IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Atty. Docket No. 06-796)

In the Application of:	)	
	)	
Fanara et al.	)	
	)	Examiner: Timothy P.
Thomas		
Serial No. 10/599,451	)	
	)	Art Unit: 1614
Filing Date: September 28, 2006	)	
	)	Confirmation No.: 9142
For: Pharmaceutical Composition of Piperazine Derivatives	)	

DECLARATION OF DOMENICO FANARA UNDER 37 CFR 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Domenico Fanara, in support of the above-identified patent application, do aver and state as follows:

1. I am the first named inventor of this application.
2. I received a Pharmacy degree from University of Liège Belgium in 1986
3. I have been employed by UCB Pharma SA since 1993 after having spent 6 years in another pharmaceutical company Galephar S.A as head of formulation development.
4. A copy of my CV is attached hereto as Exhibit A that include list of publications
5. Levocetirizine and particularly its dihydrochloride salt are known to be useful as antihistamines. Levocetirizine dihydrochloride is available in solid dosage form. The present invention is directed to a formulation that allows for the availability of levocetirizine and its salts in liquid dosage form.

6. One common problem with liquid pharmaceutical formulations in general is that the presence of water can allow for the growth of microorganisms, particularly after the seal on the product packaging has been broken, and when the contents of the packaging are exposed to dosing implements. Thus, it has become common practice to include preservatives in such formulations to prevent the growth of such microorganisms. Methyl parahydroxybenzoate and propyl parahydroxybenzoate, commonly known as methyl paraben and propyl paraben, respectively (hereinafter "MP" and "PP," together "parabens"), are frequently used for this purpose.

7. The combined parabens in typical pharmaceutical preparations is at least about 2 mg/ml, as shown by an accepted pharmaceutical treatise (see, Remington, The Science and Practice of Pharmacy, 21st ed., 2005, pp. 748-749, Ex. B, hereinafter "the Remington treatise").

8. In the course of developing liquid pharmaceutical formulations of levocetirizine and its salts, we were surprised to discover that levocetirizine itself can act as an anti-microbial. This is shown in Tables 5 and 6 of the present application, in which samples of an oral solution and oral drops containing 0.5 and 5.0 mg/ml of levocetirizine hydrochloride, respectively, and which were inoculated with various microbes, were essentially free of bacteria 14, 21, and 28 days after inoculation. The oral drop formulation that contained the higher concentration of the drug also was substantially free of fungal infection 21 and 28 days after inoculation.

9. This result was totally unexpected. Even though levocetirizine and its salts were well characterized, to our knowledge it had not been recognized prior to our invention that levocetirizine has antimicrobial properties. This led to our discovery that liquid pharmaceutical compositions of levocetirizine could be formulated with lower paraben concentrations than previously thought necessary and without additional preservatives.

10. Submitted herewith as Exhibit C are the results of testing of antimicrobial efficacy on several batches of oral drop solution having 5 mg/ml of levocetirizine, 0.3375 mg/ml MP and 0.0375 mg/ml of PP, for an MP/PP ratio

of 9 and a total parabens content of 0.375 mg/ml. The compositions contained no other preservative. The batch sizes varied from 100 L to 1000 L. The testing results confirmed that inoculated test samples of all of the batches were essentially free of both bacteria and fungus 14 and 28 days after inoculation. This result is surprising because the amount of parabens used was less than one fifth of the minimum recommended by the Remington treatise.

11. Submitted herewith as Exhibit D are the results of testing of antimicrobial efficacy on two batches of oral solution containing 0.5 mg/ml of levocetirizine, 0.675 mg/ml MP and 0.075 mg/ml of PP, for an MP/PP ratio of 9 and a total parabens content of 0.750 mg/ml. The compositions contained no other preservative. The batch sizes were each 1000 L. The testing results confirmed that inoculated test samples of both of the batches were essentially free of bacteria and two of three species of fungus 14 and 28 days after inoculation. This result is surprising because the amount of parabens used was less than one half of the minimum recommended by the Remington treatise.

