoutte's group (Gao et al., J. Cardiovasc. Pharmacol. 17:964-969; 1991). These authors observed in an *in vitro* study that nebivolol induced a dose-dependent relaxation

of pre-contracted canine coronary arteries. The effect was inhibited by either removal of the endothelium or addition of nitro-L-arginine, an inhibitor of nitric oxide synthase, suggesting that this vasodilator response was mediated via the L-arginine-NO pathway. Further experiments with the two enantiomers separately indicated that the l-enantiomer was more potent than the d-enantiomer, and as potent as nebivolol, in inducing and potentiating endothelium-dependent vascular relaxation (Gao et al., J. Cardiovasc. Pharmacol. 17:964-969; 1991).

Taken together, these studies strongly suggest that in addition to being a selective beta 1-blocker, which is related to the presence of the d-enantiomer, nebivolol also reduces peripheral vascular resistance.

7. Blood pressure lowering effects in man

- Lacourcière et al. (J. Cardiovasc. Pharmacol. 25 (4):619-624; 1995) assessed the comparative antihypertensive efficacy of 4 weeks of treatment with 5 mg nebivolol and 2.5 mg of the d-enantiomer in 30 patients with mild to moderate hypertension following a double-blind cross-over design. Unlike the animal studies with SHRs referred to in Xhonneux, the results showed similar reductions in blood pressure with the two treatments. The failure to show superiority with respect to reduction in blood pressure of nebivolol over the d-enantiomer in this small short term trial does not however mean that the two treatments are equivalent. Although cardiac function has not been assessed in the study, in the authors' opinion, the possibility that cardiac function may have improved by nebivolol is not excluded. Additionally, they think that their "results cast doubt on the clinical relevance of findings made in anesthesized animals [however, note that Van de Water studied *awake* SHRs], *in vitro* with ring preparations of dog

coronary arteries and in hemodynamic studies in human volunteers".

It is likely that the trial had insufficient assay sensitivity, that is, the trial had not enough power due to the limited number of patients to detect a potentiating effect of the l-enantiomer as observed in the animal studies mentioned above.

Other available trials in hypertensive patients beside the study discussed above in this section, for example, Breuel, Report – Double-blind placebo controlled phase II study of dl-nebivolol and its d- and l-enantiomers in patients with mild to moderate hypertension (AFB Study no 05/0454-90, dated February 2, 1993) and Van Bortel, Effect of nebivolol and its enantiomers in hypertensive patients. Comparison with placebo and atenolol. (Clinical research report, NEB-INT-4) did not show a difference between nebivolol and the d-enantiomer on blood pressure reduction. These pilot studies lacked sufficient trial sensitivity to answer that question.

- In a small trial in healthy volunteers (Van Nueten & De Cree, Cardiovasc. Drugs Ther. 12:339-344; 1998) it was shown that the beta-blocking activity of nebivolol resides in the d-enantiomer and that the l-enantiomer did not differ from placebo in its lack of effect on exercise-induced tachycardia and increases in systolic blood pressure. Nebivolol tended to reduce exercise-induced systolic blood pressure at peak plasma levels more than the d-enantiomer alone (mean values : -13.6 versus –9.7 mmHg) but the difference was not significant. Although different from the results obtained with nebivolol in spontaneously hypertensive rats as presented in the Xhonneux Declaration, this small trial in healthy normotensive volunteers was not designed to answer questions regarding the possible potentiation of the blood pressure lowering effect of the l-enantiomer on the d-enantiomer.

- Another study in healthy male volunteers (De Meirleir, Cardiovascular and metabolic effect of d-, l- and dl-nebivolol) also did not show a difference between nebivolol and the d-enantiomer on exercise induced tachycardia (a measure of beta-1 antagonism).

In summary, there are no adequate clinical trials available that address the question whether the presence of the l-enantiomer can potentiate the blood pressure lowering effect of the d-enantiomer in patients with hypertension as can be expected based on the animal data.

8. Clinical Pharmacology/ Haemodynamic studies

Several human pharmacology studies confirm that nebivolol in addition to being a highly selective beta-1 receptor antagonist also displays endothelium-dependent vasorelaxant effects and beneficial effects on cardiac performance.

- Studies using venous occlusion plethysmography during brachial artery infusion in healthy volunteers have clearly shown that nebivolol dilates the human forearm vasculature via an L-arginine/NO dependent mechanism, an effect which was not seen with atenolol (Cockcroft et al., J. Pharmac. Exp. Ther. 274:1067-1071; 1995). This vasodilator response was also observed with the individual enantiomers (the l-enantiomer was slightly more potent than the d-enantiomer). In a further trial with nebivolol only, the same group also confirmed this NO dependent vasodilator response in hypertensive patients (Dawes et al., Br. J. Clin. Pharmacol. 48:460-463; 1999).

- Bowman et al (Br. J. Clin. Pharm. 38:199-204; 1994) further demonstrated that nebivolol had NO dependent and dose-dependent venodilator effects after local infusion into a superficial hand vein in healthy volunteers.

- Himmelmann et al. (Eur. J. Clin. Pharmacol. 51:259-264; 1996) observed in a venous plethysmography study that oral nebivolol (5 mg) reduced total peripheral resistance at steady state in patients with hypertension.

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vascular endothelium and perhaps some effect on cardiac endothelium (see page 189). This beneficial effect on cardiac function of nebivolol is likely to be due not only to its peripheral vascular (arterial and venous dilator) effects, but also to more direct effects on heart function via stimulation of endocardial NO production.

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following a parallel group design. Except for stroke index, which was significantly higher after 6 hours with nebivolol than with the d-enantiomer, changes from baseline did not statistically differ between groups for most haemodynamic parameters (cardiac output, peripheral resistance); this could be related to the pronounced differences between groups observed at baseline.

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- The favourable effects on cardiac performance of nebivolol which were clearly demonstrated in the invasive haemodynamic studies discussed above, had been suggested in a series of earlier studies using systolic time intervals and equilibrium radionuclide angiocardiography, as reviewed by De Cree et al. (Acta Antwerpiensa 6:2-21; 1989). Although the technique of systolic time intervals has a number of limitations compared to the invasive, "gold standard" methods used later on by Stoleru et al., Goldstein et al., Rousseau et al., and Wisenbaugh et al. (see above), the results of these systolic time interval studies were very reproducible and lent support to the invasive data generated in later studies. The results of the systolic time interval studies were validated in the same trial by equilibrium radionuclide angiocardiography studies.

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9. Conclusion

Nebivolol is the racemic mixture of two enantiomers and can be classified as a "third generation"or "vasodilating" beta blocker with beneficial effects on systolic and diastolic cardiac performance. The drug combines highly selective beta-1 receptor blockade, mediated by the d-enantiomer, with vasodilation via stimulation of endothelial NO release which is mediated in part by the d-enantiomer but mainly by the l-enantiomer. Overall the data indicate, as clearly shown in some of the studies (e.g. Stoleru et al.), that the combination of both enantiomers is required to produce nebivolol's unique pharmacodynamic profile.

10. I finally declare that all statements herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both,

under section 1001 of Title 18 of the United States Code and such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed, this day of July 2001.

.....

Alain G. Dupont

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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NOTICE OF ALLOWANCE AND FEE(S) DUE

7590 08/16/2002

ROBERT L. MINIER
JOHNSON & JOHNSON
ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, NJ 089337003

EXAMINER	
TRAVERS, RUSSELL S	
ART UNIT	**CLASS-SUBCLASS**
1617	514-451000

DATE MAILED: 08/16/2002

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
07/825,488	01/24/1992	RAYMOND M. XHONNEUX	JAB-775	9859

TITLE OF INVENTION: METHOD OF LOWERING THE BLOOD PRESSURE

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1280	$0	$1280	11/18/2002

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE REFLECTS A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE APPLIED IN THIS APPLICATION. THE PTOL-85B (OR AN EQUIVALENT) MUST BE RETURNED WITHIN THIS PERIOD EVEN IF NO FEE IS DUE OR THE APPLICATION WILL BE REGARDED AS ABANDONED.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above. If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is changed, pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above and notify the United States Patent and Trademark Office of the change in status, or

B. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check the box below and enclose the PUBLICATION FEE and 1/2 the ISSUE FEE shown above.

☐ Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

II. PART B - FEE(S) TRANSMITTAL should be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). Even if the fee(s) have already been paid, Part B - Fee(s) Transmittal should be completed and returned. If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Box ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (REV. 04-02) Approved for use through 01/31/2004.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail Box ISSUE FEE
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7590 08/16/2002

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I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Box Issue Fee address above, or being facsimile transmitted to the USPTO, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
07/825,488	01/24/1992	RAYMOND M. XHONNEUX	JAB-775	9859

TITLE OF INVENTION: METHOD OF LOWERING THE BLOOD PRESSURE

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nonprovisional	NO	$1280	$0	$1280	11/18/2002

EXAMINER	ART UNIT	CLASS-SUBCLASS
TRAVERS, RUSSELL S	1617	514-451000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

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3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the USPTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) ❑ individual ❑ corporation or other private group entity ❑ government

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This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, D.C. 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, Washington, DC 20231.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
07/825,488	01/24/1992	RAYMOND M. XHONNEUX	JAB-775	9859

7590 08/16/2002

ROBERT L. MINIER
JOHNSON & JOHNSON
ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, NJ089337003

EXAMINER	
TRAVERS, RUSSELL S	
ART UNIT	**PAPER NUMBER**
1617	

DATE MAILED: 08/16/2002

Determination of Patent Term Extension or Adjustment under 35 U.S.C. 154 (b)
(application filed prior to June 8, 1995)

This patent application was filed prior to June 8, 1995, thus no Patent Term Extension or Adjustment applies.

PTOL-85 (REV. 04-02) Approved for use through 01/31/2004.

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EXAMINER	
TRAVERS, RUSSELL S	
ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 08/16/2002

Notice of Fee Increase on October 1, 2002

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Notice of Allowability

Application No.	Applicant(s)
07/825,488	Xhonneux et al
Examiner	**Art Unit**
Russell Travers	1617

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

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

1. ☒ This communication is responsive to *7/23/01*.

2. ☒ The allowed claim(s) is/are *2, 22, 24, and 27-29*.

3. ☐ The drawings filed on _____ are accepted by the Examiner.

4. ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____.
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   *Certified copies not received: _____.

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

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

6. ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

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

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

8. ☐ CORRECTED DRAWINGS must be submitted.

   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
   1) ☐ hereto or 2) ☐ to Paper No. _____.

   (b) ☐ including changes required by the proposed drawing correction filed _____, which has been approved by the examiner.

   (c) ☐ including changes required by the attached Examiner's Amendment/Comment or in the Office action of Paper No. _____.

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

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

Attachment(s)

1 ☐ Notice of References Cited (PTO-892)
2 ☐ Notice of Informal Patent Application (PTO-152)
3 ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
4 ☐ Interview Summary (PTO-413), Paper No. _____.
5 ☑ Information Disclosure Statement(s) (PTO-1449), Paper No(s). 46
6 ☐ Examiner's Amendment/Comment
7 ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
8 ☐ Examiner's Statement of Reasons for Allowance
9 ☐ Other

RUSSELL TRAVERS
PRIMARY EXAMINER
ART UNIT 1617

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 2 of 2

Application Number	07/825,488
Filing Date	January 24, 1992
First Named Inventor	R.M. Xhonneux et al.
Group Art Unit	1205
Examiner Name	R. Travers
Attorney Docket Number	JAB-775

OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS

	Z	Kakoki, M., et al. Effects of Vasodilatoryβ-Adrenoceptor Antagonists on Endothelium-Derived Nitric Oxide Release in Rat Kidney. Hyptertension, 1999, 33 [part II] 467-471	
	AA	LACOURCIÈRE, Y. et al., Comparative Assessment of Antihypertensive Efficacy of DL-Nebivolol and D-Nebivolol in Patients with Confirmed Mild to Moderate Hypertension, Journal of Cardiovascular Pharmacology, 25:619-624, 1995, Raven Press, Ltd., New York	
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	CC	PAUWELS, P.J., et al., The Receptor Binding Profile of the New Antihypertensive Agent Nebivolol and Its Stereoisomers Compared with Various ß-Adrenergic Blockers, Molecular Pharmacology, 34:843-851, 1988	
	DD	~~POULEUR, M., et al., A Double-Blind Randomized Comparison of the Effects of Intravenous d-/ l-Nebivolol and Atenolol Infusion on the Left Ventricular Systolic and Diastolic Function, with synopsis JRF NEB-BEL-24~~ No date	
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	RR	VAN de WATER, A., et al., Pharmacological and Hemodynamic Profile of Nebivolol, A Chemmically Novel, Potent, and Selective ß1-adrenergic Antagonist, J. Cardiovase. Pharmacol, 1988 ABSTRACT	
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 1 of 2

Application Number	07/825,488
Filing Date	January 24, 1992
First Named Inventor	R.M. Xhonneux et al.
Group Art Unit	1205
Examiner Name	R. Travers
Attorney Docket Number	JAB-775

OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS			
Examiner's Initials*	Cite No.[1]	Include name of the author (in CAPITOL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published	T[2]
	A	BOWMAN, A.J. et al., Nitric Oxide Mediated Venodilator Effects of Nebivolol, Br J Clin Pharmacology, 1994, 38: 199-204	
	B	COCKCROFT, J.R., et al., Effect of Racemic Nebivolol on Forearm Blood Flow in Healthy Volunteers, British Journal of clinical Pharmacology 35 (5) p. 542p-543p, 1993	
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7590 08/16/2002

ROBERT L. MINIER
JOHNSON & JOHNSON
ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, NJ 089337003

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Carmen A. Cafro (Depositor's name)
(Signature)
11/14/02 (Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
07/825,488	01/24/1992	RAYMOND M. XHONNEUX	JAB-775	9859

TITLE OF INVENTION: METHOD OF LOWERING THE BLOOD PRESSURE

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1280	$0	$1280	11/18/2002

EXAMINER	ART UNIT	CLASS-SUBCLASS
TRAVERS, RUSSELL S	1617	514-451000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. Use of a Customer Number is required.

2. For printing on the patent front page, list (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
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3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

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(A) NAME OF ASSIGNEE: Janssen Pharmaceutica N.V.
(B) RESIDENCE: (CITY and STATE OR COUNTRY): Belgium

Date: 3/16/89 Reel/Frame: 5054969

Please check the appropriate assignee category or categories (will not be printed on the patent) ☐ individual ☒ corporation or other private group entity ☐ government

4a. The following fee(s) are enclosed:

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Commissioner for Patents is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.

(Authorized Signature) Reg. No. 34,140 (Date) 11-14-02

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

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02 FC:8001 9.00 CH

TRANSMIT THIS FORM WITH FEE(S)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 6,545,040

Inventors: Xhonneux *et al.*

Assignee: Janssen Pharmaceutica N.V.

Title: METHOD OF LOWERING THE BLOOD PRESSURE

Issue Date: April 8, 2003

REQUEST FOR EXTENSION OF PATENT TERM
UNDER 35 U.S.C. § 156

Mail Stop: **Hatch-Waxman PTE**
Office of Patent Legal Administration
Room MDW 7D55
600 Dulany Street (Madison Building)
Alexandria, VA 22314

Sir:

Forest Laboratories, Inc. ("Forest") acting under limited power of attorney for the patent owner Janssen Pharmaceutica N.V. (Janssen) hereby requests an extension of the term of U.S. Patent No. 6,545,040 ("the '040 patent") pursuant to 35 U.S.C. § 156. A copy of the '040 patent is attached as Exhibit A. The assignment of the '040 patent from the inventors to Janssen has been recorded at reel 5054, frame 969/970 on March 16, 1989. A copy of the recorded assignment is attached as Exhibit B. A Limited Power of Attorney that appoints the undersigned to act on behalf of Janssen before the U.S. Patent and Trademark Office for the purpose of filing this Request is attached as Exhibit C.

03/24/2008 KLOGAN 00000001 503899 07825488
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A total of five copies of this Request are submitted in compliance with 37 C.F.R. § 1.740(b) and as suggested by MPEP § 2753.

As permitted by 37 C.F.R. § 1.785(b) and MPEP § 2761, Forest is concurrently filing a request for patent term extension of U.S. Patent No. 5,759,580 based upon the same regulatory review period.

The following information is submitted in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740, and follows the numerical format set forth in 37 C.F.R. § 1.740(a):

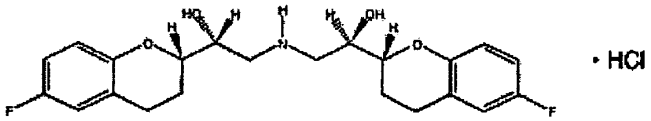
(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics.

The approved product will be marketed under the trademark BYSTOLIC™ in 2.5 mg, 5 mg, and 10 mg tablets for the treatment of hypertension. A copy of the approved package insert for BYSTOLIC™ is attached as Exhibit D. The active ingredient of BYSTOLIC™ has

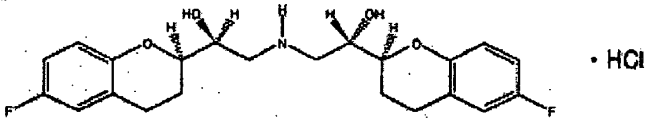
(a) the chemical name (1RS,1'RS)-1,1'-[(2RS,2'SR)-bis(6-fluoro-3,4-dihydro-2H-1-benzopyran-2-yl)]- 2,2'-iminodiethanol hydrochloride;

(b) the generic name nebivolol hydrochloride;

(c) the structural formula:



SRRR - or d-nebivolol hydrochloride



RSSS - or l-nebivolol hydrochloride

(d) the empirical formula $C_{22}H_{25}F_2NO_4 \cdot HCl$; and

(e) a molecular weight of 441.90 g/mol.

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred.

