

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of : Attorney Docket No. 2005_0232A
Shirou SAWA et al. : Confirmation No. 1756
Serial No. 10/525,006 : Group Art Unit 1627
Filed March 28, 2005 : Examiner Layla Soroush
AQUEOUS LIQUID PREPARATION : **Mail Stop: Amendment**
CONTAINING 2-AMINO-3-(4-
BROMOBENZOYL)PHENYLACETIC ACID

AMENDMENT

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

Sir:

Responsive to the Official Action dated May 6, 2011, the time for responding thereto being extended for one month in accordance with a petition for extension submitted concurrently herewith, please amend the above-identified application as follows:

Innopharma EX1015, Page 1

REMARKS

Favorable reconsideration is respectfully solicited in view of the foregoing amendments and following remarks.

Applicants wish to thank the Examiner Soroush and SPE Padmanabhan for their courtesy and assistance provided to the Applicants' representative during the personal interview held on September 1, 2011.

The claims have been amended as proposed by the Applicants and as suggested by the Examiners. Specifically, the second component has been limited to tyloxapol to expedite allowance. Such limitation is made without prejudice to the filing of a divisional application. Claim 41 has been amended to remove the "limited to" phrase, and method claims 61-62 are cancelled without prejudice.

Turning to the rejections, claims 41-48, 50-51, 53-55 and 58-59 are rejected under 35 USC 103 as unpatentable over Yanni in view of Guy. Such rejection is respectfully traversed as applied to the amended claims.

As discussed during the interview, the rejection appears to take the position that Yanni discloses in Preparation XV a composition of bromfenac with polysorbate 80. However Preparation XV does not disclose bromfenac, the acid, but an amide derivative thereof.

Moreover, Yanni teaches that bromfenac acids have problems such as difficulty in formulating stable solutions, and provoking ocular irritation. See column 1, line 60 to column 2, line 3. The object of Yanni is to make amide and ester derivatives of bromfenac which the inventors found to have better stability while having similar anti-inflammatory activity. See for example column 2, lines 23-43.

Bromfenac is mentioned in Yanni in Table 1, merely as a reference compound for comparison purposes with the novel amide and ester derivatives of Yanni. It can be seen from the description of the anti-inflammatory tests described in columns 13 and 14 that bromfenac was tested merely in a 0.1% solution of the compound, and not in a pharmaceutical composition.

The pharmaceutical compositions disclosed in the Tables of columns 16 and 17 of Yanni are directed to compositions of an "Active Agent" with polysorbate 80 and other components. The "Active Agent" is defined on lines 50-51 of column 16 to mean "one or more compounds of Formula I". The compounds of Formula I are described from the bottom of column 2 to 3. From

the definition of “Y” in the compounds, it is apparent that these compounds are limited to the amide or ester of bromfenac and do not encompass the bromfenac acid itself.

In summary, neither Preparation XV nor the remainder of Yanni disclose a composition of bromfenac as claimed, or its salt or hydrate, together with polysorbate 80 as contended in the rejection.

Moreover, Yanni teach away from using bromfenac as claimed, due to problems with obtaining stable solutions and provoking ocular irritation. See column 1 line 60 to column 2 line 3.

Therefore Yanni do not teach or suggest a composition of bromfenac with polysorbate 80.

Guy is cited for teaching the equivalency of polysorbate 80 and tyloxapol.

However Guy is directed to solving the problem of agglomeration of water insoluble steroid compounds such as loteprednol etabonate. See for example column 2, lines 45-65. On the other hand, bromfenac is a nonsteroidal compound.

Therefore one skilled in the art would not have been motivated to combine the teachings of Yanni directed to nonsteroidal compositions with Guy directed to steroidal compositions.

According to the USTPO guidelines, “[i]t is improper to combine references where the references teach away from their combination.” See MPEP § 2145, citing *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983); see also *McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1354 (Fed.Cir. 2001) (“It is well-established that references which “teach away cannot serve to create a prima facie case of obviousness.”) (citations omitted).

Moreover, the present inventors have found that tyloxapol is not equivalent to polysorbate 80 when combined with bromfenac.

The present inventors have discovered that tyloxapol has an unexpected property in stabilizing an aqueous solution of bromfenac in comparison with polysorbate 80. Please see the description of Experimental Example 1 and Table 1 on pages 14-16 of the specification.

In the Experimental Example, the stability of an aqueous solution of bromfenac was measured by storing the bromfenac solution with polysorbate 80 (see Comparison Example 1) and, separately, with tyloxapol (see A-02), under conditions of pH 7.0 at 60°C for 4 weeks. The remaining rate % of bromfenac was measured after the test.

As shown in Table 1, only 51.3% of bromfenac remained in the aqueous solution when stored with polysorbate 80. In contrast, 73.8% of bromfenac remained in the aqueous solution when stored with tyloxapol.

Thus the present inventors have found that tyloxapol has an unexpected stabilizing effect on an aqueous solution of bromfenac in comparison to polysorbate 80. Therefore the present inventors have found that tyloxapol and polysorbate 80 are not equivalent compounds. Such unequivalency, and such remarkable effects, could not have been obvious to one skilled in the art from the cited references.

For the foregoing reasons, it is respectfully submitted that the teachings of the cited references do not suggest the claimed bromfenac preparation as amended, nor the unexpected properties of the preparation.

Claims 49, 56, 60 and 64-68 are rejected under 103 as unpatentable over Yanni, Guy and Gamache.

The rejection of these claims is believed to be overcome in view of the foregoing amendments and remarks.

Lastly, claims 41-51, 53-56, 58-60 and 64-68 are provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-43 of copending application Serial No. 11/755,662.

It is believed that all other grounds of rejection have been overcome in view of the instant response. Accordingly, it is respectfully submitted that this provisional ground of rejection should be withdrawn and the application passed on to allowance.

In summary, it is believed that each ground of rejection set forth in the Official Action has been overcome, and that the application is now in condition for allowance. Accordingly such allowance is solicited.

Respectfully submitted,

Shirou SAWA et al.

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By Cheek/

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