IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of		**Confirmation No. 2612**
Masayo HIGASHIYAMA		Attorney Docket No. 2004_1016A
Serial No. 10/500,354	:	Group Art Unit 1611
Filed June 30, 2004	:	Examiner Charlesworth E. Rae
AQUEOUS LIQUID PREPARATIONS AND LIGHT-STABILIZED AQUEOUS LIQUID PREPARATIONS	:	**Mail Stop: Amendment**

AMENDMENT

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

Sir:

Responsive to the Official Action dated August 5, 2008, the time for responding thereto being extended for two months in accordance with a Petition for extension submitted concurrently herewith, please amend the above-identified application as follows:

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Amendments to the Claims

1. (Currently amended) An aqueous liquid preparation comprising, in an aqueous solution, (+)-(S)-4-[4-[(4-chlorophenyl)(2-pyridyl)methoxy]piperidino]butyric acid or a pharmacologically acceptable acid addition salt thereof, and a water-soluble metal chloride ~~as~~ in a light-stabilizing ~~agent in an aqueous solution~~effective amount.

2. (Original) The aqueous liquid preparation of claim 1, wherein the metal chloride has a concentration selected from the range of a lower limit concentration of 0.15 w/v% and an upper limit concentration of 1.5 w/v%.

3. (Previously presented) The aqueous liquid preparation of claim 1, wherein the metal chloride is at least one kind selected from sodium chloride, potassium chloride and calcium chloride.

4. (Previously presented) The aqueous liquid preparation of claim 1, wherein the (+)-(S)-4-[4-[(4-chlorophenyl)(2-pyridyl)methoxy]piperidino]butyric acid or the pharmacologically acceptable acid addition salt thereof has a concentration selected from the range of a lower limit concentration of 0.1 w/v% and an upper limit concentration of 2.0 w/v%.

5. (Previously presented) The aqueous liquid preparation of claim 1, which is an acid addition salt of (+)-(S)-4-[4-[(4-chlorophenyl)(2-pyridyl)methoxy]piperidino]butyric acid.

6. (Original) The aqueous liquid preparation of claim 5, wherein the acid addition salt is monobenzenesulfonate.

7. (Previously presented) The aqueous liquid preparation of claim 1, wherein the aqueous liquid preparation has a pH in the range of 4-8.5.

8. (Previously presented) The aqueous liquid preparation of claim 1, which is an eye drop.

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9. (Previously presented) The aqueous liquid preparation of claim 1, which is a nasal drop.

10. (Currently amended) An aqueous eye drop comprising, in an aqueous solution, (+)-(S)-4-[4-[(4-chlorophenyl)(2-pyridyl)methoxy]piperidino]butyric acid monobenzenesulfonate and sodium chloride at not less than 0.2 w/v% and not more than 0.8 w/v% ~~as~~ in a light-stabilizing ~~agent in an aqueous solution~~effective amount.

11. (Cancelled)

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REMARKS

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

Applicants confirm with thanks the Examiner's indication during the telephone conference held on August 18, 2008 that the finality of the last Office Action is withdrawn.

Applicants wish to express their sincere appreciation of the Examiner Charlesworth Rae and his supervisor, Supervisory Examiner Sharmila Landau, for their courtesy and assistance provided during the personal interview held on August 21, 2008.

Claims 1 and 10 have been amended as discussed during the interview. Specifically, claims 1 and 10 have been amended to clarify that the water-soluble metal chloride is contained in the aqueous solution in a light-stabilizing effective amount. Claims 1 and 10 have also been amended to clarify that the aqueous liquid preparation comprises the claimed ingredients in an aqueous solution. Claim 11 is cancelled without prejudice to expedite allowance.

Claims 1-10 solely rejected under 35 USC 103(a) as unpatentable over Koida et al. in view of Kita et al. and Remington's. This ground of rejection is respectfully traversed as applied to the amended claims.

As discussed during the interview, the combined teachings of the cited references fail to render obvious the claimed invention as amended. The cited Koida teaches the claimed compound but does not teach the compound in combination with any water-soluble metal chloride. The compound is only combined with mannitol, sucrose, lactose and polyethylene glycol.

Similarly, Kita teaches the claimed compound but does not teach the compound in combination with any water-soluble metal chloride.

Remington's teaches a long list of isotonicity agents which can be used to adjust the isotonicity of eye and nasal drops. Remington fails to disclose any of these agents in combination with the claimed compound. The inventors have surprisingly discovered that a small group of these isotonicity agents, namely the water-soluble metal chlorides, unexpectedly stabilize the claimed compound from light. The Examiners appeared to be persuaded by these facts during the interview.

During the interview, the Declaration of record was reviewed to determine if the comparative experiments were satisfactory to the Examiners for showing unexpected results for

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the claims. The Examiners appeared satisfied that the experiments support the unexpected light stability of the claimed compound by the claimed group of water soluble metal chlorides, based upon the results of Experiment 1 of sodium chloride, potassium chloride and calcium chloride.

Experiment 2 of the Declaration compares the light stabilizing effect of sodium chloride to the combination of glycerin and boric acid. Experiment 4 compares the light stabilizing effect of sodium chloride to glycerin. The experiment also discusses replacing glycerin with glucose or mannitol in Formulation 16, however the Table 4 does not reflect this fact.

However the Examiners suggested a side-by-side comparison of the claimed invention with the closest prior art. The closest prior art is Koida. Koida teaches combining the claimed compound with mannitol, sucrose, lactose or polyethylene glycol. The Examiners recommended that a Supplemental Declaration be filed comparing the light stabilizing activity of a claimed water soluble metal chloride with any one of mannitol, sucrose, lactose or polyethylene glycol.

Submitted herewith is a Supplemental Declaration to establish the unobviousness of the present invention from Koida et al., by clarifying the description of Experiment 4 in the earlier Declaration, which was pointed out to be indefinite by the Examiner during the interview.

Koida et al. disclose a method of preventing racemization of bepotastine, which includes addition of sugars to an oral solid preparation. As reported in the Declaration, Formulation 7 (containing 0.6% w/v% sodium chloride) remained pale-yellow and clear even after exposure to light, but Formulation 18 (containing 3.3 w/v% glucose) and Formulation 19 (containing 3.3 w/v% mannitol) both turned black green.

It has thus been clearly established that the bepotastine-stabilizing effect achieved by the addition of water-soluble metal chloride to an aqueous solution containing bepotastine cannot be achieved by the addition of sugars. As mentioned above, stabilization of bepotastine by the addition of sugars is different from stabilization of bepotastine by the addition of water-soluble metal chloride, and those of ordinary skill in the art cannot easily conceive stabilization of bepotastine achieved by the present invention by the addition of water-soluble metal chloride, from the technique of Koida et al.

In summary, it is respectfully submitted that the prior art fails to suggest the unexpected light stabilization of the claimed compound using a water-soluble metal chloride.

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