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.

14. (Withdrawn and Currently Amended) The method according to Claim 13, wherein the complex cladribine-cyclodextrin complex is saturated with cladribine.

15. (Withdrawn) The method according to Claim 13, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

16. (Withdrawn) The method according to Claim 13, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin.

17. (Withdrawn) The method according to Claim 13, wherein the amorphous cyclodextrin is hydroxypropyl-γ-cyclodextrin.

18. (Withdrawn) The method according to Claim 13, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.

19. (Withdrawn) The method according to Claim 18, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin.

20. (Withdrawn) The method according to Claim 19, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:14.

21. (Withdrawn) The method according to Claim 19, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:11.

22. (Withdrawn) The method according to Claim 18, wherein the amorphous cyclodextrin is hydroxypropyl-γ-cyclodextrin.

23. (Withdrawn and Currently Amended) The method according to ~~Claim 13~~ Claim 14, 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.

24. (Withdrawn) The method according to Claim 13, 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).

25. (Withdrawn and Currently Amended) A method for the treatment of symptoms of a cladribine-responsive condition in a subject suffering from said symptoms comprising orally administering to said subject 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.

26. (Withdrawn and Currently Amended) The method according to Claim 25, wherein the complex cladribine-cyclodextrin complex is saturated with cladribine.

27. (Withdrawn) The method according to Claim 25, wherein the cladribine-responsive condition is selected from the group consisting of multiple sclerosis, rheumatoid arthritis and leukemia.

28. (Withdrawn) The method according to Claim 27, wherein the cladribine-responsive condition is multiple sclerosis.

29. (Withdrawn) The method according to Claim 25, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

30. (Withdrawn) The method according to Claim 25, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.

31. (Withdrawn) The method according to Claim 25, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin.

32. (Withdrawn) The method according to Claim 31, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:14.

33. (Withdrawn) The method according to Claim 31, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:11.

34. (Withdrawn) The method according to Claim 25, wherein the amorphous cyclodextrin is hydropropyl-γ-cyclodextrin.

35. (Withdrawn) The method according to Claim 25, 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).

36.-55. (Cancelled)

56. (Currently Amended) 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.

57. (Currently Amended) The complex cladribine-cyclodextrin complex according to Claim 56, saturated with cladribine.

58. (Currently Amended) The complex cladribine-cyclodextrin complex according to Claim 56, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

59. (Currently Amended) The complex cladribine-cyclodextrin complex according to Claim 56, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin.

60. (Currently Amended) The complex cladribine-cyclodextrin complex according to Claim 56, wherein the amorphous cyclodextrin is hydroxypropyl-γ-cyclodextrin.

61. (Currently Amended) The complex cladribine-cyclodextrin complex according to Claim 56, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.

62. (Currently Amended) The complex cladribine-cyclodextrin complex according to Claim 61, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin.

63. (Currently Amended) The complex cladribine-cyclodextrin complex according to Claim 62, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:14.

64. (Currently Amended) The complex cladribine-cyclodextrin complex according to Claim 62, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:11.

65. (Currently Amended) The complex cladribine-cyclodextrin complex according to Claim 61, wherein the amorphous cyclodextrin is hydroxypropyl-γ-cyclodextrin.

66. (Currently Amended) The complex cladribine-cyclodextrin complex according to Claim 56, 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).

67. (Withdrawn and Currently Amended) A process for the preparation of a complex cladribine-cyclodextrin complex as claimed in Claim 56, which comprises the steps of:

(i) combining cladribine and an amorphous cyclodextrin in water at a temperature of from about [[40]] 45 to about 80°C and maintaining said temperature for a period of from about 6 to about 24 hours;

(ii) cooling the resultant aqueous solution to room temperature; and

(iii) lyophilizing the cooled solution to afford an amorphous product.

68. (Withdrawn) A process according to Claim 67, further comprising a filtration step following step (ii).

69. (Withdrawn) A process according to Claim 67, wherein step (i) is performed at a temperature of from about 45 to about 60°C.