The regulatory review occurred under Section 505(b) of the Federal Food, Drug and Cosmetic Act (FFDCA), which is codified at 21 U.S.C. § 355(b). Section 505(b) (21 U.S.C. § 355(b)) provides for the submission and approval of New Drug Applications (NDAs).

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred.

Nebivolol received permission for commercial marketing from the Food and Drug Administration (FDA) pursuant to Section 505(b) of the FFDCA (21 U.S.C. § 355(b)) on December 17, 2007. A copy of the letter from the FDA approving marketing of nebivolol is attached as Exhibit E.

(4) In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.

The active ingredient in the approved product is nebivolol hydrochloride equivalent to 2.5, 5 and 10 mg of nebivolol base. Nebivolol was not previously approved for commercial marketing or use under the FFDCA, the Public Health Service Act, or the Virus-Serum-Toxin Act prior to the approval on December 17, 2007.

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f) and an identification of the date of the last day on which the application could be submitted.

Nebivolol was approved for commercial marketing on December 17, 2007. The sixty day period expires on Friday, February 15, 2008. The present application, therefore, is timely filed within the sixty day period.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration.

Inventors: Raymond Mathieu XHONNEUX

Guy Rosalia Eugene VAN LOMMEN

Patent No.: 6,545,040

Issue Date: April 8, 2003

Expiration Date: April 8, 2020

(7) A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings.

A copy of the '040 patent is attached as Exhibit A.

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent.

No disclaimers or certificates of correction have been submitted or issued for the '040 patent. A re-examination of the '040 patent was filed on January 26, 2007 and has been assigned Application No. 90/008,356. The re-examination is currently pending.

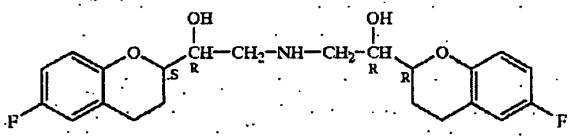
The 3½ year maintenance fee for the '040 patent has been timely paid. A copy of the receipt showing payment of the 3½ year fee is attached as Exhibit F.

(9) A statement that the patent claims the approved product, or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on:

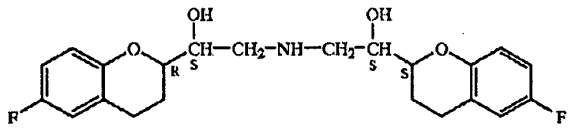
- **(i) The approved product, if the listed claims include any claim to the approved product;**
- **(ii) The method of using the approved product, if the listed claims include any claim to the method of using the approved product; and**
- **(iii) The method of manufacturing the approved product, if the listed claims include any claim to the method of manufacturing the approved product.**

The '040 patent claims pharmaceutical compositions of the approved product, nebivolol. Each applicable patent claim is set forth below together with a showing of the manner in which each applicable patent claim reads on the approved product.

> 2. A pharmaceutical composition consisting of a pharmaceutically acceptable carrier and, as active ingredients: (a) the blood pressure reducing compound [2S, αR, 2'R, α'R]- α, α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol] having the formula:



> or a pharmaceutically acceptable acid addition salt thereof; and (b) the compound [2R, αS, 2'S, α'S]- α, α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol] having the formula:



> or a pharmaceutically acceptable acid addition salt thereof.

Independent claim 2 is directed to pharmaceutical compositions of the approved product, nebivolol. Nebivolol is a racemate composed of [2S, αR, 2'R, α'R]- α, α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol] (*i.e.*, d-nebivolol or [SRRR]-nebivolol) and [2R, αS, 2'S, α'S]- α, α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2H-

1-benzopyran-2-methanol] (*i.e.*, l-nebivolol or [RSSS]-nebivolol). Claim 2 is directed to pharmaceutical compositions consisting of a pharmaceutically acceptable carrier and, as active ingredients: [SRRR]-nebivolol or a pharmaceutically acceptable acid addition salt thereof and [RSSS]-nebivolol or a pharmaceutically acceptable acid addition salt thereof.

> 3. A composition according to claim 2 wherein compound (b) is present in an amount capable of potentiating the activity of the blood pressure reducing compound (a).

The approved product includes [RSSS]-nebivolol in an amount capable of potentiating the activity of [SRRR]-nebivolol.

> 4. A composition according to claim 3 wherein the molar ratio of the compounds (a) and (b) is about 1:1.

The approved product includes [RSSS]-nebivolol and [SRRR]-nebivolol in a molar ratio of about 1:1.

> 5. A method of treating hypertension in warm blooded animals in need of such treatment which comprises administering to said warm blooded animals an effective amount of the pharmaceutical composition of claim 2.

The approved product is indicated for the treatment of hypertension. *See* Exhibit D.

> 6. A method of treating hypertension in warm blooded animals in need of such treatment which comprises administering to said warm blooded animals an effective amount of the pharmaceutical composition of claim 4.

The approved product is indicated for the treatment of hypertension. *See* Exhibit D.

(10) A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic, or human biological product:

(A) The effective date of the investigational new drug (IND) application and the IND number;

(B) The date on which a new drug application (NDA) application or a Product License Application (PLA) was initially submitted and the NDA or PLA number; and

(C) The date on which the NDA was approved or the Product License issued;

The investigational new drug (IND) application for nebivolol was assigned Application No. 33,060. Janssen Research Foundation filed the IND application on April 13, 1989 (Exhibit G). The IND was placed on clinical hold and inactivated on July 20, 1994 (Exhibit H). Janssen Research Foundation transferred the IND to Mylan Laboratories Inc. ("Mylan") effective as of May 1, 1998 (Exhibit I). On June 6, 2000, the FDA received a letter from Mylan to re-activate the IND. (Exhibit J). The IND became effective on July 6, 2000; thirty days after the FDA received the re-activation request from Mylan. *See* 21 U.S.C. § 355(i)(2).

The NDA for nebivolol hydrochloride, NDA 21-742, was submitted to the FDA on April 29, 2004 (Exhibit K).

NDA 21-742 was approved by the FDA on December 17, 2007 (Exhibit E).

(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.

Janssen Research Foundation submitted an IND application for nebivolol on April 13, 1989 (Exhibit G). The IND (No. 33,060) was placed on clinical hold and inactivated on July 20, 1994 (Exhibit H).

Janssen Research Foundation transferred ownership of the IND to Mylan Laboratories Inc. ("Mylan") as of May 1, 1998 (Exhibit I). On June 6, 2000, the FDA received a letter from Mylan to re-activate the IND (Exhibit J). 21 U.S.C. § 355(i)(2) provides that clinical investigation of a drug may begin thirty days after receipt of the IND application by the FDA. The IND therefore became effective on July 6, 2000.

After the re-activated IND became effective, Mylan and its wholly owned subsidiary Bertek Pharmaceuticals Inc. ("Bertek") began investigation of nebivolol. The studies referenced in the IND were begun and the FDA was notified of Protocol Amendments and amendments to the Chemistry, Manufacturing and Control Sections and Pharmacology Sections of the IND. Mylan also submitted the required information about investigators, and the required 15-day alert reports.

On April 29, 2004, Bertek submitted an NDA for nebivolol, which was assigned number 21-742 (Exhibit K). The NDA was approved on December 17, 2007 (Exhibit E). Mylan transferred ownership of the NDA to Forest on December 17, 2007. Exhibit L provides the chronology of regulatory review of nebivolol.

(12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of the extension claimed, including how the length of the extension was determined.

It is the opinion of the Applicant that the '040 patent is eligible for patent term extension under 35 U.S.C. § 156(a). The Applicant claims an extension of 619 days.

Statement of Eligibility of the Patent for Extension

Under 35 U.S.C. § 156(a)

Section 156(a) provides in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an application for extension is submitted; (2) the term of the patent has never been extended under 35 U.S.C. § 156(e)(1); (3) the application for extension is submitted by the owner of record of the patent or its agent and in accordance with 35 U.S.C. § 156(d)(1)-(4); (4) the product has been subject to a regulatory review period before its commercial marketing or use; and (5) except for 35 U.S.C. §§ 156(a)(5)(B) and 156(a)(5)(C), the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred.

Each of these elements is satisfied here:

(1) The term of the '040 patent expires on April 8, 2020. This application has, therefore, been submitted before the expiration of the patent term.

(2) The term of the '040 patent has never been extended under 35 U.S.C. § 156(e)(1).

(3) The application is submitted by Michael Ciraolo, an attorney for Forest, which has been appointed under a limited power of attorney to act for the owner of the '040 patent for the purpose of filing this Request. This application is submitted in accordance with 35 U.S.C. § 156(d) within the sixty-day period beginning December 17, 2007 when the product received permission for marketing under the FFDCA and contains the information required under 35 U.S.C. §§ 156(d)(1)(A)-(E).

(4) The product was the subject of IND 33,060 (filed on April 13, 1989; inactivated on July 20, 1994; re-activated effective on July 6, 2000), and NDA 21-742 (filed on April 29, 2004 and approved on December 17, 2007). Thus, the product was subject to a regulatory review period under § 505(b) of the FFDCA before its commercial marketing or use.

(5) Finally, the permission for the commercial marketing of the approved product after regulatory review under FFDCA § 505(b) is the first permitted commercial marketing of the approved product in the United States. This is confirmed by the absence of any approved NDA under which the approved product could be commercially marketed prior to December 17, 2007.

Statement as to the Length of the Extension Claimed

In Accordance with 37 C.F.R. 1.775

The term of the '040 patent should be extended by 619 days. The extension was determined according to 37 C.F.R. § 1.775 and the PTO worksheet "Calculation of Length for Patent Term Extension for a Human Drug Product" as follows:

(1)	1393	The number of days in the period beginning on the effective date of the IND (July 6, 2000) and ending on the date the NDA was initially submitted (April 29, 2004). This is the "testing phase" as defined in 37 C.F.R. § 1.775(c)(1).

(2)	1328	The number of days in the period beginning on the date the NDA was initially submitted (April 29, 2004) and ending on the date of NDA approval (December 17, 2007). This is the "approval phase" as defined in 37 C.F.R. § 1.775(c)(2).
(3)	2721	The sum of (1) and (2). This is the regulatory review period as define in 37 C.F.R. § 1.775(c).
(4)	0	The number of days in the approval phase (2) which were on and before issuance of the '040 patent. 37 C.F.R. § 1.775(d)(1)(i).
(5)	0	The number of days in the approval phase (2) during which the Applicant did not act with due diligence. 37 C.F.R. § 1.775(d)(1)(ii).
(6)	0	The sum of (4) and (5).
(7)	2721	The difference between the regulatory review period (3) and (6). 37 C.F.R. § 1.775(d)(1)(ii).
(8)	1006	The number of days of the period of the testing phase (1) which occurred prior to the issuance of the '040 patent. 37 C.F.R. § 1.775(d)(1)(i).
(9)	0	The number of days of the period of the testing phase (1) during which the Applicant failed to act with due diligence 37 C.F.R. § 1.775(d)(1)(ii).
(10)	1006	The sum of (8) and (9).
(11)	1715	The difference between the regulatory review period (7) and (10).
(12)	1393	The number of days of the testing phase (1).
(13)	1006	The number of days from (10).
(14)	387	Subtract line (13) from line (12)
(15)	193	One half of (14) 37 C.F.R. § 1.775(d)(1)(iii)[1]
(16)	1522	Subtract line (15) from line (11)
(17)	April 8, 2020	The original expiration date of the '040 patent.
(18)	June 8, 2024	The expiration date of the '040 patent if the original expiration date is extended by the number of days in line (16). 37 C.F.R. § 1.775(d)(2)
(19)	December 17, 2007	The date of approval of the application under § 505(b) of the FFDCA.

[1] 37 C.F.R. § 1.775(d)(1) provides that for purposes of subtraction, half days are ignored.

(20)	14 years	The limitation of 37 C.F.R. § 1.775(d)(3).
(21)	December 17, 2021	The number of years in (20) plus the date on (19). 37 C.F.R. § 1.775(d)(3).
(22)	December 17, 2021	The earlier of line (18) or line (21)
(23)	April 8, 2020	The original expiration date of the '040 patent.
(24)	5 years	The applicable limitation of 37 C.F.R. § 1.775(d)(5)
(25)	April 8, 2025	The number of years on (24) plus the date on (23).
(26)	December 17, 2021	The earlier of line (22) or line (25)
(27)	April 8, 2020	The original expiration date of the '040 patent
(28)	619	The number of days which is the difference between the date on line (27) and the date on line (26)

(13) A statement that the Applicant acknowledges a duty to disclose to the Commission of Patents and Trademarks and to the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and to the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought for the '040 patent by this Request as required by 37 C.F.R. § 1.765.

(14) Prescribed Fee:

Please charge the required fee of $1,120.00 as required under 37 C.F.R. § 1.20(j)(1) to Deposit Account No. 503899. The Commissioner is authorized to charge any additional fees to Deposit Account No. 503899.

(15) The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed

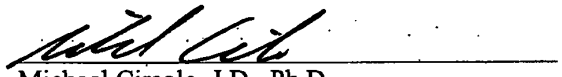
Charles Ryan
Forest Laboratories, Inc.
909 Third Avenue
New York, New York 10022
(212) 224-6633
(212) 750-9152 (fax)

In view of the foregoing, Forest, acting under limited power of attorney for the patent owner Janssen Pharmaceutica N.V., requests that the Commissioner grant an extension of 619 days to U.S. Patent No. 6,545,040.

Favorable action is earnestly solicited.

Dated: February 14, 2008

Respectfully submitted,



Michael Ciraolo, J.D., Ph.D.
Registration No.: 58,294

Forest Laboratories, Inc.
48 Mall Drive
Commack, New York 11725
(631) 858-7365
(631) 858-7441 (fax)
Attorney for Applicant

List of Exhibits

Exhibit A - U.S. Patent No. 6,545,040

Exhibit B - Assignment of the '040 patent from the inventors to Janssen

Exhibit C - Limited Power of Attorney authorizing Forest to act on behalf of Janssen

Exhibit D - Approved package insert for BYSTOLIC™

Exhibit E - FDA Approval Letter

Exhibit F - Receipt showing payment of the 3½ year maintenance fee for the '040 patent

Exhibit G - Letter dated April 13, 1989 submitting IND 33,060

Exhibit H - Letter dated July 20, 1994 inactivating IND 33,060

Exhibit I - Letter dated April 22, 1998 informing FDA of transfer of IND 33,060

Exhibit J - Letter from FDA acknowledging June 6, 2000 submission to reactivate IND 33,060

Exhibit K - Letter dated April 29, 2004 submitting NDA 21-742 to FDA

Exhibit L - Chronology of Regulatory Review of BYSTOLIC™

US006545040B1

(12) **United States Patent**
Xhonneux et al.

(10) **Patent No.: US 6,545,040 B1**
(45) **Date of Patent: Apr. 8, 2003**

(54) **METHOD OF LOWERING THE BLOOD PRESSURE**

(75) Inventors: **Raymond Mathieu Xhonneux**, Vlimmeren (BE); **Guy Rosalia Eugène Van Lommen**, Berlaar (BE)

(73) Assignee: **Janssen Pharmaceutica N.V.** (BE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **07/825,488**

(22) Filed: **Jan. 24, 1992**

Related U.S. Application Data

(63) Continuation of application No. 07/325,181, filed on Mar. 16, 1989, now abandoned, which is a continuation-in-part of application No. 07/172,747, filed on Mar. 23, 1988, now abandoned.

(51) **Int. Cl.**[7] **A61K 31/35**; A61K 31/335; A61K 31/18

(52) **U.S. Cl.** **514/451**; 514/452; 514/602

(58) **Field of Search** 514/451, 452, 514/602

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,654,362 A 3/1987 Van Lommen et al. 514/452

OTHER PUBLICATIONS

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Van de Water 110 CA:50943v 1988.*
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Van de Water, A., et al., Pharmacological and Hemodynamic Profile of Nebivolol, A Chemmically Novel, Potent, and Selective β1–adrenergic Antagonist, J. Cardiovasc. Pharmacol, 1988 Abstract.
Van de Water, A., et al., The Cardiac and Haemodynamic Effects of Cumulative Intravenous Injections of R 65 825 in Closed–Chest Anaesthetized Mongrel Dogs, Janssen Research Products Information Service, Mar. 1985.

(List continued on next page.)

Primary Examiner—Russell Travers

(57) **ABSTRACT**

A method of potentiating the effects of blood pressure reducing agents in warm-blooded animals, said method comprising administering to said warm-blooded animals of an effective amount of a blood pressure reducing agent and a 2,2'-iminobisethanol derivative.

6 Claims, No Drawings

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METHOD OF LOWERING THE BLOOD PRESSURE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of our application Ser. No. 07/325,181, filed on Mar. 16, 1989, (now abandoned) which in turn was a continuation-in-part of application Ser. No. 07/172,747, filed on Mar. 23, 1988 now abandoned.

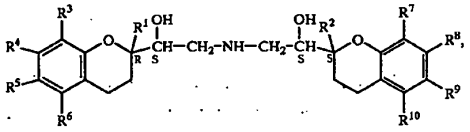
BACKGROUND OF THE INVENTION

In U.S. Pat. No. 4,654,362 there are described 2,2'-iminobisethanol derivatives having β adrenergic blocking properties. It now has been found that a certain class of isomers of said bisethanol derivatives potentiate the activity of blood pressure reducing agents.

DESCRIPTION OF THE INVENTION

The present invention is concerned with a group of compounds capable of potentiating the effects of blood pressure reducing agents, said compounds being represented by the formula

(I)



or the pharmaceutically acceptable acid addition salts thereof, wherein

R^1 and R^2 each independently are hydrogen or C_{1-6}alkyl;

R^3, R^4, R^5, R^6, R^7, R^8, R^9 and R^{10} each independently are hydrogen, halo, C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxy, cyano, carboxy or C_{1-6}alkyloxycarbonyl; or two vicinal radicals of R^3, R^4, R^5, R^6, R^7, R^8, R^9 and R^{10} taken together may form a —CH=CH—CH=CH— or $—(CH_2)_4—$ radical.

