IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	**MAIL STOP AMENDMENT**
Nicholas Bodor et al.	)	Group Art Unit: 1623
Application No.: 10/551,205	)	Examiner: JONATHAN S LAU
Filed: November 14, 2006	)	Confirmation No.: 4092
For: ORAL FORMULATIONS OF CLADRIBINE	)	

REPLY AND AMENDMENT

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

Sir:

In response to the Office Action dated April 4, 2008, please first amend the above-identified patent application as follows:

AMENDMENTS TO THE SPECIFICATION:

Please replace the paragraph at page 22, lines 8-16 of the specification with the following amended paragraph:

> The compositions of the invention are particularly suitable as modalities for the treatment of any cladribine-responsive disease. Several disease states responsive to cladribine are well-documented in the literature (see *infra).* For any target disease state, an effective amount of the complex cladribine-cyclodextrin ~~comples~~ complex, *i.e.* the amorphous mixture of the optimized amorphous saturated cladribine-amorphous cyclodextrin complex with amorphous free cladribine as described above is used (e.g., an amount ~~affective~~ effective for the treatment of multiple sclerosis, rheumatoid arthritis, or leukemia).

Please replace the paragraph at page 23, lines 7-28, of the specification with the following amended paragraph:

> Moreover, the route of administration for which the therapeutically effective dosages are taught in the literature should be taken into consideration. While the instant compositions optimize the bioavailability of cladribine following oral administration, it will be appreciated that even optimal bioavailability from oral dosage forms is not expected to approach bioavailability ~~obtain~~ obtained after intravenous administration, particularly at early time points. Thus, it is often appropriate to increase a dosage suggested for intravenous administration to arrive at a suitable dosage for incorporation into a solid oral dosage form. At the present time, it is envisioned that, for the treatment of multiple sclerosis, 10 mg of cladribine in the instant complex cladribine-cyclodextrin complex in the instant solid dosage form would be administered once per day for a period of five to seven days in the first month, repeated for another period of five to seven days in the second month, followed by ten months of no treatment. Alternatively the patient would

be treated with 10 mg of cladribine in the instant complex cladribine-cyclodextrin complex in the instant dosage form once per day for a period of five to seven days per month for a total of six months, followed by eighteen months of no treatment. ~~For further dosing information, see also U.S. Provisional Patent Application No.~~ [[_____]] ~~[IVAX0021-P-USA/Attorney Docket No. 033935-011], and U.S. Provisional Patent Application No.~~ [[_____]] ~~[IVAX0022-P-USA/Attorney Docket No. 033935-012], both entitled "Cladribine Regimen for Treating Multiple Sclerosis", both filed on March 25, 2004 and incorporated by reference herein in their entireties.~~

AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application:

LISTING OF CLAIMS:

1. (Currently Amended) A pharmaceutical composition comprising a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture consisting of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form, said composition comprising no significant amount of free crystalline cladribine therein.

2. (Currently Amended) The pharmaceutical composition according to Claim 1, wherein the complex cladribine-cyclodextrin complex is saturated with cladribine.

3. (Previously Presented) The composition according to Claim 1, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

4. (Previously Presented) The composition according to Claim 1, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin.

5. (Previously Presented) The composition according to Claim 1, wherein the amorphous cyclodextrin is hydroxypropyl-γ-cyclodextrin.

6. (Previously Presented) The composition according to Claim 1, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.

7. (Original) The composition according to Claim 6, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin.

8. (Original) The composition according to Claim 7, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:14.

9. (Original) The composition according to Claim 7, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:11.

10. (Original) The composition according to Claim 6, wherein the amorphous cyclodextrin is hydroxypropyl-γ-cyclodextrin.

11. (Currently Amended) The composition according to ~~Claim 1~~ Claim 2, wherein the approximate molar ratio of cladribine to amorphous cyclodextrin corresponds to a point located on the curve of a phase solubility diagram for saturated complex cladribine-cyclodextrin complexes, said curve defining complex saturated complexes of cladribine in varying concentrations of the cyclodextrin.

12. (Previously Presented) The composition according to Claim 1, wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b).

13. (Withdrawn and Currently Amended) A method for enhancing the oral bioavailability of cladribine comprising orally administering to a subject in need thereof a pharmaceutical composition comprising a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture consisting of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form, said composition comprising no significant amount of free crystalline cladribine therein.

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