70. (Withdrawn) A process according to Claim 67, wherein step (i) is performed at a temperature of from about 45 to about 50°C.

71. (Withdrawn) A process according to Claim 69, wherein step (i) is performed with stirring.

72. (withdrawn) A process according to Claim 71, wherein step (i) is performed for a period of from about 6 to about 9 hours.

73. (Withdrawn) A process according to Claim 67, wherein step (ii) is performed for a period of from about 6 to about 9 hours.

74. (Withdrawn) A process according to Claim 67, wherein step (iii) comprises an initial freezing stage in which the solution is cooled to from about -40 to about -80° C, and held at said temperature for a period of from about 2 to about 4 hours.

75. (Withdrawn) A process according to Claim 74, wherein, in the initial freezing stage of step (iii), the solution is cooled to about -45°C.

76. (Withdrawn) A process according to Claim 67, wherein 12.00 parts by weight of cladribine and 172.50 parts by weight of hydroxypropyl-β-cyclodextrin are introduced in step (i).

77. (Withdrawn) A process according to Claim 67, wherein 16.35 parts by weight of cladribine and 172.50 parts by weight of hydroxypropyl-β-cyclodextrin are introduced in step (i).

78. (Withdrawn) A process according to Claim 76, wherein 825 parts by volume of water are introduced in step (i).

79. (Withdrawn) A process according to Claim 67, wherein the lyophilization step (iii) comprises:

(a) an initial freezing stage in which the complexation solution is brought to from about -40°C to about -80°C for approximately 2 to 4 hours;

(b) a primary drying stage at about -25°C for approximately 80 to 90 hours; and

(c) a secondary drying stage at about 30°C for approximately 15 to 20 hours.

80. (Withdrawn) A process according to Claim 79, wherein stage (a) of the lyophilization is conducted at about -45°C for approximately 3 to 4 hours.

81. (Withdrawn) A process according to Claim 79, wherein stage (b) of the lyophilization is conducted under a pressure of about 100 mTorr.

82. (Currently Amended) A pharmaceutical composition obtainable by a process comprising the steps of:

(i) combining cladribine and an amorphous cyclodextrin in water at a temperature of from about [[40]] 45 to about 80°C and maintaining said temperature for a period of from about 6 to about 24 hours;

(ii) cooling the resultant aqueous solution to room temperature;

(iii) lyophilizing the cooled solution to afford an amorphous product; and

(iv) formulating the amorphous product into a solid oral dosage form.

83. (Original) A pharmaceutical composition according to Claim 82, wherein the process further comprises a filtration step following step (i) or (ii).

84. (Previously Presented) A pharmaceutical composition according to Claim 82, wherein step (i) of the process is performed at a temperature of from about 45 to about 60°C.

85. (Previously Presented) A pharmaceutical composition according to Claim 82, wherein step (i) of the process is performed at a temperature of from about 45 to about 50°C.

86. (Previously Presented) A pharmaceutical composition according to Claim 84, wherein step (i) of the process is performed with stirring.

87. (Original) A pharmaceutical composition according to Claim 86, wherein step (i) of the process is performed for a period of from about 6 to about 9 hours.

88. (Previously Presented) A pharmaceutical composition according to Claim 82, wherein step (ii) of the process is performed for a period of from about 6 to about 9 hours.

89. (Previously Presented) A pharmaceutical composition according to Claim 82, wherein step (iii) comprises an initial freezing stage in which the solution is cooled to from about -40 to about -80°C, and held at said temperature for a period of from about 2 to about 4 hours.

90. (Original) A pharmaceutical composition according to Claim 89, wherein, in the initial freezing stage of step (iii), the solution is cooled to about -45°C.

91. (Previously Presented) A pharmaceutical composition according to Claim 82, wherein 12.00 parts by weight of cladribine and 172.50 parts by weight of the hydroxypropyl-β-cyclodextrin are introduced in step (i) of the process.

92. (Previously Presented) A pharmaceutical composition according to Claim 82, wherein 16.35 parts by weight of cladribine and 172.50 parts by weight of the hydroxypropyl-β-cyclodextrin are introduced in step (i) of the process.