As used in the foregoing definitions the term halo is generic to fluoro, chloro, bromo and iodo; the term "C_{1-6}alkyl" defines straight and branch chained saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as, for example, methyl, ethyl, 1-methylethyl, 1,1-dimethylethyl, propyl, 2-methylpropyl, butyl, pentyl, hexyl and the like.

The descriptors R and S as used in the above formula (I) indicate the absolute configuration at the respective carbon atoms. The carbon atom bearing R^1 has the R configuration, whereas the carbon atoms bearing the hydroxy functions and the carbon atoms bearing R^2 have the S configuration.

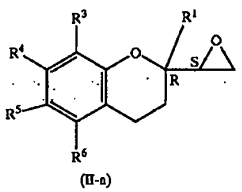
Preferred compounds of formula (I) are those wherein R^3, R^4, R^6, R^7, R^8, and R^{10} are hydrogen.

Particularly preferred are those preferred compounds wherein R^5 and R^9 are hydrogen or halo, particularly fluoro.

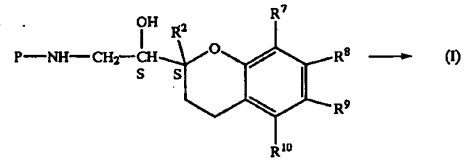
The most preferred compound is [2R,αS,2'S,αS]-α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol] or a pharmaceutically acceptable acid addition salt thereof.

The compounds of formula (I) can be prepared following the procedures described in U.S. Pat. No. 4,654,362. Some particular ways of obtaining the compounds of formula (I) will be described hereinafter in some more detail.

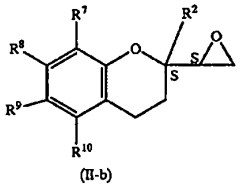
The compounds of formula (I) can be prepared by reacting an oxirane of formula (II-a) or (II-b) with an amine of formula (III-a) or (III-b).



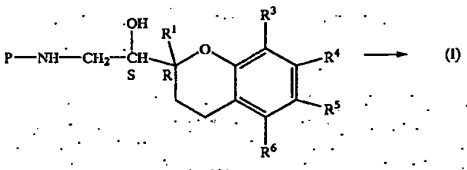
(II-a)



(III-a)



(II-b)



(III-b)

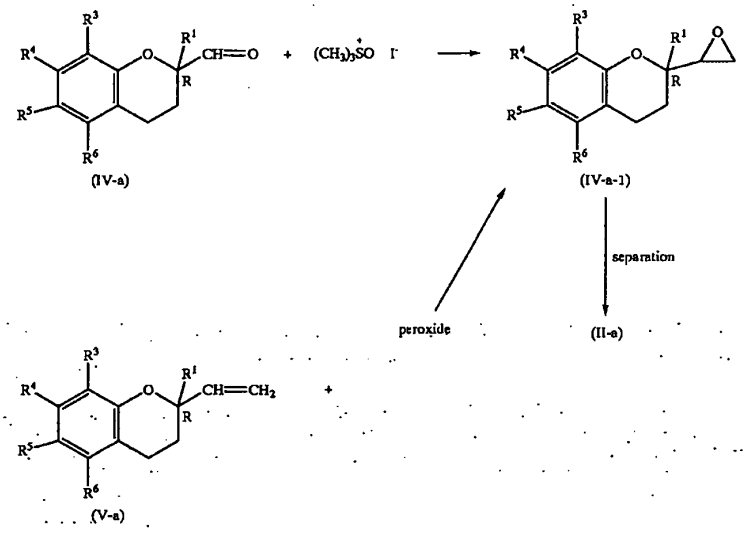
In (III-a) and (III-b), P is either hydrogen or an appropriate protecting group, for example an allyl group, or in particular P may be a benzyl group. Or, a reagent $P—NH_2$ may be reacted with (II-a) and (II-b) in a one-pot procedure. The above described reactions to prepare a compound of formula (I) may be conducted in a reaction-inert solvent such as, for example, an aromatic hydrocarbon, e.g. benzene or methylbenzene; an alkanol, e.g. methanol, ethanol, propanol; a ketone, e.g. 2-propanone, 4-methyl-2-pentanone; an ether, e.g. 1,4-dioxane, tetrahydrofuran, 1,1'-oxybisethane; a dipolar aprotic solvent, e.g. N,N-dimethylformamide or N,N-dimethylacetamide and the like solvents. In certain instances, in order to increase the reaction rate, it may be appropriate to heat the reaction mixture.

If in the above reactions P is other than hydrogen, the N-protected derivatives of formula (I) are obtained wherefrom the compounds of formula (I) themselves can be obtained by a deprotection reaction. For example, where P is allyl, by reaction with an appropriate noble metal compound such as $PdCl_2$ or $Rh[P(C_6H_5)_3]Cl$, or where P is benzyl, by a catalytic hydrogenation procedure, e.g. palladium or platinum on charcoal in a suitable solvent such as an ether, e.g. 1,4-dioxane, tetrahydrofuran, an alkanol, e.g. methanol, ethanol, an alkoxyalkanol, e.g. methoxyethanol and the like.

The intermediates of formula (II-a) or (III-b) are obtained by the reaction of the amine $P\text{-}KH_2$ with (II-b) or (II-a) or, by reacting a reagent P_2NH, for example dibenzylamine, with (II-b) or (II-a) and subsequently selectively removing one of the P-groups, e.g. when P is benzyl by a catalytic

hydrogenation procedure using one equivalent hydrogen. The afore described reactions to prepare (III-a) or (III-b) are conducted following the same procedures as described hereinabove for the preparation of the compounds (I).

The starting materials (II-a) are obtained by an oxirane formation reaction from an aldehyde of formula (IV-a), e.g. by reaction of the latter with a trimethylsulfoxonium halide, or from an ethylene of formula (V-a) by reaction of the latter with a peroxide, e.g. a haloperbenzoic acid. In the same way, the intermediate (II-b) is obtained from the corresponding S-isomers (IV-b) or (V-b). The oxiranes of formula (IV-a-1) obtained in the aforementioned oxirane-formation reaction are separated in their stereoisomers, e.g. by HPLC or selective crystallization.



The compounds of formula (IV-a), (IV-b), (V-a) or (V-b) are obtained by a suitable separation procedure, i.e. by HPLC, or by a reduction reaction of the corresponding optically active racemic acids whereas (IV-a) or (IV-b) can be converted to (V-a) or (V-b) by a Wittig reaction. The said corresponding optically active acids in turn can be obtained by conventional separation techniques, i.e. by salt or amide formation with an optically active reagent and a selective crystallization procedure or a HPLC separation.

The compounds of formula (I) have basic properties and, consequently, they may be converted to their therapeutically active non-toxic acid addition salt forms by treatment with appropriate acids, such as, for example, inorganic acids, such as hydrohalic acid, e.g. hydrochloric, hydrobromic and the like, and sulfuric acid, nitric acid, phosphoric acid and the like; or organic acids, such as, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propane-tricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids.

Conversely, the salt form can be converted by treatment with alkali into the free base form.

The compounds of formula (I) with the exception of (RSSS)-α,α'-[iminobis(methylene)bis(3,4-dihydro-2H-1-benzopyran-2-methanol] ethanedioate(1:1) are deemed to be novel compounds and constitute in an additional feature to the present invention.

The compounds of formula (I) and the pharmaceutically acceptable acid addition salts thereof potentiate the activity of blood pressure reducing agents. In particular they potentiate the reduction of the blood pressure and of the heart rate.

As blood pressure reducing agents of which the activity is potentiated there may be mentioned agents having adrenergic and/or vasodilating activity. In particular such agents may be the compounds mentioned in U.S. Pat. Nos. 3,663,607 and 3,836,671, in particular atenolol; U.S. Pat. Nos. 3,337,628 and 3,520,919, in particular propranolol; U.S. Pat. No. 3,873,600, in particular metoprolol; U.S. Pat. No. 3,511,836, in particular prazosin; U.S. Pat. No. 2,484,029, in particular hydralazine; U.S. Pat. No. 2,928,829 in particular guanethidine; U.S. Pat. No. 2,503,059, in particular phentolamine; U.S. Pat. No. 3,261,859, in particular verapamil; U.S. Pat. No. 3,485,847 in particular nifedipine; U.S. Pat. No. 3,910,924, in particular carteolol; German Pat. Nos. 2,458,624 and 2,458,625, in particular celiprolol. A particular group of blood pressure reducing compounds are the compounds of U.S. Pat. No. 4,654,362 other than the compounds of formula (I) and in particular the enantiomers of the compounds of formula (I), i.e. the SRRR-isomers. A particular compound is [2S,αR,2'R,α'R]-α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol. These groups of active ingredients are listed with the purpose of providing representative examples but not with the purpose of restricting the scope of the present invention. The said SRRR isomers and the said particular compound can be prepared following the same procedures as previously described for the preparation of the compounds of formula (I), but starting from the enantiomers of the intermediates (II-a), (III-a), (II-b) and (III-b). The latter enantiomers in turn can be obtained as described hereinabove for the preparation of (II-a), (III-a), (II-b) and

(III-b), but starting from the enantiomers of (IV-a) or (V-a) and isolating the appropriate stereoisomers in stereochemical separation procedures. The enantiomers of (IV-a) and (V-a) in the same way can be obtained as described for the preparation of (IV-a) and (V-a) starting from the appropriate enantiomeric starting materials and/or isolating the appropriate stereoisomers in stereochemical separations.

The compounds of formula (I) and the acid addition salts thereof may be administered before, during or after the administration of the blood pressure reducing agent provided that the time of the administration of the compounds of formula (I) in relation to the administration of the blood pressure reducing agent allows the compound of formula (I) to be effective in potentiating the effects of the blood pressure reducing agent. Preferably the compound of formula (I) and the blood pressure reducing agent are administered in the form of suitable compositions. Said compositions are meant to also comprise products containing a compound of formula (I) as defined hereinabove and a blood-pressure reducing agent as a combined preparation for simultaneous, separate or sequential use in blood-pressure reducing therapy. Such products may for example comprise a kit comprising a container with a suitable composition containing a compound of formula (I) and another container containing a composition with a blood pressure reducing agent. Such product may have the advantage that the physician wishing to administer blood pressure reducing therapy can select, based on the diagnosis of the patient to be treated, the appropriate amounts of both components and the sequence of administration.

When administered during the administration of the blood pressure reducing agent, a composition containing both the blood pressure reducing agent and the active ingredient of formula (I) may particularly be convenient.

In a further aspect of the present invention there is provided a composition comprising an amount capable of potentiating the effects of blood pressure reducing agents of a compound of formula (I) as defined hereinabove and a blood pressure reducing agent. In the said composition, the molar ratio between the compound of formula (I) and the blood pressure reducing agent may be other than 1:1, but in particular may be 1:1. The amount of the active ingredient of formula (I) in such composition will be so that a potentiating effect on the effects of the blood-pressure reducing agent is obtained; the amount of the blood pressure reducing agent will be so that when potentiated, a blood pressure reducing effect is obtained upon administration. In particular, it is contemplated that the molar ratio of the compound of formula (I) to the blood pressure reducing compound may be situated between 50:1 and 1:50, in particular between 20:1 and 1:20, or between 10:1 and 1:10, or between 5:1 and 1:5, more particularly between 2:1 and 1:2. Particular such compositions are those wherein the blood pressure reducing agent is one of the agents pertaining to the patents cited hereinabove, and more particularly the agents specifically mentioned hereinabove.

The present invention also provides a composition comprising a pharmaceutically acceptable carrier and as active ingredient an amount capable of potentiating the effects of blood pressure reducing agents of a novel compound of formula (I) or a pharmaceutically acceptable acid-addition salt thereof, as defined hereinabove.

To prepare such pharmaceutical compositions, an effective amount of the particular compound or compounds, in base or acid-addition salt form, as the active ingredient or active ingredients is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause a significant deletorious effect to the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment. Acid addition salts of (I) due to their increased water solubility over the corresponding base form, are obviously more suitable in the preparation of aqueous compositions.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

The present invention also concerns a method of potentiating the effects of blood pressure reducing agents in warm-blooded animals in need of blood pressure reducing medication, said method comprising administering to said warm-blooded animals of an effective amount of a blood pressure reducing agent and a compound of formula (I) as defined hereinabove.

Or alternatively, the present invention concerns a method of lowering the blood pressure in warm-blooded animals suffering therefrom, said method comprising administering to said warm-blooded animals of an effective amount of a blood pressure reducing agent and a compound of formula (I) as defined hereinabove.

Those of skill in treating subjects suffering from an increased blood pressure could easily determine the effective amount from the test results presented hereinafter. In general it is contemplated that an effective daily dose of the compounds of formula (I) or their pharmaceutically acceptable acid-addition salts would be from 0.01 mg/kg to 50 mg/kg

body weight, in particular from 0.1 mg/kg to 10 mg/kg body weight and preferably from 0.1 mg/kg to 1 mg/kg body weight.

All above cited references are incorporated herein by reference.

The following examples are intended to illustrate and not to limit the scope of the present invention in all its aspects. Unless otherwise stated all parts therein are by weight.

Whenever used in the following examples "A" refers to the isomer which was first isolated and "B" to the one which was subsequently isolated.

Experimental Part

A. Preparation of the Intermediates

EXAMPLE 1

a) A mixture of 63.4 parts of 6-fluoro-4-oxo-4H-1-benzopyran-2-carboxylic acid and 400 parts of acetic acid was hydrogenated at normal pressure and at room temperature with 3 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was stirred in petroleumether. The product was filtered off and dried in vacuo at 70° C., yielding 49 parts (83%) of 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid (int. 1).

b) To a stirred solution of 9.75 parts of intermediate 1 in 90 parts of methylbenzene were added 16 parts of thionyl chloride. The mixture was stirred for 2 hours at 60° C. The reaction mixture was evaporated. The residue was taken up twice in 45 parts of methylbenzene and the latter was evaporated each time. The residue was taken up in 90 parts of methylbenzene. There were added first 10.5 parts of N,N-diethylethanamine and then a solution of 14.25 parts of (+)-1,2,3,4,4a,9,10,10a-octa-hydro-1,4a-dimethyl-7-(1-methylethyl)-1-phenanthrenemethanamine [(+)-dehydroabiethylamine] in 45 parts of methylbenzene. After stirring for 2 hours, the organic layer was washed successively with water, a sodium hydroxide solution 10%, a hydrochloric acid solution 10% and water, dried, filtered and evaporated. The residue was taken up in 120 parts of warm ethanol. The product was filtered off and crystallized from ethanol, yielding 6.6 parts (28.4%) of (A)-6-fluoro-3,4-dihydro-N-[dehydroabiethyl]-2H-1-benzopyran-2-carboxamide (int. 2).

c) A mixture of 6.8 parts of intermediate 2, 75 parts of acetic acid and 36 parts of concentrated hydrochloric acid was stirred for 24 hours at reflux temperature. After cooling, the reaction mixture was poured into water. The product was extracted with 1,1'-oxybisethane. The extract was washed twice with water, dried, filtered and evaporated. The residue was taken up in 1,1'-oxybisethane. 5 Parts of a sodium hydroxide solution were added. The product was filtered off, taken up in trichloromethane and treated with 50 parts of a hydrochloric acid solution 10%. The organic layer was dried, filtered and evaporated, yielding 1.1 parts of (+)-(S)-6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid; mp. 99.7° C. $[\alpha]_D^{25}$=+14.88° (c=1% in DMF) (int. 3).

d) To a stirred solution of 22.5 parts of intermediate 3 in 180 parts of tetrahydrofuran were added 18.7 parts of 1,1'-carbonylbis[1H-imidazole]. The whole was stirred for 1 hour at room temperature and cooled to −70° C. 136 Parts of a 25% solution of [bis(2-methylpropyl)]aluminum hydride in methylbenzene were added dropwise during a period of 20 minutes. Upon completion, stirring was continued for 20 minutes at −70° C. 40 Parts of methanol were added and the mixture was poured into water. The product was extracted with 1,1'-oxybisethane. The extract was washed successively with a hydrochloric acid solution 10%, water and a sodium hydrogen carbonate solution, dried, filtered and evaporated, yielding 12 parts (57.9%) of (+)-(S)-6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxaldehyde as an oily residue (int. 4).

e) 6.3 Parts of a sodium hydride dispersion 50% were washed twice with petroleum ether and then taken up in 250 parts of dimethyl sulfoxide. 29 Parts of trimethylsulfoxonium iodide were added during a period of 30 minutes and stirring was continued for 20 minutes. A solution of 12 parts of intermediate 4 in 10 parts of dimethyl sulfoxide was added dropwise and upon completion, the mixture was stirred for 30 minutes. The reaction mixture was poured into water and the product was extracted with 1,1'-oxybisethane. The extract was washed three times with water, dried, filtered and evaporated. The residue was purified by column chromatography (HPLC) over silica gel using a mixture of methylbenzene and ethyl acetate (90:10 by volume) as eluent. The pure fractions were collected and the eluent was evaporated, yielding 2.1 parts (9.8%) of (+)-[S(S)]-6-fluoro-3,4-dihydro-2-oxiranyl-2H-1-benzopyran as an oily residue (int. 5).

