UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COALITION FOR AFFORDABLE DRUGS VI LLC

PETITIONER

V.

GRÜNENTHAL GMBH

PATENT OWNER

CASE NO.: UNASSIGNED
PATENT NO. 7,994,364
FILED: DECEMBER 10, 2009
ISSUED: AUGUST 9, 2011
INVENTORS: ANDREAS FISCHER, *ET AL.*

TITLE: CRYSTALLINE FORMS OF (-)-(1R,2R)-3-(3-DIMETHYLAMINO-1-ETHYL-2-METHYLPROPYL)-PHENOL HYDROCHLORIDE

DECLARATION OF RON BIHOVSKY, PH. D

I, Ron Bihovsky, declare as follows:

I. PROFESSIONAL BACKGROUND

1. I make this declaration based on my personal knowledge, consideration of the materials I discuss herein, and my expert opinions.

2. I am an organic chemistry and medicinal chemistry expert. I have served as an expert in numerous biotechnology and pharmaceutical cases, many requiring laboratory investigation. In my laboratory, I also synthesize organic compounds for the pharmaceutical, biotechnology, and agrochemical industries. I have more than 35 years of academic and industrial chemistry experience. My research has resulted in 50 publications in refereed journals, 15 granted U.S. Patents, and numerous foreign patents.

3. I obtained my Bachelor of Science degree in chemistry from the State University of New York, Stony Brook in 1970. I earned a Ph.D. in organic chemistry from the University of California, Berkeley, and was a National Institute of Health postdoctoral fellow at the University of Wisconsin, Madison. My research included synthesis and structure elucidation of biologically-active molecules. Subsequently, I worked as a professor of organic chemistry at Stony Brook University, where I preformed organic chemistry research, synthesized natural products, supervised graduate students and postdoctoral fellows, and taught classes including graduate level organic synthesis.

4. I then worked in the pharmaceutical industry as a medicinal chemist in roles of increasing responsibility at Berlex Laboratories and Cephalon Inc. where I synthesized numerous classes of small molecules ranging from heterocycles to peptide mimetics as potential pharmaceuticals.

5. In 2001, I founded Key Synthesis LLC, an organic chemistry

laboratory located in the Philadelphia, Pennsylvania metropolitan area. Key Synthesis is fully equipped to conduct custom organic synthesis, contract medicinal chemistry research and process research for the pharmaceutical and biotechnology industries. I am currently the president of Key Synthesis LLC. I also utilize my laboratory to conduct experiments to investigate the validity of pharmaceutical patent claims.

6. My qualifications are further detailed in my curriculum vitae, a copy of which is attached hereto as Exhibit 1015.

7. I have been asked to provide my opinions and views based upon my review and analysis of the literature cited below, as well as my education, training, and experience in organic synthesis.

II. FEES

8. I have no financial interest in the outcome of this litigation. I invoice at a rate of $300 per hour for consulting and $350 per hour plus expenses for laboratory work or testimony.

III. MATERIALS REVIEWED

9. I have reviewed certain patents pertaining to tapentadol hydrochloride and crystalline forms thereof: U.S. Patent No. 7,994,364 ("the '364 patent") (Ex. 1001); U.S. Patent No. 6,344,558 ("the '558 patent") (Ex. 1018); EP 0 693 475 ("the '475 patent") (Ex. 1006); WO 03/035053 (Ex. 1009); and EP 1612203 (Ex. 1022).

IV. LEVEL OF ORDINARY SKILL IN THE ART

10. A person of ordinary skill in the art ("POSA") in connection with the '364 patent would typically have a Ph.D. in fields relevant to small molecule drug development, such as biochemistry, medicinal chemistry, organic chemistry, or the equivalent, or a bachelor's degree in the same field(s) with four to six years of

practical experience.

V. TAPENTADOL HYDROCHLORIDE SYNTHESIS

11. I was asked in May 2015, to prepare Form B of tapentadol hydrochloride according to the examples in the ’364 and ’475 patents. The ’364 patent describes Form A (Examples 1 - 6) and Form B (Examples 7 – 9 and 16). The ’364 patent (Examples 1 – 7) states that tapentadol hydrochloride was prepared according to Example 25 (which references Examples 1, 2, and 24) of the ’475 patent. The examples in the ’475 and ’364 patents have also been published in U.S. Patent No. 6,344,558 and EP 1612203, respectively.

12. Specifically, according to the ’364 patent (Examples 1 – 4 and 6), Form A of tapentadol hydrochloride was prepared by recrystallization from various solvents or (Example 5) by cooling to - 40 °C.

13. Additionally, according to the ’364 patent, Form B of tapentadol hydrochloride was prepared in Example 7 by treating a solution of tapentadol dissolved in 2-butanone with trimethylchlorosilane (TMSCl) and water. Example 7 of the ’364 patent states that Form B was prepared according to Example 25 of the ’475 patent, which in turn refers to Example 24 of the ’475 patent.

14. I note that the ’364 patent provides no evidence that the crystalline solid obtained from the Example 7 procedure produced the XRPD pattern in Figure 4 of the ’364 patent which is attributed to the Form B polymorph. Furthermore, the ’364 patent contains no indication of how the polymorph identified as Form B in Figure 4 was prepared. Example 7 of the ‘364 patent is the only example for preparation of Form B which follows the ’475 patent’s method for obtaining tapentadol HCl, but it does not explicitly link the ‘364 patent’s Figure 4 XRPD pattern to Example 7 and the synthetic procedure of the ’475 patent. At best, Example 7 confirms that “Form B … was generated as proven by X-ray powder diffraction and by RAMAN microscopic analysis,” without any indication of yield

or percent purity. Thus, a POSA would not reasonably conclude that the Form B XRPD pattern of the ’364 patent’s Figure 4 was produced using the ’364 patent’s procedure of Example 7, as derived from the ’475 patent’s Example 25. In contrast, as described below, when I repeated the procedure described in Example 7, I obtained Form A or a mixture of Form A and Form B.

15. Further, according to the ’364 patent, Examples 8, 9, and 16, Form B of tapentadol hydrochloride was also prepared by heating milled or cryoground (cryogrinded) Form A of tapentadol hydrochloride.

16. The ratios of Form A to Form B, summarized in this declaration, were determined by Dr. William Mayo and his colleagues at H&M Analytical Services. The reported ratios of A:B were determined by the ratios of the strong peak areas at 18.045° and 18.240° respectively.

17. In the experiments which follow, my notebook reference number is included in parentheses.

A. Obtaining tapentadol hydrochloride (Form A) for use in synthesizing Form B

18. I obtained tapentadol hydrochloride (Form A) from Dr. William Mayo at H&M Analytical Services. This sample was supplied by MedChem Express, catalog number HY-70042 / CY-0879, batch number 03046. Documentation supplied with the sample included NMR and mass spectra which are consistent with the structure. Purity and enantiomeric excess were stated to be greater than 99%. I also obtained the NMR of the sample and confirmed that it was consistent with the NMR provided by MedChem Express. I observed that the sample was a fine white solid, melting at 204–207 °C. Dr. Mayo obtained the X-Ray Diffraction (“XRD”) pattern from this sample and informed me that the X-ray powder pattern was consistent with Form A of tapentadol hydrochloride. I stored the sample at 5 °C. (No. 10-194-1)

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