93. (Previously Presented) A pharmaceutical composition according to Claim 91, wherein 825 parts by volume of water are introduced in step (i) of the process.

94. (Previously Presented) A pharmaceutical composition according to Claim 82, wherein the lyophilization step (iii) of the process comprises:

(a) an initial freezing stage in which the complexation solution is brought to from about -40°C to about -80°C for approximately 2 to 4 hours;

(b) a primary drying stage at about -25°C for approximately 80 to 90 hours; and

(c) a secondary drying stage at about 30°C for approximately 15 to 20 hours.

95. (Original) A pharmaceutical composition according to Claim 94, wherein stage (a) of the lyophilization is conducted at about -45°C for approximately 3 to 4 hours.

96. (Previously Presented) A pharmaceutical composition according to Claim 94, wherein stage (b) of the lyophilization is conducted under a pressure of about 100 mTorr.

97. (Previously Presented) A pharmaceutical composition according to Claim 82, wherein the formulation step (iv) of the process comprises blending the complex with magnesium stearate and compressing into tablets.

98. (Original) A pharmaceutical composition according to Claim 97, wherein magnesium stearate is pre-mixed with sorbitol powder before blending with the complex.

REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the following remarks.

THE DRAWINGS

Applicants appreciate the Examiner's acceptance of the drawing as filed.

INFORMATION DISCLOSURE STATEMENTS

Applicants thank the Examiner for considering the four Information Disclosure Statements previously filed herein.

FILING DATES TO WHICH CLAIMS ARE ENTITLED

The Examiner has assessed the filing dates to which he believes the claims which he has examined are entitled. Thus, Claims 1-12, 56-66 and 82-98 have been assessed by the Examiner in regard to the earliest filing date to which he believes they are entitled.

Applicants have amended Claim 82 hereinabove so that step (i) is conducted at a temperature from about 45 to about 80°C rather than from about 40 to about 80°C as previously recited. This revised range is not only supported by the instant application (e.g., page 13, lines 21-25) but also by page 12, lines 20-23, of Provisional Appln. No. 60/541,247, filed February 4, 2004; moreover, step (ii) is disclosed at least on page 14, line 3 and in Example 2 of 60/541,247; step (iii) at least on page 14, line 6 and Example 2 of 60/541,247; and step (iv) at least on page 17, lines 25-27, page 18, lines 7-10 and Example 3 of 60/541,247. Claim 88 is supported at least by page 12, lines 20-22 of 60/541,247. Thus, applicants concur with the Examiner that the filing dates of Claims 1-11, 56-65, 84, 86 and 87 are the filing date of Application No. 60/541,247, filed February 4, 2004, but add that the filing dates of Claims 82 and 88 are also the February 4, 2004 filing date of Application No. 60/541,247.

Applicants concur with the Examiner's assessment that Claims 12, 66, 83, 85 and 89 are entitled to the effective filing date of the present application; however, as

a national phase application, this application and thus Claims 12, 66, 83, 85 and 89 are entitled to the international filing date of PCT/US04/09387, that is, March 26, 2004. The Examiner's reference to November 14, 2006 as the filing date for these claims is incorrect, that date simply being the date on which the requirements of the last of the 371(c)(1), (c)(2) and (c)(4) requirements were received by the USPTO. In the official Notice of Acceptance of Application under 35 U.S.C. 371 and 37 C.F.R. 1.495, it is clearly stated: "The filing date of the above identified application is the international filing date of the international application (Article 11(3) and 35 U.S.C. 363)."

Despite the foregoing, it is not understood why the Examiner has found it necessary to assess the priority dates of the examined claims, as no art has been cited which would make it necessary to make such an assessment.