EXAMPLE 2

a) In the procedure described hereinabove in example 1b) 6.1 parts (26.3%) of the compound (B)-6-fluoro-3,4-dihydro-N-[dehydroabiethyl]-2H-1-benzopyran-2-carboxamide (int. 6) was obtained as a residue.

b) A mixture of 6.1 parts of intermediate 6, 75 parts of acetic acid and 36 parts of concentrated hydrochloric acid was stirred for 24 hours at reflux temperature. The reaction mixture was poured into water. The product was extracted with 1,1'-oxybisethane. The extract was washed twice with water, dried, filtered and evaporated in vacuo. The residue was crystallized from petroleum ether. The product was filtered off and dried, yielding 0.9 parts of (−)-(R)-6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid; mp. 102.5° C. $[\alpha]_D^{25}$=−13.39° (c=1% in DMF) (int. 7).

c) To a stirred and refluxed solution of 36 parts of intermediate 7 in 400 parts of methanol were added 1.8 parts of sulfuric acid. The mixture was further and refluxed for 4 hours. After cooling, the reaction mixture was evaporated. The residue was taken up in 1,1'-oxybisethane. The mixture was washed successivily twice with a sodium hydrogen carbonate solution and once with water, dried, filtered and evaporated, yielding 33 parts (82.6%) of (−)-(R)-methyl 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxylate as an oily residue (int. 8).

d) To a stirred and cooled (−80° C.) solution of 33 parts of intermediate 8 in 450 parts of methylbenzene were added dropwise 255 parts of a solution of [bis(2-methylpropyl)] aluminium hydride in methylbenzene under nitrogen atmosphere. Stirring was continued for 30 minutes at −80° C. 16 Parts of methanol were added and the reaction mixture was poured into water. The mixture was acidified with hydrochloric acid and the two layers were separated. The organic phase was dried, filtered and evaporated, yielding an oily residue of 32 parts (the residue was set aside). 9.6 Parts of a sodium hydride dispersion 50% were washed first three times with petroleumether and then taken up in 500 parts of dimethyl sulfoxide. 44 parts of trimethylsulfoxonium iodide were added portionwise and after complete addition, the whole was stirred for 20

minutes at room temperature. To the thus obtained mixture was added dropwise a solution of 32 parts of the oily residue, which was set aside (see above), in 20 parts of dimethyl sulfoxide. Upon completion, stirring was continued for 20 minutes at room temperature. The whole was poured into water and the product was extracted with 2,2'-oxybispropane. The extract was dried, filtered and evaporated. The residue was separated by column chromatography (HPLC) over silica gel using a mixture of hexane and ethyl acetate (80:20 by volume) as eluent. The desired fractions were collected and the eluent was evaporated, yielding 8.2 parts (24.8%) of (−)-[R(S)]-6-fluoro-3,4-dihydro-2-oxiranyl-2H-1-benzopyran as a residue (int. 9).

e) A solution of 8.2 parts of intermediate 9 and 20 parts of benzenemethanamine in 80 parts of methanol was stirred overnight at room temperature. The reaction mixture was evaporated and the residue was taken up in 2,2'-oxybispropane. The precipitated product was filtered off and crystallized from acetonitrile. The product was filtered off and dried, yielding 4.6 parts (38.1%) of (−)-[R(S)]-6-fluoro-3,4-dihydro-α-[[(phenylmethyl)amino]methyl]-2H-1-benzopyran-2-methanol (int. 10).

B. Preparation of the Final Compounds

EXAMPLE 3

a) A solution of 1.8 parts of intermediate 5 and 2 parts of intermediate 10 in 40 parts of ethanol was stirred for 4 hours at reflux temperature. The reaction mixture was evaporated, yielding 3.5 parts (100%) of [2R,αS,2'S,α'S]-α,α'-[[(phenylmethyl)imino]bismethylene]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol] as a residue (int. 11).

b) A mixture of 3.5 parts of intermediate 11 and 250 parts of 2-methoxyethanol was hydrogenated at normal pressure and at room temperature with 2 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was taken up in trichloromethane and purified by column chromatography over silica gel using trichloromethane as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized twice from acetonitrile. The product was filtered off and dried, yielding 1.2 parts (42%) of [2R,αS,2'S,α'S]-α,α'-iminobismethylene]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol]; mp. 142.7° C. (compound 1).

EXAMPLE 4

A mixture of 19.4 parts of (RS,SS)-α,α'-[[(phenylmethyl)imino]bis(methylene)bis[3,4-dihydro-2H-1-benzopyran-2-methanol], prepared as described in U.S. Pat. No. 4,654,362 (see compound 16 in the experimental part of the latter; the designation "A⁻B⁺ referring to the RSSS isomer) and 243 parts of 2-methoxyethanol was hydrogenated at normal pressure and at room temperature with 2 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the reaction mixture was filtered over diatomaceous earth and evaporated. The residue was crystallized twice from acetonitrile, yielding 6.8 parts (43.8%) of (RS,SS)-α,α'-[iminobis(methylene)]bis[3,4-dihydro-2H-1-benzopyran-2-methanol]; mp. 136.1° C. (compound 2).

EXAMPLE 5

A mixture of 6 parts of intermediate 10, 5 parts of (SS)-3,4-dihydro-2-oxiranyl-2H-1-benzopyran, prepared as described in example 17 of U.S. Pat. No. 4,654,362 (intermediate 53, the designation "B⁺" referring to the SS-isomer) and 119 parts of ethanol was refluxed for 18 hours. The reaction mixture was evaporated and the residue was added to 275 parts of 2-methoxyethanol and hydrogenated at normal pressure and at room temperature with 2 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was crystallized from acetonitrile, yielding 3.8 parts (49.3%) of (RSSS)-α-[[[2-(3,4-dihydro-2H-1-benzopyran-2-yl)-2-hydroxyethyl]amino]methyl]-6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol; mp. 154.2° C. (compound 3).

EXAMPLE 6

Following the same procedures as described in example 5 and starting from (SS)-6-fluoro-3,4-dihydro-α-[[(phenylmethyl)amino]methyl]-2H-1-benzopyran-2-methanol (obtained from the reaction of intermediate 5 with benzenemethanamine) and (SR)-3,4-dihydro-2-oxiranyl-2H-1-benzopyran (obtained as described in example 17, compound 52 of U.S. Pat. No. 4,654,362; the designation "A⁻" referring to the SR isomer) there was also prepared (SSSR)-α-[[[2-(3,4-dihydro-2H-1-benzopyran-2-yl)-2-hydroxyethyl]amino]-methyl]-6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol; mp. 140.7° C. (compound 4).

C. Pharmacological Examples

Adult spontaneous hypertensive rats (6 months of age) were anesthetized by ether inhalation. The femoral artery was dissected and cannulated, and the catheter was connected to a strain-gauge blood pressure transducer. When the animals were fully awake, they were restrained and the systolic and diastolic arterial blood pressure were continuously recorded. An observation period of at least 30 min preceded the administration of the test compound. All test compounds were dissolved in 20% polypropylene glycol and injected intraperitoneally. After administration of the test drug the systolic and diastolic arterial blood pressure and the heart rate were recorded during a period of 120 minutes. The average blood pressure and heart rate was calculated from the results obtained at various time intervals after administration of the test drug. The following table illustrates the difference between treated and untreated animals expressed as a percentage (Δ%) in the systolic and diastolic blood pressure and the heart rate.

Δ% Changes (average 120 min) in systolic and diastolic (SBP, DBP) and in heart rate (HR) in spontaneous hypertensive rats

	-	Hydralazine	Guanethidine	Phentolamine
	1.25 mpk	0.63 mpk	2.5 mpk	0.63 mpk
SBP	0	−7.5	−9.3	−9.85
DBP	+2.1	−9.9	−6.2	−13.1
HR	0.5	−1.45	−7.9	+5.1

	Hydralazine 0.63 mpk + * 1.25	Guanethidine 2.5 mpk + * 1.25	Phentolamine 0.63 mpk + * 1.25
SBP	−20.9	−15.7	−16.7

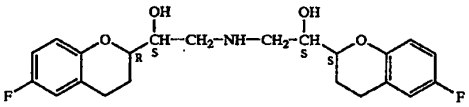
-continued

DBP		−28	−16.7	−21.2	
HR		−3.6	−17.6	+0.9	
	* 2.5 mpk	Atenolol 10 mpk	Propranolol 5 mpk	Metoprolol 10 mpk	Prazosin 0.01 mpk
SBP	−7	−3.7	−2	−1.2	−10.9
DBP	0	+5.9	+12.4	+12.8	−11.3
HR	0	−28.1	−20.7	−16.6	+1.6
		Atenolol 10 mpk + * 2.5	Propranolol 5 mpk + * 2.5	Metoprolol 10 mpk + * 2.5	Prazosin 0.01 mpk + * 2.5
SBP		−21	−9.6	−12.7	−27.6
DBP		−21	+3.2	−4	−28.7
HR		−32	−33.1	−28.25	−6.8

* = [2R,αS,2'S,α'S]-α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol]. (compound 1).

What is claimed is:

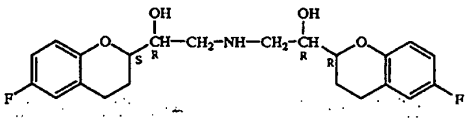
1. A composition consisting of the compound [2R,αS,2'S,α'S]-α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol] having the formula:



or a pharmaceutically acceptable acid addition salt thereof.

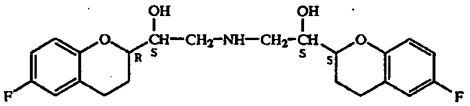
2. A pharmaceutical composition consisting of a pharmaceutically acceptable carrier and, as active ingredients:

(a) the blood pressure reducing compound [2S,αR, 2'R, α'R]-α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol] having the formula:



or a pharmaceutically acceptable acid addition salt thereof; and

(b) the compound [2R,αS,2'S,α'S]-α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol] having the formula:



or a pharmaceutically acceptable acid addition salt thereof.

3. A composition according to claim 2 wherein compound (b) is present in an amount capable of potentiating the activity of the blood pressure reducing compound (a).

4. A composition according to claim 3 wherein the molar ratio of the compounds (a) and (b) is about 1:1.

5. A method of treating hypertension in warm blooded animals in need of such treatment which comprises administering to said warm blooded animals an effective amount of the pharmaceutical composition of claim 2.

6. A method of treating hypertension in warm blooded animals in need of such treatment which comprises administering to said warm blooded animals an effective amount of the pharmaceutical composition of claim 4.

* * * * *

JAB 600
Joint Inventors

ASSIGNMENT

U.S.A.

Serial No......
Filed:.....

WHEREAS, Raymond Mathieu Xhonneux, citizen of Belgium, residing at Hei-ende 58, B-2151-Vlimmeren, Belgium and Guy Rosalia Eugène Van Lommen, citizen of Belgium, residing at Klers 34, 2590 Berlaar, Belgium

(hereinafter called "Assignors"), have made certain new and useful inventions or discoveries relating to

METHOD OF LOWERING THE BLOOD PRESSURE

for which they have on the 19 th *day of* January , *19* 89, *executed an application for Letters Patent of the United States; and*

WHEREAS, JANSSEN PHARMACEUTICA N.V.

a corporation of the State of Belgium , *(hereinafter called "Assignee"), is desirous of acquiring the entire right, title, and interest therein:*

NOW, THEREFORE, BE IT KNOWN that for and in consideration of the sum of One Dollar and other valuable considerations to them moving, the receipt of which they hereby acknowledge, Assignors have sold, assigned, and transferred, and do hereby sell, assign, and transfer unto said Assignee the entire right, title, and interest in and to all said inventions and discoveries disclosed in said application, whose identification above by serial number and filing date, when available is hereby authorized, and in and to said application, all substitutions, divisions, and continuations thereof, and in and to all Letters Patent, United States and foreign, that may be granted for said inventions and discoveries, and in and to all extensions, renewals, and reissues thereof, the same to be held and enjoyed by said Assignee, its successors and assigns, as fully and entirely as the same would have been held and enjoyed by Assignors if this Assignment and sale had not been made;

And Assignors hereby authorize and request the Commissioner of Patents of the United States to issue said Letters Patent in accordance with this Assignment;

And for the consideration aforesaid, Assignors covenant and agree with said Assignee that they have a full and unencumbered title to the inventions and discoveries above described and hereby assigned, which title they warrant unto said Assignee, its successors and assigns;

And for the consideration aforesaid, Assignors further covenant and agree that they will, whenever requested, but without cost to them promptly communicate to said Assignee or its representatives any facts known to them relating to said inventions and discoveries, testify in any interference or legal proceedings involving said inventions and discoveries, and execute any additional papers that may be necessary to enable said Assignee or its representatives, successors, nominees, or assigns to secure full and complete protection for the said inventions and discoveries or that may be necessary to vest in said Assignee the complete title to the said inventions and discoveries and patents hereby conveyed and to enable it to record said title.

IN TESTIMONY WHEREOF, Assignors have hereunto set their hands and seals this 25th *day of* January , *1989* .

Raymond M. Xhonneux ..... *(L.S.)*

Guy R.E. Van Lommen ..... *(L.S.)*

STATE
COUNTY OF } *ss.*

BE IT REMEMBERED, That on this 25th *day of* January , *19* 89, *before me, a Notary Public, personally appeared* Raymond M. Xhonneux and Guy R.E. Van Lommen *who I am satisfied are the persons named in and who executed the foregoing instrument in my presence, and I having first made known to them the contents thereof, they did acknowledge that they signed, sealed, and delivered the same as their voluntary act and deed for the uses and purposes therein expressed.*

..... *Notary Public*

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REEL: 5054 FRAME 970

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PATENT & TRADEMARK OFFICE
MAR 16 89

COMMISSIONER OF PATENTS
AND TRADEMARKS OFFICE

APOSTILLE
(Convention de La Haye du 5 octobre 1961)

1. Pays : Belgique
Le présent acte public
2. a été signé par Mme J. Coppens Inspecteur
du Contrôle
4. [illegible] 1989
5. à Bruxelles
7. par le Ministère des Affaires Etrangères, du Commerce
Extérieur et de la Coopération au Développement
8. sous n° 0266
9. Sceau/timbre :
10. Signature :

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No. 6,545,040 Issued: April 8, 2003

Inventors: Raymond Mathieu Xhonneux, Vlimmeren, Guy Rosalia Eugene Van Lommen, Berlaar

Title: METHOD OF LOWERING THE BLOOD PRESSURE

Limited Power of Attorney

The undersigned, who is empowered to sign this certificate on behalf of the assignee, hereby appoints the following practitioners for the limited purpose of filing and prosecuting an extension of U.S. Patent No. 6,545,040 pursuant to 35 U.S.C. §156(d) and 37 C.F.R. §1.740:

Charles Ryan, Esq. (Registration Number 39,013)
Michael Ciraolo, Esq. (Registration Number 58,294)

Forest Laboratories, Inc.
909 Third Avenue
New York, NY 10022
Phone: 631-858-7300
Fax: 631-864-7253

Certification Under 37 C.F.R. §3.73(b):

Janssen Pharmaceutica N.V., a Belgium Corporation, certifies that it is the assignee of the entire right, title and interest in the patent application identified above by virtue of either:

☒ A chain of title from the inventor(s), or the patent application identified above, to the current assignee as shown below:

From: Raymond Mathieu Xhonneux and Guy Rosalia Eugene Van Lommen
To: Janssen Pharmaceutica N.V.
The document was recorded in the Patent and Trademark Office at Reel 005054, Frame 0969, or for which a copy thereof is attached

☒ Copies of assignments or other documents in the chain of title are attached.

The undersigned has reviewed all the documents in the chain of title of the patent application identified above and, to the best of undersigned's knowledge and belief, title is in the assignee identified above.

The undersigned (whose title is supplied below) is empowered to sign this certificate on behalf of the assignee.

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

1/29/08
Date

Signature

Ellen Ciambrone Coletti

Proxy Holder

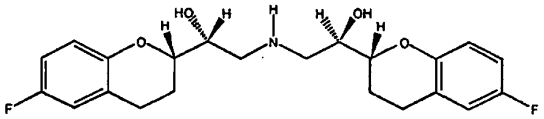
Janssen Pharmaceutica N.V.
Company

BYSTOLIC™
(nebivolol) Tablets
2.5 mg, 5 mg and 10 mg

Rx only

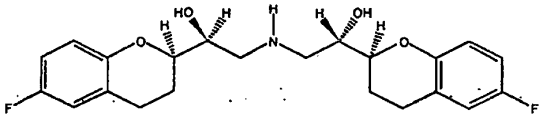
DESCRIPTION

The chemical name for the active ingredient in BYSTOLIC (nebivolol) tablets is (1RS,1'RS)-1,1'-[(2RS,2'SR)-bis(6-fluoro-3,4-dihydro-2H-1-benzopyran-2-yl)]-2,2'-iminodiethanol hydrochloride. Nebivolol is a racemate composed of d-Nebivolol and l-Nebivolol with the stereochemical designations of [SRRR]-nebivolol and [RSSS]-nebivolol, respectively. Nebivolol's molecular formula is ($C_{22}H_{25}F_2NO_4$•HCl) with the following structural formula:



• HCl

SRRR - or d-nebivolol hydrochloride



• HCl

RSSS - or l-nebivolol hydrochloride

MW: 441.90 g/mol

Nebivolol hydrochloride is a white to almost white powder that is soluble in methanol, dimethylsulfoxide, and N,N-dimethylformamide, sparingly soluble in ethanol, propylene glycol, and polyethylene glycol, and very slightly soluble in hexane, dichloromethane, and methylbenzene.

BYSTOLIC as tablets for oral administration contains nebivolol hydrochloride equivalent to 2.5, 5, and 10 mg of nebivolol base. In addition, BYSTOLIC contains the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, D&C Red #27 Lake, FD&C Blue #2 Lake, FD&C Yellow #6 Lake, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch, polysorbate 80, and sodium lauryl sulfate.

CLINICAL PHARMACOLOGY

General

Nebivolol is a β-adrenergic receptor blocking agent. In extensive metabolizers (most of the population) and at doses less than or equal to 10 mg, nebivolol is preferentially β_1 selective. In poor metabolizers and at higher doses, nebivolol inhibits both β_1 and β_2 - adrenergic receptors. Nebivolol lacks intrinsic sympathomimetic and membrane stabilizing activity at therapeutically relevant concentrations. At clinically relevant doses, BYSTOLIC does not demonstrate α_1-

adrenergic receptor blockade activity. Various metabolites, including glucuronides, contribute to β-blocking activity.

