DOCKET NO.: JAB-775/JJ-0171 **PATENT**

REPLACEMENT REQUEST FOR REEXAMINATION IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant Raymond Mathieu Xhonneux,
and Guy Rosalia Eugène Van Lommen

Filed: January 24, 1992

Patent No.: 6,545,040 B1

Application No.: 07/825,488

Issued: April 8, 2003

Patentee: Janssen Pharmaceutica

For: Method Of Lowering The Blood Pressure

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MAIL STOP EX PARTE REEXAM
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLACEMENT REQUEST FOR *EX PARTE* REEXAMINATION PURSUANT TO 37 CFR § 1.510

☒ This is a Replacement Request for Reexamination of patent number **6,545,040 B1** issued **April 8, 2003**. The originally-filed Request for Reexamination was filed on December 1, 2006.

☒ The name and address of the person requesting reexamination is **Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse, Belgium.**

☒ Reexamination of claim(s) **1-6** is requested.

☒ The attached detailed request includes at least the following items:

- ☒ A statement identifying each potential substantial new question of patentability based on prior patents and printed publications. 37 CFR § 1.510(b)(1).
- ☒ An identification of every claim for which reexamination is requested, and a detailed explanation of the pertinency and manner of applying the cited prior art to every claim for which reexamination is requested. 37 CFR § 1.510(b)(2).

☒ A replacement PTO-1449 is submitted herewith listing those publications discussed herein.

☒ The Commissioner is hereby requested to grant an extension of time for the appropriate length of time, should one be necessary, in connection with this filing or any future filing submitted to the U.S. Patent and Trademark Office in the above-identified application during the pendency of this application. The Commissioner is further authorized to charge any fees related to any such extension of time to Deposit Account 23-3050. This sheet is provided in duplicate.

☒ The requester's correspondence address (if different than above) is Customer Number 45511 which is:

Woodcock Washburn LLP, Cira Centre, 12th Floor, 2929 Arch Street,

Philadelphia, PA 19104-2891

Detailed Request For Reexamination

Janssen Pharmaceutica N.V. ("the Patent Owner") respectfully requests reexamination of claims 1-6 of U.S. Patent No. 6,545,040 ("the 040 Patent") which issued on April 8, 2003, in the names of Raymond Mathieu Xhonneux and Guy Rosalia Eugène Van Lommen.

I. Statement Identifying Each Potential Substantial New Question of Patentability Based on Prior Patent And Printed Publications

This Request for Reexamination is filed in view of three documents that are said to be directed to nebivolol. The documents were referenced in a letter to Patent Owner's representative from Mr. Giovanni Viti of the Menarini Patent Office (Exhibit A hereto), and appear to have published before the earliest priority date of the 040 Patent:

1. De Crée, *et al.,* Subacute Hemodynamic Effects of Nebivolol in Man at Rest and During Exercise; *Angiology*, June 1987; 38(6): 440-448.

2. De Crée, *et al.,* Haemodynamic Effects in Man During Exercise of a Single Oral Dose of Narbivolol (R 67555), a New Beta-1-Adrenoceptor Blocking Agent: A Comparative Study with Atenolol, Pindolol, and Propranolol; *Drug Dev Res,* 1986; 8: 109-118.

3. De Crée, *et al.,* Hemodynamic Effects in Men of Nebivolol, A Chemically Novel Selective Beta-1-Adrenoceptor Blocking Drug, Comparing the Results of Systolic Time Intervals with Radionuclide Angiocardigraphy; Abstract, Thirty-Fourth Annual Meeting of the American College of Angiology, Paradise Island (Bahamas), October 18-23, 1987.

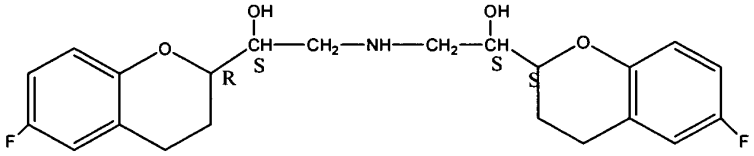
These documents arguably raise a question as to the validity of claim 1 to 6 of the 040 Patent. It appears that the Patent Owner was aware of Document 2 during prosecution of the 040 Patent and may have been aware of one or more of the other documents mentioned in Exhibit A.

II. Identification of Claims For Which Reexamination is Requested

The 040 Patent has two independent claims. Independent claim 1 is directed to a composition consisting of the RSSS isomer of α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol] or a pharmaceutically acceptable acid addition salt thereof. Independent claim 2 is directed to a composition consisting of a pharmaceutically acceptable carrier and, as active ingredients, the SRRR and RSSS isomers of α,α'-

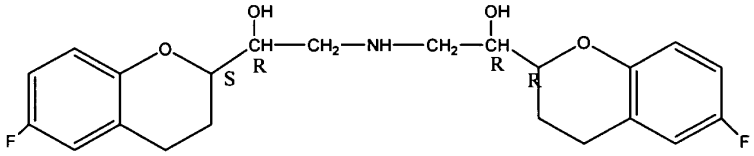
[iminobismethylene]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol] or a pharmaceutically acceptable acid addition salt thereof. The claims of the 040 patent are reproduced below:

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:



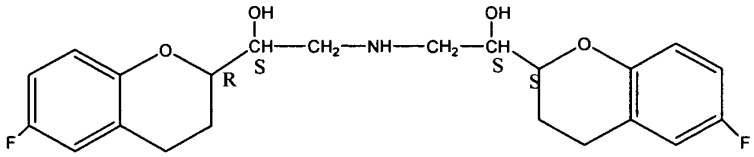
or a pharmaceutically acceptable acid addition salt thereof.

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-dihydr o-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.

III. Detailed Explanation of the Pertinency of the Documents to the Claims

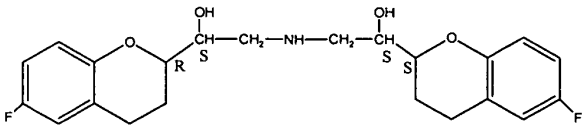
The claimed inventions are based, in part, on the discovery that combining two of the ten possible stereoisomers of α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol] , *i.e.,* the RSSS and SRRR enantiomers, provides unexpected and unique properties.

Documents 1 to 3 that were authored by De Crée, *et al.* and published before the earliest priority date of the 040 Patent describe studies on the effects of nebivolol in select subjects. "Nebivolol" is the name currently associated with a drug comprising a racemic mixture of the RSSS and SRRR enantiomers of α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol]. This drug is marketed in many countries outside North America under the brand name Nebilet® for the treatment of hypertension.

Because Documents 1 to 3 refer to studies on the effects of nebivolol, a question is raised as to whether they anticipate claims 2 to 6 of the 040 patent under 35 U.S.C. §102 and whether they render claim 1 obvious under 35 U.S.C. §103.

Table 1 provides a claim chart identifying disclosure in Documents 1 to 3 that is potentially relevant to claims 1 to 6 of the 040 patent.

TABLE 1

Claims of 040 Patent	Documents 1 -3
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	Document 1 states in its abstract that seven volunteers received a daily oral dose of 5 mg nebivolol for seven days. Document 2 refers to narbivolol as equivalent to R67555. Document 3 refers to nebivolol as R67555. Nebivolol is identified as a product from Janssen Pharmaceutica.

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