ELECTIONS/RESTRICTIONS

Applicants' election, with traverse, of the invention of Group I, Claims 1-12, 56-66 and 82-98 has been acknowledged and acted upon. Applicants continue to maintain that the amorphous nature of the various entities which make up the complex, that is the intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex which is formulated into a solid dosage form is not disclosed or suggested by Schultz et al. even when read in conjunction with WO 97/18839, as Schultz et al.'s melt extrusion product would not be inherently the same as applicants' Claim 1 product. Applicants' reasons for so stating are set forth in the discussion of the references herein below. Based on the discussion below, applicants submit that because the elected claims are in fact patentable over the art of record, there is indeed the unifying feature to all of the claims which applicants pointed to earlier. Therefore, the withdrawn claims should be rejoined and examined.

OBJECTIONS TO THE SPECIFICATION

The disclosure has been objected to because of the blanks identifying provisional application numbers on page 23. By the foregoing amendment,

applicants have deleted the entire sentence containing the blanks because the applications in question have been abandoned.

The disclosure has also been objected to because of a typographical error on page 22, line 12. Applicants have corrected the error by the foregoing amendment.

It is believed that these amendments overcome the objections to the specification.

CLAIM REJECTIONS - 35 U.S.C. § 112

Claims 2, 11 and 57 are also rejected under 35 U.S.C. § 112, second paragraph, as being indefinite because of use of the term "saturated." Applicants submit that the claims are indeed clear and particularly point out and distinctly claim what applicants regard as their invention.

The Federal Circuit has made it very clear that definiteness of claim language must not be analyzed in a vacuum but rather (1) in light of applicants' specification, (2) in light of the prior art, and (3) in light of the manner in which the claims would be interpreted by one of ordinary skill in the relevant art. When analyzed in accord with Federal Circuit decisions, applicants' claims are definite. Applicants' claims are understandable and define what they regard as their invention; according to the C.C. P.A. decision *In re Kamal et al. (CCPA 1968) 158 USPQ 120*, such claims meet the requirements of the second paragraph of 35 U.S.C. § 112. In an effort to make these claims and others containing similar language even clearer, applicants have modified the language that refers to the saturated complexes to make it clear that it is the complex cladribine-cyclodextrin complexes which are saturated. Applicants have also modified the language of Claim 11; it would of course be apparent to the person of ordinary skill that applicants were referring to a point on the curve of the phase solubility diagram. The claims as amended have the same scope as prior to the amendment; these are not narrowing amendments but merely clarification of the subject matter to which the claims were previously directed.

The Examiner has noted that the term "saturated" is not defined in the claims, but applicants submit that it is the function of the specification, not the claims, to define terms. Applicants have certainly explained what they mean by saturated, not only by the disclosure at page 10, lines 1-13, but also by the disclosure at page 6,

line 20 to page 7, line 2; by the disclosure beginning at page 13, line 14 through page 14, line 16, which details the procedure used to develop the phase solubility curve; and by the disclosure at page 15, lines 5-29. Very specific information is given, not only as to time and temperature and subsequent filtration, on page 13, lines 21-26, but also in the discussion extending from page 16, line 1 to page 17, line 14. The phase solubility diagram and the discussion of the phase solubility diagram in Example 1 (and by reference, the complexation portion of Example 2) describe exactly how this phase solubility diagram/curve was generated. One of ordinary skill need only select a point on the phase solubility curve to identify the proportion of cladribine and cyclodextrin appropriate for the described saturated complexes for the conditions used in applicants' study. Alternatively, one of ordinary skill can repeat applicants' study to obtain the same curve, or can create his/her own phase solubility diagram for other conditions which he/she selects. The point is that applicants' work is reproducible, based on the teachings of their specification; selection of the same conditions as described will afford the same results; thus, the meaning of the claims which use the word "saturated" and which refer to the phase solubility diagram is clear to one of ordinary skill. As to the Examiner's complaint that no standard is given such as temperature, pressure or solvent, this is manifestly untrue for it is perfectly clear that the solvent disclosed in the specification is water and that the temperature and time are discussed with particularity in the specification, including the Examples, as already pointed out. Pressure is not mentioned because the work was carried out at atmospheric pressure, as would be understood by the skilled worker (who would know that pressure need be indicated only if it deviates from atmospheric pressure). Therefore, while there is no need to determine the amounts for each composition, at least when the cyclodextrin is hydroxypropyl-β-cyclodextrin or even hydroxypropyl-γ-cyclodextrin (page 17, lines 9-14) and the phase solubility curve provided by applicants can be used, it would be a very routine matter for one of ordinary skill to create such a curve for other amorphous cyclodextrins or to merely combine cladribine with the chosen cyclodextrin using the conditions specified by applicants and then remove excess cladribine. This is a simple procedure given all of applicants' teachings; it is not rocket science but rather is well within the skill in the art.