Pharmacodynamics

The mechanism of action of the antihypertensive response of BYSTOLIC has not been definitively established. Possible factors that may be involved include: (1) decreased heart rate, (2) decreased myocardial contractility, (3) diminution of tonic sympathetic outflow to the periphery from cerebral vasomotor centers, (4) suppression of renin activity and (5) vasodilation and decreased peripheral vascular resistance.

Pharmacokinetics

Nebivolol is metabolized by a number of routes, including glucuronidation and hydroxylation by CYP2D6. The active isomer (d-nebivolol) has an effective half-life of about 12 hours in CYP2D6 extensive metabolizers (most people), and 19 hours in poor metabolizers and exposure to d-nebivolol is substantially increased in poor metabolizers. This has less importance than usual, however, because the metabolites, including the hydroxyl metabolite and glucuronides (the predominant circulating metabolites), contribute to β-blocking activity.

Plasma levels of d–nebivolol increase in proportion to dose in EMs and PMs for doses up to 20mg. Exposure to l-nebivolol is higher than to d-nebivolol but l-nebivolol contributes little to the drug's activity as d-nebivolol's beta receptor affinity is > 1000-fold higher than l-nebivolol. For the same dose, PMs attain a 5-fold higher Cmax and 10-fold higher AUC of d-nebivolol than do EMs. d-Nebivolol accumulates about 1.5-fold with repeated once-daily dosing in EMs.

Absorption and Distribution

Absorption of BYSTOLIC is similar to an oral solution. The absolute bioavailability has not been determined.

Mean peak plasma nebivolol concentrations occur approximately 1.5 to 4 hours post-dosing in EMs and PMs.

Food does not alter the pharmacokinetics of nebivolol. Under fed conditions, nebivolol glucuronides are slightly reduced. BYSTOLIC may be administered without regard to meals.

The *in vitro* human plasma protein binding of nebivolol is approximately 98%, mostly to albumin, and is independent of nebivolol concentrations.

Metabolism and Excretion

Nebivolol is predominantly metabolized via direct glucuronidation of parent and to a lesser extent via N-dealkylation and oxidation via cytochrome P450 2D6. Its stereospecific metabolites contribute to the pharmacologic activity (see **Drug Interactions**).

After a single oral administration of ^{14}C-nebivolol, 38% of the dose was recovered in urine and 44% in feces for EMs and 67% in urine and 13% in feces for PMs. Essentially all nebivolol was excreted as multiple oxidative metabolites or their corresponding glucuronide conjugates.

Drug-Interactions

Drugs that inhibit CYP2D6 can be expected to increase plasma levels of nebivolol. When BYSTOLIC is co-administered with an inhibitor or an inducer of this enzyme, patients should be closely monitored and the nebivolol dose adjusted according to blood pressure response. *In vitro* studies have demonstrated that at therapeutically relevant concentrations, d- and l-nebivolol do not inhibit any cytochrome P450 pathways.

Digoxin: Concomitant administration of BYSTOLIC (10 mg once daily) and digoxin (0.25 mg once daily) for 10 days in 14 healthy adult individuals resulted in no significant changes in the pharmacokinetics of digoxin or nebivolol (see **PRECAUTION, Drug Interactions**).

Warfarin: Administration of BYSTOLIC (10 mg once daily for 10 days) led to no significant changes in the pharmacokinetics of nebivolol or R- or S-warfarin following a single 10 mg dose of warfarin. Similarly, nebivolol has no significant effects on the anticoagulant activity of warfarin, as assessed by Prothrombin time and INR profiles from 0 to 144 hours after a single 10 mg warfarin dose in 12 healthy adult volunteers.

Diuretics: No pharmacokinetic interactions were observed in healthy adults between nebivolol (10 mg daily for 10 days) and furosemide (40 mg single dose), hydrochlorothiazide (25 mg once daily for 10 days), or spironolactone (25 mg once daily for 10 days).

Ramipril: Concomitant administration of BYSTOLIC (10 mg once daily) and ramipril (5 mg once daily) for 10 days in 15 healthy adult volunteers produced no pharmacokinetic interactions.

Losartan: Concomitant administration of BYSTOLIC (10 mg single dose) and losartan (50 mg single dose) in 20 healthy adult volunteers did not result in pharmacokinetic interactions.

Fluoxetine: Fluoxetine, a CYP2D6 inhibitor, administered at 20 mg per day for 21 days prior to a single 10 mg dose of nebivolol to 10 healthy adults, led to an 8-fold increase in the AUC and 3-fold increase in Cmax for d-nebivolol (see **PRECAUTIONS, Drug Interactions**).

Histamine-2 Receptor Antagonists: The pharmacokinetics of nebivolol (5 mg single dose) were not affected by the co-administration of ranitidine (150 mg twice daily). Cimetidine (400 mg twice daily) causes a 23% increase in the plasma levels of d-nebivolol.

Charcoal: The pharmacokinetics of nebivolol (10 mg single dose) were not affected by repeated co-administration (4, 8, 12, 16, 22, 28, 36, and 48 hours after nebivolol administration) of activated charcoal (Actidose-Aqua®).

Sildenafil: The co-administration of nebivolol and sildenafil decreased AUC and Cmax of sildenafil by 21 and 23% respectively. The effect on the Cmax and AUC for d -nebivolol was also small (< 20%). The effect on vital signs (e.g., pulse and blood pressure) was approximately the sum of the effects of sildenafil and nebivolol.

Other Concomitant Medications: Utilizing population pharmacokinetic analyses, derived from hypertensive patients, the following drugs were observed not to have an effect on the pharmacokinetics of nebivolol: acetaminophen, acetylsalicylic acid, atorvastatin, esomeprazole, ibuprofen, levothyroxine sodium, metformin, sildenafil, simvastatin, or tocopherol.

Protein Binding: No meaningful changes in the extent of *in vitro* binding of nebivolol to human plasma proteins were noted in the presence of high concentrations of diazepam, digoxin, diphenylhydantoin, enalapril, hydrochlorothiazide, imipramine, indomethacin, propranolol, sulfamethazine, tolbutamide, or warfarin. Additionally, nebivolol did not significantly alter the protein binding of the following drugs: diazepam, digoxin, diphenylhydantoin, hydrochlorothiazide, imipramine, or warfarin at their therapeutic concentrations.

Special Populations

Renal Disease: The apparent clearance of nebivolol was unchanged following a single 5 mg dose of BYSTOLIC in patients with mild renal impairment (ClCr 50 to 80 mL/min, n=7), and it was reduced negligibly in patients with moderate (ClCr 30 to 50 mL/min, n=9), but by 53% in patients with severe renal impairment (ClCr <30 mL/min, n=5). The dose of BYSTOLIC should be adjusted in patients with severe renal impairment. BYSTOLIC should be used with caution in patients receiving dialysis, since no formal studies have been conducted in this population (see **DOSAGE AND ADMINISTRATION**).

Hepatic Disease: d-Nebivolol peak plasma concentration increased 3-fold, exposure (AUC) increased 10-fold, and the apparent clearance decreased by 86% in patients with moderate hepatic impairment (Child-Pugh Class B). The starting dose should be reduced in patients with moderate hepatic impairment. No formal studies have been performed in patients with severe hepatic impairment and nebivolol should be contraindicated for these patients (see **DOSAGE AND ADMINISTRATION**).

Clinical Studies

The antihypertensive effectiveness of BYSTOLIC as monotherapy has been demonstrated in three randomized, double-blind, multi-center, placebo-controlled trials at doses ranging from 1.25 to 40 mg for 12 weeks (Studies 1, 2, and 3). A fourth placebo-controlled trial demonstrated additional antihypertensive effects of BYSTOLIC at doses ranging from 5 to 20 mg when administered concomitantly with up to two other antihypertensive agents (ACE inhibitors, angiotensin II receptor antagonists, and thiazide diuretics) in patients with inadequate blood pressure control.

The three monotherapy trials included a total of 2016 patients (1811 BYSTOLIC, 205 placebo) with mild to moderate hypertension who had baseline diastolic blood pressures (DBP) of 95 to 109 mmHg. Patients received either BYSTOLIC or placebo once daily for twelve weeks. Two of these monotherapy trials (Studies 1 and 2) studied 1716 patients in the general hypertensive population with a mean age of 54 years, 55% males, 26% non-Caucasians, 7% diabetics and 6% genotyped as PMs. The third monotherapy trial (Study 3) studied 300 Black

patients with a mean age of 51 years, 45% males, 14% diabetics, and 3% as PMs.

Placebo-subtracted blood pressure reductions by dose for each study are presented in **Table 1.** Most studies showed increasing response to doses above 5 mg.

Table 1. Placebo-Subtracted Least-Square Mean Reductions in Trough Sitting Systolic/Diastolic Blood Pressure (SiSBP/SiDBP mmHg) by Dose in Studies with Once Daily BYSTOLIC

	Nebivolol dose (mg)					
	1.25	2.5	5.0	10	20	30-40
Study 1	-6.6*/-5.1*	-8.5*/-5.6*	-8.1*/-5.5*	-9.2*/-6.3*	-8.7*/-6.9*	-11.7*/-8.3*
Study 2			-3.8/-3.2*	-3.1/-3.9*	-6.3*/-4.5*	
Study 3¶		-1.5/-2.9	-2.6/-4.9*	-6.0*/-6.1*	-7.2*/-6.1*	-6.8*/-5.5*
Study 4^			-5.7*/-3.3*	-3.7*/-3.5*	-6.2*/-4.6*	

* $p<0.05$ based on pair-wise comparison vs placebo
¶ Study enrolled only African Americans.
^ Study on top of one or two other antihypertensive medications.

Study 4 enrolled 669 patients with a mean age of 54 years, 55% males, 54% Caucasians, 29% Blacks, 15% Hispanics, 1% Asians, 14% diabetics, and 5% PMs. BYSTOLIC, 5 mg to 20 mg, administered once daily concomitantly with stable doses of up to two other antihypertensive agents (ACE inhibitors, angiotensin II receptor antagonists, and thiazide diuretics) resulted in significant additional antihypertensive effects over placebo compared to baseline blood pressure.

Effectiveness was similar in subgroups analyzed by age and sex. Effectiveness was established in Blacks, but as monotherapy the magnitude of effect was somewhat less than in Caucasians.

The blood pressure lowering effect of BYSTOLIC was seen within two weeks of treatment and was maintained over the 24-hour dosing interval.

INDICATIONS AND USAGE

BYSTOLIC is indicated for the treatment of hypertension. BYSTOLIC may be used alone or in combination with other antihypertensive agents.

CONTRAINDICATIONS

BYSTOLIC is contraindicated in patients with severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (unless a permanent pacemaker is in place), or severe hepatic impairment (Child-Pugh >B), and in patients who are hypersensitive to any component of this product.

WARNINGS

Abrupt Cessation of Therapy
Patients with coronary artery disease treated with BYSTOLIC should be advised against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in patients with coronary artery disease following the abrupt discontinuation of therapy with β-blockers. Myocardial infarction and ventricular arrhythmias may occur with or without preceding exacerbation of the angina pectoris. Even patients without overt coronary artery disease should be cautioned against interruption or abrupt discontinuation of therapy. As with other β-blockers, when discontinuation of BYSTOLIC is planned, patients should be carefully observed and advised to minimize physical activity. BYSTOLIC should be tapered over 1 to 2 weeks when possible. If the angina worsens or acute coronary insufficiency develops, it is recommended that BYSTOLIC be promptly reinstituted, at least temporarily.

Cardiac Failure
Sympathetic stimulation is a vital component supporting circulatory function in the setting of congestive heart failure, and β-blockade may result in further depression of myocardial contractility and precipitate more severe failure. In patients who have compensated congestive heart failure, BYSTOLIC should be administered cautiously. If heart failure worsens, discontinuation of BYSTOLIC should be considered.

Angina and Acute Myocardial Infarction
BYSTOLIC was not studied in patients with angina pectoris or who had a recent MI.

Bronchospastic Diseases
In general, patients with bronchospastic diseases should not receive β-blockers.

Anesthesia and Major Surgery
If BYSTOLIC is to be continued perioperatively, patients should be closely monitored when anesthetic agents which depress myocardial function, such as ether, cyclopropane, and trichloroethylene, are used. If β-blocking therapy is withdrawn prior to major surgery, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

The β-blocking effects of BYSTOLIC can be reversed by β-agonists, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Additionally, difficulty in restarting and maintaining the heartbeat has been reported with β-blockers.

Diabetes and Hypoglycemia
β-blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Nonselective β-blockers may potentiate insulin-induced hypoglycemia and delay recovery of serum glucose levels. It is not known whether nebivolol has these effects. Patients subject to spontaneous hypoglycemia, or diabetic patients receiving insulin or oral hypoglycemic agents,

should be advised about these possibilities and nebivolol should be used with caution.

Thyrotoxicosis
β-blockers may mask clinical signs of hyperthyroidism, such as tachycardia. Abrupt withdrawal of β-blockers may be followed by an exacerbation of the symptoms of hyperthyroidism or may precipitate a thyroid storm.

Peripheral Vascular Disease
β-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease. Caution should be exercised in these patients.

Non-dihydropyridine Calcium Channel Blockers
Because of significant negative inotropic and chronotropic effects in patients treated with β-blockers and calcium channel blockers of the verapamil and diltiazem type, caution should be used in patients treated concomitantly with these agents and ECG and blood pressure should be monitored.

PRECAUTIONS
Use with CYP2D6 inhibitors
Nebivolol exposure increases with inhibition of CYP2D6 (see **Drug Interactions**). The dose of BYSTOLIC may need to be reduced.

Impaired Renal Function
BYSTOLIC should be used with caution in patients with severe renal impairment because of decreased renal clearance. BYSTOLIC has not been studied in patients receiving dialysis.

Impaired Hepatic Function
BYSTOLIC should be used with caution in patients with moderate hepatic impairment because of decreased metabolism. Since BYSTOLIC has not been studied in patients with severe hepatic impairment, BYSTOLIC is contraindicated in this population (see **CLINICAL PHARMACOLOGY, Special Populations** and **DOSAGE AND ADMINISTRATION**).

Risk of Anaphylactic Reactions
While taking β-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reactions.

In patients with known or suspected pheochromocytoma, an alpha-blocker should be initiated prior to the use of any β-blocker.

Information for Patients
Patients should be advised to take BYSTOLIC regularly and continuously, as directed. BYSTOLIC can be taken with or without food. If a dose is missed, the patient should take the next scheduled dose only (without doubling it). Patients should not interrupt or discontinue BYSTOLIC without consulting the physician.

Patients should know how they react to this medicine before they operate automobiles, use machinery, or engage in other tasks requiring alertness.

Patients should be advised to consult a physician if any difficulty in breathing occurs, or if they develop signs or symptoms of worsening congestive heart failure such as weight gain or increasing shortness of breath, or excessive bradycardia.

Patients subject to spontaneous hypoglycemia, or diabetic patients receiving insulin or oral hypoglycemic agents, should be cautioned that β-blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Nebivolol should be used with caution in these patients.

Drug Interactions
BYSTOLIC should be used with care when myocardial depressants or inhibitors of AV conduction, such as certain calcium antagonists (particularly of the phenylalkylamine [verapamil] and benzothiazepine [diltiazem] classes), or antiarrhythmic agents, such as disopyramide, are used concurrently. Both digitalis glycosides and β-blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia.

BYSTOLIC should not be combined with other β-blockers. Patients receiving catecholamine-depleting drugs, such as reserpine or guanethidine, should be closely monitored, because the added β-blocking action of BYSTOLIC may produce excessive reduction of sympathetic activity. In patients who are receiving BYSTOLIC and clonidine, BYSTOLIC should be discontinued for several days before the gradual tapering of clonidine.

CYP2D6 Inhibitors: Use caution when BYSTOLIC is co-administered with CYP2D6 inhibitors (quinidine, propafenone, fluoxetine, paroxetine, etc.) (see **CLINICAL PHARMACOLOGY, Drug Interactions**).

Carcinogenesis, Mutagenesis, Impairment of Fertility
In a two-year study of nebivolol in mice, a statistically significant increase in the incidence of testicular Leydig cell hyperplasia and adenomas was observed at 40 mg/kg/day (5 times the maximally recommended human dose of 40 mg on a mg/m^2 basis). Similar findings were not reported in mice administered doses equal to approximately 0.3 or 1.2 times the maximum recommended human dose. No evidence of a tumorigenic effect was observed in a 24-month study in Wistar rats receiving doses of nebivolol 2.5, 10 and 40 mg/kg/day (equivalent to 0.6, 2.4, and 10 times the maximally recommended human dose). Co-administration of dihydrotestosterone reduced blood LH levels and prevented the Leydig cell hyperplasia, consistent with an indirect LH-mediated effect of nebivolol in mice and not thought to be clinically relevant in man.

A randomized, double-blind, placebo- and active-controlled, parallel-group study in healthy male volunteers was conducted to determine the effects of nebivolol on adrenal function, luteinizing hormone, and testosterone levels. This study demonstrated that 6 weeks of daily dosing with 10 mg of nebivolol had no

significant effect on ACTH-stimulated mean serum cortisol $AUC_{0\text{-}120\ min}$, serum LH, or serum total testosterone.

Effects on spermatogenesis were seen in male rats and mice at ≥40 mg/kg/day (10 and 5 times the MRHD, respectively). For rats the effects on spermatogenesis were not reversed and may have worsened during a four week recovery period. The effects of nebivolol on sperm in mice, however, were partially reversible.

Mutagenesis: Nebivolol was not genotoxic when tested in a battery of assays (Ames, in vitro mouse lymphoma $TK^{+/-}$, in vitro human peripheral lymphocyte chromosome aberration, in vivo Drosophila melanogaster sex-linked recessive lethal, and in vivo mouse bone marrow micronucleus tests).