12. I have reviewed the references cited by the U.S. Patent and Trademark Office against this application.

13. WO 02/47680 of DeLongueville et al. relates to earlier work on cetirizine and its optically active isomers, performed by the present assignee. The only mention of any specific preservative is at page 6, lines18-22, which states, "As an example of a composition according to the present invention, the following formulation of a syrup (oral drops) is preferred: cetirizine dihydrochloride, methyl- and propyparaben, saccharinum, and purified water." There is no teaching or suggestion as to the relative amounts of any of these components of the composition. As one skilled in the art, upon reading this disclosure I would understand that the amount of total parabens intended was at least the minimum of 2 mg/ml as set forth in the Remington treatise and as generally understood at that time as being a typical concentration of preservative for a liquid pharmaceutical product.

14. Gilliland et al., *J. Applied. Bacteriology*, 1992, 72, 252-257 ("Gilliland 1"), reports a study on the effect of temperature on the kill rate of *E. coli* by methyl and propyl parabens. Solutions containing 0.12% MP (1.2 mg/ml) and 0.012% PP (.12 mg/ml) were evaluated at temperatures of 34, 37, 40, and 42°C, which are well beyond the temperatures at which most pharmaceutical compositions are stored. The combined parabens in the tested solutions was 1.32 mg/ml, more than 10% higher than the 1.125 mg/ml maximum parabens concentration of our invention. The longest time period over which measurements were made was 28 hours (Fig. 5) so that the results cannot be properly extrapolated to pharmaceutical compositions which require long-term storage. No pharmaceutical component of any type was included in the formulations evaluated. In a test run in which the temperature of the sample was constantly altered rather than being held at a steady state, the authors found that the viable count of *E. coli* showed variability that was too high to enable adequately precise rate constants to be calculated, such that the method was of little value in that experiment (p. 257). The amount of parabens used in Gilliland 1 is outside the claims of our invention; the experiments of Gilliland were conducted at different temperatures, and for much shorter times than the experiments of our application. For at least these reasons, as one skilled in the art, it is my opinion that Gilliland I would be afforded little weight by those of ordinary skill in the art with respect to its relevance to the present invention and does not teach or suggest a pharmaceutical solution of levocetirizine or one of its salts, and with a combined parabens of no more than 1.125 mg/ml.

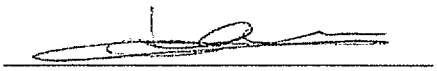
15. Gilliland et al., *J. Applied. Bacteriology*, 1992, 72, 258-261 ("Gilliland 2"), reports a study on whether methyl and propyl paraben act synergistically. Various solutions were prepared with MP at either 0.12% or 0.14%, and with PP at 0.012% and 0.014%. These concentration levels were selected because at these levels the kill rate was slow enough that the rate constants could be calculated; higher concentrations killed bacteria too quickly for the required sampling to be carried out satisfactorily. (p. 259) To me, as one skilled in the

art, this suggests that the concentrations selected for study were not necessarily optimal for use in a pharmaceutical composition that have to be essentially free of such bacteria. I also note that the time period over which testing was done was about six hours, so that the results cannot be properly extrapolated to pharmaceutical compositions which require long-term storage.

16. Doron discloses compositions that significantly reduce E.coli, but at paraben concentration that are 37% and 248% greater than the concentrations used in our invention. As one skilled in the art, this reference suggests to me that at the MP/PP ratios of Doron, a much greater total concentration of parabens is necessary to achieve a composition that remains substantially free of bacteria than was achieved with our invention.

17. As one skilled in the art, the combination of Doron, DeLongueville, Gilliland I and Gilliland II does not teach or suggest that a pharmaceutical formulation could be prepared that is maintained substantially free of bacteria and having the a total of MP and PP of no greater than 1.125 mg/ml, and no other preservative. Gilliland I and II were thermal and kinetic studies of parabens. The authors indicate that the concentrations chosen were those that facilitated their measurements; there is no suggestion that the concentrations chosen for evaluation in these studies would be suitable for use in actual pharmaceutical compositions.

I hereby state that I have been warned that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. 1001), and that such willful false statements may jeopardize the validity of the application or document or any registration resulting therefrom, and I declare that all statements made of my own knowledge are true; and all statements made on information and belief are believed to be true.



Domenico Fanara

Date: 23/11/2010

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