Pregnancy: Teratogenic Effects. Pregnancy Category C:
Decreased pup body weights occurred at 1.25 and 2.5 mg/kg in rats, when exposed during the perinatal period (late gestation, parturition and lactation). At 5 mg/kg and higher doses (1.2 times the MRHD), prolonged gestation, dystocia and reduced maternal care were produced with corresponding increases in late fetal deaths and stillbirths and decreased birth weight, live litter size and pup survival. Insufficient numbers of pups survived at 5 mg/kg to evaluate the offspring for reproductive performance.

In studies in which pregnant rats were given nebivolol during organogenesis, reduced fetal body weights were observed at maternally toxic doses of 20 and 40 mg/kg/day (5 and 10 times the MRHD), and small reversible delays in sternal and thoracic ossification associated with the reduced fetal body weights and a small increase in resorption occurred at 40 mg/kg/day (10 times the MRHD). No adverse effects on embryo-fetal viability, sex, weight or morphology were observed in studies in which nebivolol was given to pregnant rabbits at doses as high as 20 mg/kg/day (10 times the MRHD).

Labor and Delivery
Nebivolol caused prolonged gestation and dystocia at doses ≥5 mg/kg in rats (1.2 times the MRHD). These effects were associated with increased fetal deaths and stillborn pups, and decreased birth weight, live litter size and pup survival rate, events that occurred only when nebivolol was given during the perinatal period (late gestation, parturition and lactation).

No studies of nebivolol were conducted in pregnant women. BYSTOLIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
Studies in rats have shown that nebivolol or its metabolites cross the placental barrier and are excreted in breast milk. It is not known whether this drug is excreted in human milk.

Because of the potential for β-blockers to produce serious adverse reactions in nursing infants, especially bradycardia, BYSTOLIC is not recommended during nursing.

Geriatric Use
Of the 2800 patients in the U.S. sponsored placebo-controlled clinical hypertension studies, 478 patients were 65 years of age or older. No overall differences in efficacy or in the incidence of adverse events were observed between older and younger patients.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established. Pediatric studies in ages newborn to 18 years old have not been conducted because of incomplete characterization of developmental toxicity and possible adverse effects on long-term fertility (see **Carcinogenesis, Mutagenesis and Impairment of Infertility**).

ADVERSE REACTIONS

The data described below reflect worldwide clinical trial exposure to BYSTOLIC in 6545 patients, including 5038 patients treated for hypertension and the remaining 1507 subjects treated for other cardiovascular diseases. Doses ranged from 0.5 mg to 40 mg. Patients received BYSTOLIC for up to 24 months, with over 1900 patients treated for at least 6 months, and approximately 1300 patients for more than one year. In placebo-controlled clinical trials comparing BYSTOLIC with placebo, discontinuation of therapy due to adverse events was reported in 2.8% of patients treated with nebivolol and 2.2% of patients given placebo. The most common adverse events that led to discontinuation of BYSTOLIC were headache (0.4%), nausea (0.2%) and bradycardia (0.2%).

Adverse Reactions in Controlled Trials
Table 2 lists treatment-emergent signs and symptoms that were reported in three 12-week, placebo-controlled monotherapy trials involving 1597 hypertensive patients treated with either 5 mg, 10 mg or 20-40 mg of BYSTOLIC and 205 patients given placebo and for which the rate of occurrence was at least 1% of patients treated with nebivolol and greater than the rate for those treated with placebo in at least one dose group.

Table 2. Treatment-Emergent Adverse Events with an Incidence (over 6 weeks) ≥ 1% in BYSTOLIC-treated Patients and at a Higher Frequency than Placebo-Treated Patients

	Placebo (n = 205) (%)	Nebivolol 5 mg (n = 459) (%)	Nebivolol 10 mg (n = 461) (%)	Nebivolol 20-40 mg (n = 677) (%)
Headache	6	9	6	7
Fatigue	1	2	2	5
Dizziness	2	2	3	4
Diarrhea	2	2	2	3
Nausea	0	1	3	2
Insomnia	0	1	1	1
Chest pain	0	0	1	1

Bradycardia	0	0	0	1
Dyspnea	0	0	1	1
Rash	0	0	1	1
Peripheral edema	0	1	1	1

Other Adverse Events Observed During Worldwide Clinical Trials
Listed below are other reported adverse events with an incidence of at least 1% in the more than 5300 patients treated with BYSTOLIC in controlled or open-label trials, whether or not attributed to treatment, except for those already appearing in Table 2, terms too general to be informative, minor symptoms, or events unlikely to be attributable to drug because they are common in the population. These adverse events were in most cases observed at a similar frequency in placebo-treated patients in the controlled studies.

Body as a whole: asthenia.

Gastrointestinal System Disorders: abdominal pain

Metabolic and Nutritional Disorders: hypercholesterolemia and hyperuricemia

Nervous System Disorders: paraesthesia

Laboratory
In controlled monotherapy trials, BYSTOLIC was associated with an increase in BUN, uric acid, triglycerides and a decrease in HDL cholesterol and platelet count.

Events Identified from Spontaneous Reports of BYSTOLIC Received Worldwide.
The following adverse events have been identified from spontaneous reports of BYSTOLIC received worldwide and have not been listed elsewhere. These adverse events have been chosen for inclusion due to a combination of seriousness, frequency of reporting or potential causal connection to BYSTOLIC. Events common in the population have generally been omitted. Because these events were reported voluntarily from a population of uncertain size, it is not possible to estimate their frequency or establish a causal relationship to BYSTOLIC exposure: abnormal hepatic function (including increased AST, ALT and bilirubin), acute pulmonary edema, acute renal failure, atrioventricular block (both second and third degree), bronchospasm, erectile dysfunction, hypersensitivity (including urticaria, allergic vasculitis and rare reports of angioedema), myocardial infarction, pruritus, psoriasis, Raynaud's phenomenon, peripheral ischemia/claudication, somnolence, syncope, thrombocytopenia, various rashes and skin disorders, vertigo, and vomiting.

OVERDOSAGE
In clinical trials and worldwide postmarketing experience there were reports of BYSTOLIC overdose. The most common signs and symptoms associated with BYSTOLIC overdosage are bradycardia and hypotension. Other important adverse events reported with BYSTOLIC overdose include cardiac failure,

dizziness, hypoglycemia, fatigue and vomiting. Other adverse events associated with β-blocker overdose include bronchospasm and heart block.

The largest known ingestion of BYSTOLIC worldwide involved a patient who ingested up to 500 mg of BYSTOLIC along with several 100 mg tablets of acetylsalicylic acid in a suicide attempt. The patient experienced hyperhydrosis, pallor, depressed level of consciousness, hypokinesia, hypotension, sinus bradycardia, hypoglycemia, hypokalemia, respiratory failure and vomiting. The patient recovered.

Due to extensive drug binding to plasma proteins, hemodialysis is not expected to enhance nebivolol clearance.

If overdose occurs, BYSTOLIC should be stopped and general supportive and specific symptomatic treatment should be provided. Based on expected pharmacologic actions and recommendations for other β-blockers, the following general measures should be considered when clinically warranted:

Bradycardia: Administer IV atropine. If the response is inadequate, isoproterenol or another agent with positive chronotropic properties may be given cautiously. Under some circumstances, transthoracic or transvenous pacemaker placement may be necessary.

Hypotension: Administer IV fluids and vasopressors. Intravenous glucagon may be useful.

Heart Block (second or third degree): Patients should be carefully monitored and treated with isoproterenol infusion. Under some circumstances, transthoracic or transvenous pacemaker placement may be necessary.

Congestive Heart Failure: Initiate therapy with digitalis glycoside and diuretics. In certain cases, consideration should be given to the use of inotropic and vasodilating agents.

Bronchospasm: Administer bronchodilator therapy such as a short acting inhaled β_2-agonist and/or aminophylline.

Hypoglycemia: Administer IV glucose. Repeated doses of IV glucose or possibly glucagon may be required.

In the event of intoxication where there are symptoms of shock, treatment must be continued for a sufficiently long period consistent with the 12-19 hour effective half-life of BYSTOLIC. Supportive measures should continue until clinical stability is achieved.

Call the National Poison Control Center (800-222-1222) for the most current information on β-blocker overdose treatment.

DOSAGE AND ADMINISTRATION

The dose of BYSTOLIC should be individualized to the needs of the patient. For most patients, the recommended starting dose is 5 mg once daily, with or without food, as monotherapy or in combination with other agents. For patients requiring further reduction in blood pressure, the dose can be increased at 2-week

intervals up to 40 mg. A more frequent dosing regimen is unlikely to be beneficial.

Renal Impairment
In patients with severe renal impairment (ClCr less than 30 mL/min) the recommended initial dose is 2.5 mg once daily; upward titration should be performed cautiously if needed. BYSTOLIC has not been studied in patients receiving dialysis (see **CLINICAL PHARMACOLOGY, Special Populations**).

Hepatic Impairment
In patients with moderate hepatic impairment, the recommended initial dose is 2.5 mg once daily; upward titration should be performed cautiously if needed. BYSTOLIC has not been studied in patients with severe hepatic impairment and therefore it is not recommended in that population (see **PRECAUTIONS** and **CLINICAL PHARMACOLOGY, Special Populations**).

Geriatric Patients
It is not necessary to adjust the dose in the elderly (see above and **PRECAUTIONS, Geriatric Use**).

CYP2D6 Polymorphism (see **CLINICAL PHARMACOLOGY, Pharmacokinetics**)
No dose adjustments are necessary for patients who are CYP2D6 poor metabolizers. The clinical effect and safety profile observed in poor metabolizers were similar to those of extensive metabolizers.

HOW SUPPLIED
BYSTOLIC is available as tablets for oral administration containing nebivolol hydrochloride equivalent to 2.5, 5, and 10 mg of nebivolol.

BYSTOLIC tablets are triangular-shaped, biconvex, unscored, differentiated by color and are engraved with "FL" on one side and the number of mg (2 ½ , 5, or 10) on the other side. BYSTOLIC tablets are supplied in the following strengths and package configurations:

BYSTOLIC			
Tablet Strength	**Package Configuration**	**NDC #**	**Tablet Color**
2.5 mg	Bottle of 30	0456-1402-30	Light Blue
	Bottle of 100	0456-1402-01	
5 mg	Bottle of 30	0456-1405-30	Beige
	Bottle of 100	0456-1405-01	
	10 x 10 Unit Dose	0456-1405-63	
10 mg	Bottle of 30	0456-1410-30	Pinkish -Purple
	Bottle of 100	0456-1410-01	
	10 x 10 Unit Dose	0456-1410-63	

Store at 20° to 25°C (68° to 77°F). [See USP for Controlled Room Temperature.]

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

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Rev. 12/07

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-742

NDA APPROVAL

Mylan Bertek Pharmaceuticals Inc.
Attention: Ms. Andrea Miller
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Ms. Miller:

Please refer to your new drug application (NDA) originally submitted April 30, 2004, and resubmitted May 30 and December 5, 2007 under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for nebivolol 2.5, 5, and 10 mg Tablets.

We acknowledge receipt of your submissions dated December 2, 4, and 5, 2007.

The December 5, 2007 submission constituted a complete response to our November 30, 2007 approvable letter.

This new drug application provides for the use of Bystolic (nebivolol) 2.5, 5, and 10 mg Tablets for the treatment of hypertension alone or in combination with other antihypertensive agents.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

NDA 21-742 was not referred to an advisory committee for review because there are several previously approved agents in the β-blocker class of drugs, evaluation of the safety data did not reveal particular safety issues that were unexpected for this class, and the design and results of the efficacy trials did not pose particular concerns.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 21-742."

We acknowledge your November 30, 2007 submission containing final printed carton and container labels.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PEDIATRIC RESEARCH EQUITY ACT (PREA)

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application because there is evidence suggesting that nebivolol would not be safe in all pediatric age groups. The safety concern is the possible risk of changes in long-term fertility. Given the availability of many β-blockers with properties similar to nebivolol, there seems no good reason to pursue pediatric studies.

POSTMARKETING COMMITMENT

We remind you of the agreed-upon postmarketing study commitment listed below.

1. Conduct a placebo-controlled withdrawal study following at least three months of treatment.

Final Protocol Submission:	by 04/2008
Study Start:	by 10/2008
Final Report Submission:	by 12/2010

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments should be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence.**"

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
HFD-001, Suite 5100
5515 Security Lane
Rockville, MD 20852

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, please call Dan Brum, Pharm.D., MBA, Regulatory Health Project Manager, at (301)796-0578.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CC: Enclosed agreed-upon labeling text

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Temple
12/17/2007 05:53:53 PM

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NEW BRUNSWICK NJ 08933-7003

MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
6,545,040	$900.00	$0.00	09/25/06	07/825,488	04/08/03	01/24/92	04	NO	JAB-775

PTOL-439 (Rev. 09/2006)

[redacted]

April 13, 1989

Raymond J. Lipicky, MD, Director
Division of Cardio-Renal Drug Products/HFN-110
Central Documents Room
Food and Drug Administration
Park Building Room 214
12420 Parklawn Drive
Rockville, MD 20857

RE: ORIGINAL IND
NEBIVOLOL HCl TABLETS
SERIAL #000

Dear Dr. Lipicky:

Enclosed is an original IND for nebivolol HCl (R 67,555) tablets. Nebivolol is a selective beta blocking drug to be used in hypertension.

As indicated in Section 6, the first study to be conducted under this IND will be a two-4-week period, cross-over with atenolol and a concurrent parallel placebo arm. The effects of 5 mg and 10 mg of nebivolol and 50 mg and 100 mg of atenolol on blood pressure and on left ventricular function will be compared. The investigator for this study is:

Geza Simon, M.D.
Hypertension Clinic
Veterans Administration Medical Center
Minneapolis, MN 55417

Sections 8 and 9 include data which support this study. They contain toxicology data in rats and dogs up to six months, and report on human use of up to 10 mg daily over 4 weeks in over 100 patients.

Data on beta-cyclodextrin, an inactive ingredient in nebivolol tablets, are included in the two volumes comprising Section 10.

Please contact me at (201) 524-9170 if you have any questions.

Sincerely,

Ruth Wasserman

Ruth Wasserman
Assistant Director
Regulatory Affairs

RW:io

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

INVESTIGATIONAL NEW DRUG APPLICATION (IND)

(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) Part 312)

Form Approved: OMB No. 0910-0014
Expiration Date: November 30, 1987.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
Janssen Research Foundation

2. DATE OF SUBMISSION
April 13, 1989

3. ADDRESS *(Number, Street, City, State and Zip Code)*
40 Kingsbridge Road
Piscataway, NJ 08855-3998

4. TELEPHONE NUMBER *(Include Area Code)*
(201) 524-9170

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
Nebivolol Tablets (R67,555)

6. IND NUMBER *(If previously assigned)*

7. INDICATION(S) *(Covered by this submission)*
Hypertension

8. PHASE (S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ☐ PHASE 1 ☒ PHASE 2 ☐ PHASE 3 ☐ OTHER _____ *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR 314.420)*, AND PRODUCT LICENSE APPLICATIONS *(21 CFR Part 601)* REFERRED TO IN THIS APPLICATION.

10. SERIAL NUMBER: 0 0 0

IND submissions should be consecutively numbered. The initial IND should be numbered "Serial Number: 000." The next submission (i.e., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*

☒ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)

PROTOCOL AMENDMENT(S):	INFORMATION AMENDMENT(S):	IND SAFETY REPORT(S):
☐ NEW PROTOCOL	☐ CHEMISTRY/MICROBIOLOGY	☐ INITIAL WRITTEN REPORT
☐ CHANGE IN PROTOCOL	☐ PHARMACOLOGY/TOXICOLOGY	☐ FOLLOW-UP TO A WRITTEN REPORT
☐ NEW INVESTIGATOR	☐ CLINICAL	

☐ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☐ RESPONSE TO CLINICAL HOLD

☐ GENERAL CORRESPONDENCE ☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED ☐ OTHER _____ *(Specify)*

Refer to the designated CFR citations before checking any of the following:

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	IND NUMBER ASSIGNED:
		DIVISION ASSIGNMENT:

FORM FDA 1571 (8/87) PREVIOUS EDITION IS OBSOLETE.

JANSSEN • PHARMACEUTICA • RESEARCH FOUNDATION •

July 20, 1994

Raymond J. Lipicky, MD, Director
Division of Cardio-Renal Drug Products/HFD-110
Attention: Document Control Room #16B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: IND #33,060
Nebivolol Hydrochloride Tablets
ANNUAL REPORT
REQUEST FOR INACTIVE STATUS
Serial No.: 029

Dear Dr. Lipicky:

Enclosed is the annual progress report for nebivolol tablets for the period covering May 13, 1993 to May 12, 1994.

At this time we wish to inactivate our IND for nebivolol hydrochloride tablets. All clinical investigations conducted under IND 39,389 are closed. No additional patients will be entered under this IND. All unused supplies of the investigational drug have been returned and disposed of according to 21 CFR § 312.59 and written records maintained in accordance with 21 CFR § 312.57.

We want to emphasize that IND 39,389 is presently being discontinued; the IND is not abandoned and all manufacturing and quantitative formulation data are to remain confidential in accordance with 21 CFR § 312.130 and 314.430. We request that all trade secret and privileged or confidential commercial information remain unavailable for public disclosure (21 CFR § 20.61).

If you have any questions, please contact me at (609) 730-3065.

Sincerely,

Ruth Wasserman
Director/Regulatory Affairs

Enclosure

JANSSEN AT WASHINGTON CROSSING
1125 TRENTON-HARBOURTON ROAD
POST OFFICE BOX 200
TITUSVILLE, NEW JERSEY 08560-0200

JANSSEN • PHARMACEUTICA • • RESEARCH FOUNDATION •

April 22, 1998

Raymond J. Lipicky, M.D., Director
Division of Cardio-Renal Drug Products (HFD-110)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: IND # 33,060
Nebivolol hydrochloride Tablets
Transfer of Ownership

Dear Dr. Lipicky:

We wish to inform you that all the rights and responsibilities for IND # 33,060, nebivolol hydrochloride, will be transferred to MYLAN LABORATORIES INC., 781 Chestnut Ridge Road, Morgantown, West Virginia, 26504-4310. The transfer of this application is effective on May 1, 1998.

Please note that on July 20, 1994, Janssen requested that IND 33,060 be placed on inactive status.

Please contact Robin Keen, Manager, Regulatory Operations, at (609) 730-3062 if you have any questions regarding this submission.

Sincerely,

Janice K. Bush, MD
Vice President, Regulatory Affairs

g:\regulato\opsgroup\keen\trans_IND.nebivolol.doc

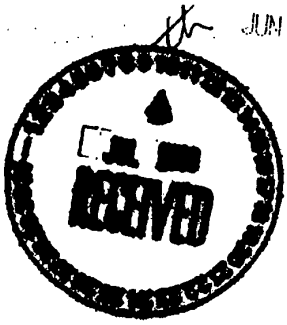
JANSSEN AT WASHINGTON CROSSING
1125 TRENTON-HARBOURTON ROAD
POST OFFICE BOX 200
TITUSVILLE, NEW JERSEY 08560-0200

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

IND 33,060

JUN 30



Mylan Pharmaceuticals, Inc.
Attention: Mr. Frank R. Sisto
P.O. Box 4310
781 Chestnut Ridge Road
Morgantown, WV 26504-4310

Dear Mr. Sisto:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for nebivolol (R67,555) tablets .

We also refer to your submission dated June 5, 2000, received June 6, 2000, notifying us of your intent to reactivate this IND.

As provided by 21 CFR 312.45(d), studies in humans may not be initiated until 30 days after the date of receipt shown above. If, on or before 30 days after FDA receipt date [Note: FDA receipt date is counted as day 0], we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies, we will notify you immediately that (1) clinical studies may not be initiated under this IND ("clinical hold") or that (2) certain restrictions apply to clinical studies under this IND ("partial clinical hold"). In the event of such notification, you must not initiate or you must restrict such studies until you have submitted information to correct the deficiencies, and we have notified you that the information you submitted is satisfactory.

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, to either of the following addresses:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, Rm 5002
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, please contact:

Ms. Zelda McDonald
Regulatory Project Manager
(301) 594-5333

Sincerely yours,

Natalia Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

BERTEK
PHARMACEUTICALS INC.

April 29, 2004

Douglas Throckmorton, MD, Director
Division of Cardio-Renal Drug Products, HFD 143
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Attn: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

RE: Nebivolol Tablets 1.25mg, 2.5mg, 5mg, 10mg and 20mg
NDA #21-742

Dear Dr. Throckmorton:

Pursuant to 21 CFR 314.50 (b)(1), Bertek Pharmaceuticals Inc. is submitting this Original New Drug Application for Nebivolol Tablets. The information and data submitted in this application support the use of Nebivolol Tablets for the management of hypertension when used alone or in combination with other antihypertensive agents.

The enclosed application consists of an electronic archival copy as was discussed with the Agency during the November 25, 2003 pre-NDA Meeting. Also one paper volume accompanies the electronic submission. In accordance with FDA's January 1999 Guidance for Industry entitled Providing Regulatory Submissions in Electronic Format, this paper volume includes the NDA cover letter, signed Application Form (Form FDA 356h), signed User Fee Cover Sheet (Form FDA 3397), signed Financial Certification Form (Form FDA 3454), Signed Patent Information, Pediatric Information Deferral Certification, Debarment Certification, Field Copy Certification, and Note to Reviewer describing the organization of the electronic NDA). Pursuant to the November 25, 2003 pre-NDA Meeting and an April 05, 2004 telephone conversation with the Agency, paper copies of selected sections of the application will be provided to the reviewers as desk copies upon request.

The archival copy of the submission is provided on 20/40 DLT-format tape and is an approximate total of 12 gigabytes. The tape was created using BackupExec version 8.6 for Windows NT. The electronic submission was published using CoreDossier version 5.5.3. The submission is certified as virus-free based on a scan of the electronic media using InoculateIT software, version 4.53, manufactured by Computer Associates. Details of the organization of the electronic submission and linking conventions are described in the attached Note to Reviewer.

781 Chestnut Ridge Road ◆ Morgantown, WV 26505-2356 ◆ (304) 285-6420 ◆ (888) 8-BERTEK ◆ Fax: (888) 329-2785 ◆ Web: www.bertek.com

Pursuant to the Prescription Drug User Fee Act of 1992, a check (check no. 158166 in the amount of $573,500.00) was sent to the Food and Drug Administration in Pittsburgh, PA on March 26, 2004. The application has been assigned the User Fee Identification Number 4747.

In accordance with 21 CFR 314.50 (j), Bertek is claiming exclusivity as provided for in 21 CFR 314.108(b)(2). Bertek believes that upon approval of this application we will be entitled to five years exclusivity during which no person may submit a 505(b)(2) application or abbreviated new drug application under section 505(j) of the Act for a drug product that contains the same active moiety that is in Nebivolol Tablets. To the best of Bertek's knowledge, a drug has not been previously approved under section 505(b) of the Act that contains any active moiety in the drug Nebivolol Tablets.

Pursuant to 21 CFR 314.55 (b), Bertek is requesting a deferral of the submission of pediatric use information until after the referenced New Drug Application is approved for the treatment of hypertension in adults. A certification requesting this pediatric deferral is provided in this NDA.

Bertek Pharmaceuticals Inc. considers the information in this application to be confidential and proprietary. We request that no information from the application be disclosed to third parties without first obtaining written consent from Bertek.

All correspondence regarding this application should be directed to the attention of the undersigned at Bertek Pharmaceuticals Inc., P. O. Box 4310, 781 Chestnut Ridge Road, Morgantown, WV, 26504-4310. Telephone and facsimile inquiries may also be directed to the undersigned at telephone number (304) 599-2595, extension 6869 and/or facsimile number (304) 285-6407.

Sincerely,

Andrea B. Miller, R.Ph., Esq.
Vice President
Regulatory Affairs

ABM/gjn

Enclosures

Chronology of Regulatory Review of BYSTOLIC™

April 13, 1989	**Janssen Filed IND**
July 20, 1994	**Janssen requested that the IND be placed on Inactive Status**
May 1, 1998	Inactive IND transferred to Mylan from Janssen
November 8, 1998	Meeting with FDA and Mylan
June 5, 2000	Mylan Reactivated IND
July 5, 2000	**Effective date IND became reactivated**
July 7, 2000	Meeting with FDA and Mylan - Development Program
September 29, 2000	Meeting with FDA and Mylan - Development Program
April 11, 2001	Meeting with FDA and Mylan - Development Program
August 11, 2001	PK Studies Initiated
September 17, 2001	Clinical Studies Initiated (NEB 305 - First patient in)
October 18, 2003	Clinical Studies Completed (NEB 321 - Last patient out)
November 25, 2003	Pre-NDA meeting held with FDA
April 29, 2004	**NDA submitted**
July 12, 2004	FDA acknowledged receipt and filing of the NDA (PDUFA Date 02/28/05)
February 24, 2005	FDA Reset the PDUFA Action Date (5/31/05)
May 31, 2005	FDA issued an APPROVABLE Action letter (requesting additional studies)
June 2005 - April 2006	Requested Studies conducted
April 21, 2006	Meeting with FDA to discuss acceptability of studies in response to Approvable Letter.
May 2006-March 2007	Additional requested studies conducted.
April 27, 2007	Response submitted to the Approvable Letter
May 18, 2007	FDA notified Mylan that the April 27, 2007 response did not constitute a complete response
May 30, 2007	Response submitted to May 18, 2007 letter with NEB PK 03 final CSR
June 19, 2007	FDA acknowledged receipt and filing of the response as Class II resubmission (PDUFA Date – 11/30/07)

November 30, 2007	FDA issued a second APPROVABLE Letter
December 5, 2007	Response submitted to the APPROVABLE Letter
December 13, 2007	FDA acknowledged receipt and filing of the response as a Class I resubmisison (PDUFA Date – 2/5/08)
December 17, 2007	**NDA approval**

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

MAR 2 4 2008

Office of Regulatory Policy
Food and Administration
10903 New Hampshire Ave., Bldg. 51, Rm. 6222
Silver Spring, MD 20993-0002

Attention: Beverly Friedman

The attached application for patent term extension of U.S. Patent No. 6,545,040 was filed on February 14, 2008, under 35 U.S.C. § 156. The applicant has also applied for a Patent Term Extension for U.S. Patent No. 5,759,580 for NDA No. 21-742.

The assistance of your Office is requested in confirming that the product identified in the application, BYSTOLIC™, has been subject to a regulatory review period within the meaning of 35 U.S.C. § 156(g) before its first commercial marketing or use and that the application for patent term extension was filed within the sixty-day period after the product was approved. Since a determination has not been made whether the patent in question claims a product which has been subject to the Federal Food, Drug and Cosmetic Act, or a method of manufacturing or use of such a product, this communication is NOT to be considered as notice which may be made in the future pursuant to 35 U.S.C. § 156(d)(2)(A).

Our review of the application to date indicates that the subject patent would be eligible for extension of the patent term under 35 U.S.C. § 156.

Inquiries regarding this communication should be directed to the undersigned at (571) 272-7755 (telephone) or (571) 273-7755 (facsimile).

Mary C. Till
Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: Charles Ryan
Forest Laboratories Inc.
909 Third Avenue
New York, New York 10022

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JUN 10 2008

Re: Bystolic
U.S. Patent Nos. 5,759,580 and 6,545,040
Docket Nos. FDA-2008-E-0268
And FDA-2008-E-0267

The Honorable Jon Dudas
Under Secretary of Commerce for Intellectual Property
Director of the United States Patent and Trademark Office
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Director Dudas:

This is in regard to the applications for patent term extension for U.S. Patent Nos. 5,759,580 and 6,545,040 filed by Forest Laboratories, Inc., under 35 U.S.C. § 156. The human drug product claimed by the patents is Bystolic (nebivolol hydrochloride), which was assigned new drug application (NDA) No. 21-742.

A review of the Food and Drug Administration's official records indicates that this product was subject to a regulatory review period before its commercial marketing or use, as required under 35 U.S.C. § 156(a)(4). Our records also indicate that it represents the first permitted commercial marketing or use of the product, as defined under 35 U.S.C. § 156(f)(1), and interpreted by the courts in *Glaxo Operations UK Ltd. v. Quigg*, 706 F. Supp. 1224 (E.D. Va. 1989), *aff'd*, 894 F. 2d 392 (Fed. Cir. 1990).

The NDA was approved on December 17, 2007, which makes the submission of the patent term extension application on February 14, 2008, timely within the meaning of 35 U.S.C. § 156(d)(1).

Should you conclude that the subject patent is eligible for patent term extension, please advise us accordingly. As required by 35 U.S.C. § 156(d)(2)(A) we will then determine the applicable regulatory review period, publish the determination in the *Federal Register*, and notify you of our determination.

Please let me know if we can be of further assistance.

Sincerely yours,

Jane A. Axelrad

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

cc: Charles Ryan
Forest Laboratories, Inc.
909 Third Avenue
New York, NY 10022

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

JUL 30 2008

Office of Regulatory Policy
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, Rm. 6222
Silver Spring, MD 20993-0002

Attention: Beverly Friedman

Dear Ms. Axelrad:

Transmitted herewith is a copy of the application for patent term extension of U.S. Patent No. 6,545,040. The application was filed on February 14, 2008, under 35 U.S.C. § 156. Please note that the Applicant also has sought patent term extension for the regulatory review period of NDA No. 21-742 for U.S. Patent No. 5,759,580.

The patent claims a product that was subject to regulatory review under the Federal Food, Drug and Cosmetic Act. Subject to final review, the subject patent is considered to be eligible for patent term extension. Thus, a determination by your office of the applicable regulatory review period is necessary. Accordingly, notice and a copy of the application are provided pursuant to 35 U.S.C. § 156(d)(2)(A).

Inquiries regarding this communication should be directed to the undersigned at (571)272-7755 (telephone) or (571) 273-7755 (facsimile).

Mary C. Till
Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: Charles Ryan
Forest Laboratories Inc.
909 Third Avenue
New York, New York 10022

RE: BYSTOLIC® (nebivolol hydrochloride)
FDA Docket No. FDA-2008-E-0267

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAY 10 2010

Re: Bystolic
Patent Nos. 5,759,580 and 6,545,040
Docket Nos.: FDA-2008-E-0268
FDA-2008-E-0267

The Honorable David J. Kappos
Undersecretary of Commerce for Intellectual Property
Director of the United States Patent and Trademark Office
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Director Kappos:

This is in regard to the applications for patent term extension for U.S. Patent Nos. 5,759,580 and 6,545,040, filed by Forest Laboratories, Inc., under 35 U.S.C. § 156 et seq. We have reviewed the dates contained in the applications and have determined the regulatory review period for Bystolic (nebivolol hydrochloride), the human drug product claimed by the patents.

The total length of the regulatory review period for Bystolic (nebivolol hydrochloride) is 6,790 days. Of this time, 5,463 days occurred during the testing phase and 1,327 days occurred during the approval phase.

1. The date an exemption under subsection 505(i) of the Federal Food, Drug, and Cosmetic Act involving this drug product became effective: May 17, 1989.

   The applicant claims July 6, 2000, as the date the investigational new drug application (IND) became effective. However, FDA records indicate that the IND originally became effective on May 17, 1989, which was thirty days after FDA receipt of the original IND.

2. The date the application was initially submitted with respect to the human drug product under section 505 of the Federal Food, Drug, and Cosmetic Act: April 30, 2004.

   The applicant claims April 29, 2004, as the date the new drug application (NDA) for Bystolic (NDA 21-742) was initially submitted. However, FDA records indicate that NDA 21-742 was submitted on April 30, 2004.

3. The date the application was approved: December 17, 2007.

   FDA has verified the applicant's claim that NDA 21-742 was approved on December 17, 2007.

This determination of the regulatory review period by FDA does not take into account the effective date of the patent, nor does it exclude one-half of the testing phase as required by 35 U.S.C. § 156(c)(2).

Please let me know if we can be of further assistance.

Sincerely yours,

Jane A. Axelrad

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

cc: Charles Ryan
Forest Laboratories, Inc.
909 Third Avenue
New York, NY 10022

annualized cost to respondents is estimated at $3,793.00. There are no capital costs to report. There are no operating or maintenance costs to report.

Direct Comments to OMB

Written comments and/or suggestions regarding the item(s) contained in this notice, especially regarding the estimated public burden and associated response time, should be directed to the: Office of Management and Budget, Office of Regulatory Affairs, *OIRA_submission@omb.eop.gov* or by fax to 202–395–6974, *Attention:* Desk Officer for NIH. To request more information on the proposed project or to obtain a copy of the data collection reports and instrument, contact Kathy Kranzfelder, Director, NIDDK Office of Communications and Public Liaison, Building 31, Room 9A06, MSC2560, Bethesda, MD 20852 or e-mail your request, including your address to: *KranzfelderK@mail.nih.gov.* To request more information on the proposed project or to obtain a copy of the data collection reports and instrument, contact Kathy Kranzfelder, Director, NIDDK Office of Communications and Public Liaison, Building 31, Room 9A06, MSC2560, Bethesda, MD 20852. You may also submit comment and data by electronic mail (e-mail) at *KranzfelderK@mail.nih.gov.*

Dated: June 14, 2010.

Lynell Nelson,

NIDDK Project Clearance Liaison, National Institutes of Health.

[FR Doc. 2010–14793 Filed 6–17–10; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket Nos. FDA–2008–E–0268 and FDA–2008–E–0267]

Determination of Regulatory Review Period for Purposes of Patent Extension; BYSTOLIC; U.S. Patent Nos. 5,759,580 and 6,545,040

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined the regulatory review period for BYSTOLIC and is publishing this notice of that determination as required by law. FDA has made the determination because of the submission of applications to the Director of Patents and Trademarks, Department of Commerce, for the extension of a patent which claims that human drug product.

ADDRESSES: Submit electronic comments to *http://www.regulations.gov.* Submit written comments and petitions to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Beverly Friedman, Office of Regulatory Policy, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 6222, Silver Spring, MD 20993–0002 301–796–3602.

SUPPLEMENTARY INFORMATION: The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98–417) and the Generic Animal Drug and Patent Term Restoration Act (Public Law 100–670) generally provide that a patent may be extended for a period of up to 5 years so long as the patented item (human drug product, animal drug product, medical device, food additive, or color additive) was subject to regulatory review by FDA before the item was marketed. Under these acts, a product's regulatory review period forms the basis for determining the amount of extension an applicant may receive.

A regulatory review period consists of two periods of time: A testing phase and an approval phase. For human drug products, the testing phase begins when the exemption to permit the clinical investigations of the human drug product becomes effective and runs until the approval phase begins. The approval phase starts with the initial submission of an application to market the human drug product and continues until FDA grants permission to market the drug product. Although only a portion of a regulatory review period may count toward the actual amount of extension that the Director of Patents and Trademarks may award (for example, half the testing phase must be subtracted as well as any time that may have occurred before the patent was issued), FDA's determination of the length of a regulatory review period for a human drug product will include all of the testing phase and approval phase as specified in 35 U.S.C. 156(g)(1)(B).

FDA recently approved for marketing the human drug product BYSTOLIC (nebivolol hydrochloride). BYSTOLIC is indicated for the treatment of hypertension. Subsequent to this approval, the Patent and Trademark Office received two patent term restoration applications for BYSTOLIC (U.S. Patent Nos. 5,759,580 and 6,545,040) from Forest Laboratories, Inc., and the Patent and Trademark Office requested FDA's assistance in determining the patents' eligibilities for patent term restoration. In a letter dated June 10, 2008, FDA advised the Patent and Trademark Office that this human drug product had undergone a regulatory review period and that the approval of BYSTOLIC represented the first permitted commercial marketing or use of the product. Thereafter, the Patent and Trademark Office requested that FDA determine the product's regulatory review period.

FDA has determined that the applicable regulatory review period for BYSTOLIC is 6,790 days. Of this time, 5,463 days occurred during the testing phase and 1,327 days occurred during the approval phase. These periods of time were derived from the following dates:

1. *The date an exemption under subsection 505(i) of the Federal Food, Drug, and Cosmetic Act (the act) (U.S.C. 355 (i)) involving this drug product became effective*: May 17, 1989. The applicant claims July 6, 2000, as the date the investigational new drug application (IND) became effective. However, FDA records indicate that the IND originally became effective on May 17, 1989, which was 30 days after FDA receipt of the original IND.

2. *The date the application was initially submitted with respect to the human drug product under section 505(b) of the Federal Food, Drug, and Cosmetic Act*: April 30, 2004. The applicant claims April 29, 2004, as the date the new drug application (NDA) for BYSTOLIC (NDA 21–742) was initially submitted. However, FDA records indicate that NDA 21–742 was submitted on April 30, 2004.

3. *The date the application was approved*: December 17, 2007. FDA has verified the applicant's claim that NDA 21–742 was approved on December 17, 2007. This determination of the regulatory review period establishes the maximum potential length of a patent extension. However, the U.S. Patent and Trademark Office applies several statutory limitations in its calculations of the actual period for patent extension. In its applications for patent extension, this applicant seeks 1,828 days of patent term extension for U.S. Patent No. 5,759,580 and 619 days of patent term extension for U.S. Patent No. 6,545,040.

Anyone with knowledge that any of the dates as published are incorrect may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments and ask for a redetermination by August 17, 2010. Furthermore, any interested person may petition FDA for a determination

regarding whether the applicant for extension acted with due diligence during the regulatory review period by December 15, 2010. To meet its burden, the petition must contain sufficient facts to merit an FDA investigation. (See H. Rept. 857, part 1, 98th Cong., 2d sess., pp. 41–42, 1984.) Petitions should be in the format specified in 21 CFR 10.30.

Comments and petitions should be submitted to the Division of Dockets Management. Three copies of any mailed information are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments and petitions may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

Dated: May 10, 2010.

Jane A. Axelrad,

Associate Director for Policy, Center for Drug Evaluation and Research.

[FR Doc. 2010–14814 Filed 6–17–10; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Disease Control and Prevention

Disease, Disability, and Injury Prevention and Control

Special Emphasis Panel (SEP): Cooperative Agreement Program for the National Academic Centers of Excellence in Youth Violence Prevention (U01), Funding Opportunity Announcement (FOA) CE10–004, Initial Review

In accordance with section 10(a)(2) of the Federal Advisory Committee Act (Pub. L. 92–463), the Centers for Disease Control and Prevention (CDC) announces the aforementioned meeting:

Times and Dates: 8 a.m.–5 p.m., July 22, 2010 (Closed). 8 a.m.–5 p.m., July 23, 2010 (Closed).

Place: Embassy Suites Atlanta—Buckhead, 3285 Peachtree Road, NE., Atlanta, Georgia 30305, Telephone: 404–261–7733.

Status: The meetings will be closed to the public in accordance with provisions set forth in Section 552b(c)(4) and (6), Title 5, U.S.C., and the Determination of the Director, Management Analysis and Services Office, CDC, pursuant to Section 10(d) of Public Law 92–463.

Matters to be Discussed: The meeting will include the initial review, discussion, and evaluation of applications received in response to "Cooperative Agreement Program for the National Academic Centers of Excellence in Youth Violence Prevention (U01), FOA CE10–004."

Agenda items are subject to change as priorities dictate.

Contact Person for More Information: J. Felix Rogers, Ph.D., M.P.H., NCIPC/ERPO, CDC, 4770 Buford Highway, NE., M/S F63, Atlanta, Georgia 30341–3724, Telephone (770) 488–4334. The Director, Management Analysis and Services Office has been delegated the authority to sign **Federal Register** notices pertaining to announcements of meetings and other committee management activities for both CDC and the Agency for Toxic Substances and Disease Registry.

Dated: June 10, 2010.

Elaine L. Baker,

Director, Management Analysis and Services Office, Centers for Disease Control and Prevention.

[FR Doc. 2010–14772 Filed 6–17–10; 8:45 am]

BILLING CODE 4163–18–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2010–N–0295]

Web-Based Public Meeting To Discuss Issues Related to the Development of an Enforcement Action Plan; Request for Data, Information, and Views

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of Web-based public meeting; request for data, information, and views.

SUMMARY: The Food and Drug Administration (FDA), Center for Tobacco Products is announcing that it is hosting a Web-based public meeting to discuss issues regarding the development of an enforcement action plan to enforce restrictions on promotion and advertising of menthol and other cigarettes to youth, including youth in minority communities. FDA is seeking participation in the Web-based public meeting and data, information, and views from all interested parties, including, but not limited to, public health organizations, minority community groups and leaders, other stakeholders with demonstrated expertise and experience in serving minority communities, groups serving youth, patient groups, advertising agencies, the regulated industry, and other interested parties. This Web-based public meeting and the data, information, and views we receive are intended to help FDA in developing an enforcement action plan. FDA is seeking input on a number of specific issues, but is interested in other pertinent information as well.

DATES: The Web-based public meeting will be held on June 30, 2010, from 9 a.m. to 5 p.m. EDT. Persons interested in participating in the Web-based public meeting must submit written or electronic registration by close of business on June 23, 2010. Submit written and electronic data, information, and views by August 2, 2010.

ADDRESSES: Submit data, information, and views electronically to *http://www.regulations.gov.* Submit written data, information, and views to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic registration to *CTPCompliance@fda.hhs.gov.* Submit written registration to Anthony W. Lee, Center for Tobacco Products, Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850.

FOR FURTHER INFORMATION CONTACT: Anthony W. Lee, Center for Tobacco Products, Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850–3229, 877–287–1373, email: *AnthonyW.Lee@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION:

I. Background

The Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) (Public Law 111–31; 123 Stat. 1776) was enacted on June 22, 2009, providing FDA with the authority to regulate tobacco products in order to protect the public health generally and to reduce tobacco use by minors. Tobacco products are responsible for more than 440,000 deaths each year in the United States (Ref. 1). In enacting the Tobacco Control Act, Congress found, among other things, that the use of tobacco products by children is a pediatric disease and virtually all new users of tobacco products are under the minimum legal age to purchase such products (sections 2(1) and (4) of the Tobacco Control Act). Advertising, marketing, and promotion of tobacco products have been "especially directed to attract young persons to use tobacco products, and these efforts have resulted in increased use of such products by youth" (section 2(15) of the Tobacco Control Act).

Additionally, the rates of tobacco use and tobacco-related mortality are higher among certain racial and ethnic groups, including American Indian and Alaska Natives, and African-American men. As the National Cancer Institute (NCI) noted in Monograph 19, "[t]argeting of various population groups—including * * * specific racial and ethnic

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

FEB 18 2011

Re: Bystolic
Patent Nos. 5,759,580 and 6,545,040
Docket Nos. FDA-2008-E-0267
FDA-2008-E-0268

The Honorable David J. Kappos
Under Secretary of Commerce for Intellectual Property
Director of the United States Patent and Trademark Office
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Director Kappos:

This is in regard to the patent term extension applications for U.S. Patent Nos. 5,759,580 and 6,545,040 filed by Forest Laboratories, Inc. under 35 U.S.C. § 156. The patents claim Bystolic (nebivolol hydrochloride), new drug application (NDA) 21-742.

In the June 18, 2010, issue of the Federal Register (75 Fed. Reg. 34749), the Food and Drug Administration published its determination of this product's regulatory review period, as required under 35 U.S.C. § 156(d)(2)(A). The notice provided that on or before December 15, 2010, 180 days after the publication of the determination, any interested person could file a petition with FDA under 35 U.S.C. § 156(d)(2)(B)(i) for a determination of whether the patent term extension applicant acted with due diligence during the regulatory review period.

The 180-day period for filing a due diligence petition pursuant to this notice has expired and FDA has received no such petition. Therefore, FDA considers the regulatory review period determination to be final.

Please let me know if we can provide further assistance.

Sincerely yours,

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

cc: Charles Ryan
Forest Laboratories, Inc.
909 Third Avenue
New York, NY 10022

UNITED STATES PATENT AND TRADEMARK OFFICE

AUG 1 2011

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Charles Ryan
Forest Laboratories Inc.
909 Third Avenue
New York, New York 10022

In Re: Patent Term Extension
Application for
U.S. Patent No. 6,545,040

NOTICE OF FINAL DETERMINATION AND REQUIREMENT FOR ELECTION

A determination has been made that U.S. Patent No. 6,545,040, claims of which cover the human drug product BYSTOLIC® (nebivolol hdrochloride), is eligible for patent term extension under 35 U.S.C. § 156. The period of extension has been determined to be 618 days.

A single request for reconsideration of this final determination as to the length of extension of the term of the patent may be made if filed within one month of the date of this notice. Extensions of time under 37 CFR § 1.136(a) are not applicable to this time period.

Applicant also has applied for patent term extension of U.S. Patent No. 5,759,580 based on the regulatory review period for BYSTOLIC® (nebivolol hdrochloride).

When patent term extension applications are filed for extension of the terms of different patents based upon the same regulatory review period for a product, the certificate of extension is issued to the patent having the earliest date of issuance, unless applicant elects a different patent. In the absence of an election by applicant within one month of the date of this notice, and in accordance with 37 CFR 1.785(b), the application for patent term extension in the above-identified patent, U.S. Patent No. 6,545,040, will be denied. Accordingly, the application for patent term extension of the patent having the earlier date of issuance will be granted, i.e., a certificate of extension will be issued to U.S. Patent No. 5,759,580. In the absence of a request for reconsideration, and if U.S. Patent No. 6,545,040 is elected, the Director will issue to the applicant a certificate of extension, under seal, for a period of 618 days in U.S. Patent No. 6,545,040.

The period of extension, if calculated using the Food and Drug Administration determination of the length of the regulatory review period published in the Federal Register of June 18, 2010 (75 Fed. Reg. 34749), would be 1,521 days. Under 35 U.S.C. § 156(c):

$$\text{Period of Extension} = \text{RRP} - \text{PGRRP} - \text{DD} - \tfrac{1}{2}(\text{TP} - \text{PGTP})^{1}$$

[1] Consistent with 35 U.S.C. § 156(c), "RRP" is the total number of days in the regulatory review period, "PGRRP" is the number of days of the RRP which were on and before the date on which the patent issued, "DD" is the number of days of the RRP that the applicant did not act with due diligence, "TP" is the testing phase period described in paragraphs (1)(B)(i), (2)(B)(i), (3)(B)(i), (4)(B)(i), and (5)(B)(i) of subsection (g) of 35 U.S.C. § 156, and "PGTP" is the number

= 6,790 - 5,075 - 0 - ½ (5,463 - 5,075)
= 1,521 days (4.2 years)

Since the regulatory review period began May 17, 1989, before the patent issued (April 8, 2003), only that portion of the regulatory review period occurring after the date the patent issued has been considered in the above determination of the length of the extension period 35 U.S.C. § 156(c). (From May 17, 1989, to and including April 8, 2003, is 5,075 days; this period is subtracted from the number of days occurring in the testing phase according to the FDA determination of the length of the regulatory review period.) No determination of a lack of due diligence under 35 U.S.C. § 156(c)(1) was made.

However, the 14 year exception of 35 U.S.C. § 156(c)(3) operates to limit the term of the extension in the present situation, because it provides that the period remaining in the term of the patent measured from the date of approval of the approved product plus any patent term extension cannot exceed fourteen years. The period of extension calculated above, 1,521 days, would extend the patent from April 8, 2020, to June 7, 2024, which is beyond the 14-year limit (the approval date is December 17, 2007, thus, the 14 year limit is December 17, 2021). The period of extension is thus limited to 618 days, by operation of 35 U.S.C. § 156(c)(3). Accordingly, the period of extension is the number of days to extend the term of the patent from its original expiration date, April 8, 2020, to and including December 17, 2021 or 618 days.

The limitations of 35 U.S.C. 156(g)(6) do not operate to further reduce the period of extension determined above.

Upon issuance of the certificate of extension, the following information will be published in the Official Gazette:

U.S. Patent No.:	6,545,040
Granted:	April 8, 2003
Original Expiration Date[2]:	April 8, 2020
Applicant:	Raymond M. Xhonneux et al.
Owner of Record:	Janssen Pharmaceutica N.V.
Title:	Method of Lowering The Blood Pressure
Product Trade Name:	BYSTOLIC® (nebivolol hdrochloride)
Term Extended:	618 days

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of days of the TP which were on and before the date on which the patent issued, wherein half days are ignored for purposes of the subtraction of ½ (TP - PGTP).

[2]Subject to the provisions of 35 U.S.C. § 41(b).

Expiration Date of Extension: December 17, 2021

Any correspondence with respect to this matter should be addressed as follows:

By mail: Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450.

By FAX: (571) 273-7755

Telephone inquiries related to this determination should be directed to the undersigned at (571) 272-7755.

Mary C. Till
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Associate Commissioner
for Patent Examination Policy

cc: Office of Regulatory Policy
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, Rm. 6222
Silver Spring, MD 20993-0002

Attention: Beverly Friedman

RE: BYSTOLIC® (nebivolol hydrochloride)
Docket No.: FDA-2008-E-0-268

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 6,545,040

Inventors: Xhonneux *et al.*

Assignee: Janssen Pharmaceutica N.V.

Title: METHOD OF LOWERING THE BLOOD PRESSURE

Issue Date: April 8, 2003

ELECTION OF PATENT TERM EXTENSION UNDER 35 U.S.C. § 156

Mail Stop: **Hatch-Waxman PTE**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner for Patents:

On August 1, 2011, a Notice of Final Determination and Requirement for Election was mailed indicating that applications were filed for extension of the terms of U.S. Patent Nos. 6,545,040 and 5,759,580 based on the same regulatory review period for Bystolic® (nebivolol hydrochloride). The Notice indicates that one patent should be elected for extension.

Forest Laboratories, Inc. acting under limited power of attorney for the patent owner Janssen Pharmaceutica N.V. hereby (i) requests the express withdrawal of the application for extension of the term of U.S. Patent No. 5,759,580; and (ii) elects an extension of the term of U.S. Patent No. 6,545,040 pursuant to 35 U.S.C. § 156. Accordingly, it is respectfully requested that a certificate of extension is issued granting an extension of 618 days to U.S. Patent No. 6,545,040.

It is believed that no additional fees are required in connection with this request. If any additional fees are required the Commissioner is hereby authorized to charge any payment to Deposit Account No. 503899.

Dated: August 16, 2011

Respectfully submitted,

/Michael Ciraolo/
Michael Ciraolo, J.D., Ph.D.
Registration No.: 58,294

Forest Laboratories, Inc.
48 Mall Drive
Commack, New York 11725
(631) 858-7365
(631) 858-7441 (fax)

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

OCT 4 2011

Charles Ryan
Forest Laboratories Inc.
909 Third Avenue
New York, New York 10022

In Re: Patent Term Extension
Application for
U.S. Patent No. 6,545,040

Dear Mr. Ryan:

A certificate under 35 U.S.C. § 156 is enclosed extending the term of U.S. Patent No. 6,545,040 for a period of 618 days. While a courtesy copy of this letter is being forwarded to the Food and Drug Administration (FDA), you should directly correspond with the FDA regarding any required changes to the patent expiration dates set forth in the Patent and Exclusivity Data Appendix of the Orange Book (Approved Drug Products with Therapeutic Equivalence Evaluations) or in the Patent Information set forth in the Green Book (FDA Approved Animal Drug Products). Effective August 18, 2003, patent submissions for publication in the Orange Book and Docket *95S-0117 need to be submitted on form FDA-3542 which may be downloaded from FDA's Electronic Forms Download Website: http://www.fda.gov/opacom/morechoices/fdaforms/default.html (http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3542.pdf).

Inquiries regarding this communication should be directed to the undersigned by telephone at (571) 272-7755, or by e-mail at mary.till@uspto.gov.

Mary C. Till
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Associate Commissioner
for Patent Examination Policy

cc: Office of Regulatory Policy
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, Rm. 6222
Silver Spring, MD 20993-0002

Attention: Beverly Friedman

RE: BYSTOLIC® (nebivolol hydrochloride)
Docket No.: FDA-2008-E-0268

UNITED STATES PATENT AND TRADEMARK OFFICE

(12) CERTIFICATE EXTENDING PATENT TERM
UNDER 35 U.S.C. § 156

(68)	PATENT NO.	:	6,545,040
(45)	ISSUED	:	April 8, 2003
(75)	INVENTOR	:	Raymon Mathiew Xhonneux et al.
(73)	PATENT OWNER	:	Janssen Pharmaceutica N.V.
(95)	PRODUCT	:	BYSTOLIC® (nebivolol hdrochloride)

This is to certify that an application under 35 U.S.C. § 156 has been filed in the United States Patent and Trademark Office, requesting extension of the term of U.S. Patent No. 6,545,040 based upon the regulatory review of the product BYSTOLIC® (nebivolol hdrochloride) by the Food and Drug Administration. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

(94) 618 days

from April 8, 2020, the original expiration date of the patent, subject to the payment of maintenance fees as provided by law, with all rights pertaining thereto as provided by 35 U.S.C. § 156(b).

I have caused the seal of the United States Patent and Trademark Office to be affixed this 30th day of September 2011.

David J. Kappos

David J. Kappos
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office