For at least the reasons set forth above, applicants submit that the 35 U.S.C. § 112, second paragraph, rejection is untenable and should be withdrawn.

CLAIM REJECTIONS - 35 U.S.C. § 102

Claims 1-15, 11, 56-60, 82-90 and 84-98 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Schultz et al. U.S. Patent No. 6,194,395, as evidenced by Baert et al. WO 97/18839.

Before discussing the cited references, applicants would like to discuss the amendments made to the claims hereinabove which make clearer what applicants regard as their invention. The Examiner is thanked for his very thorough review of the specification and the claim language, which has made it possible for applicants to see that some of their original language might have been open to misinterpretation while other language could be interpreted more broadly than they had intended. The amendments to Claims 2, 11 and 57 (as well as to withdrawn claims containing corresponding language) clarify that it is the entire complex cladribine-cyclodextrin complex which is saturated and that the point is located on the curve defining the saturated complexes as in the Figure. Applicants have also amended Claims 1 and 56 (and thus their dependent claims as well), as well as corresponding withdrawn claims, so that both Claims 1 and 56 now specify that the complex cladribine-cyclodextrin complex 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. This of course excludes anything else from the complex. Claim 1, drawn to a pharmaceutical composition comprising the complex, has been further amended (as have the withdrawn claims containing corresponding language) to specify that the composition comprises no significant amount of free crystalline cladribine therein. This means that no significant amount of free cladribine can be detected considering the sensitivity of the analytical method; see Example 2, page 31, lines 3-13, where this language finds specific support. Applicants teach throughout this application that free crystalline cladribine which is not in the complex is excluded; see for example, page 13, lines 19-28; page 16, lines 1-12 and 13-28; page 20, line 28 to page 21, line 11; page 21, lines 24-29; Example 1, pages 26-28;

and Example 2, page 28, line 3 to page 29, line 26 and of course page 31, lines 3-13. As described, excess cladribine is typically removed from solutions of the complex by filtering it off after the complex complex has been formed in water; subsequent lyophilization of the filtered solution and minimal further processing affords the claimed solid oral dosage form. Therefore, the claim amendments clearly do not introduce new matter.

The Examiner states that Schultz et al. disclose a solid pharmaceutical oral dosage form comprising cladribine and cyclodextrin and applicants agree. However, the Examiner claims that Schultz et al.'s disclosure meets the limitations of instant Claims 1 and 56, which applicants regard as an unwarranted conclusion. Similarly, applicants find no evidence in Schultz et al. that the Schultz et al. solid product is substantially identical to a product-by-process meeting the limitations of instant Claims 82-90 and 94-96.

Schultz et al. disclose the use of either crystalline or amorphous cyclodextrins for their compositions, since some of those named by the patentees are known to be crystalline while others are known to be amorphous. Applicants' complexes and compositions utilize only amorphous cyclodextrins. Thus, many cyclodextrins disclosed by Schultz et al. would be inoperative in the present invention, as they would afford crystalline rather than amorphous products. In stating that the limitations of Claims 3-5 and 58-60 are met by Schultz et al., the Examiner is focusing only on the cyclodextrins in common; he does not address the basic differences between the Schultz et al. solid dosage form and applicants' products. Applicants will agree, however, that Schultz et al.'s preferred cyclodextrin is hydroxypropyl- β -cyclodextrin, which is a cyclodextrin also specified in many of applicants' claims. Again, applicants do not dispute that the excipients may be (but are not necessarily) the same, but this does not arrive at the products of instant Claims 3 and 58 or 97 or 98. As to the amounts of cladribine and cyclodextrin, Schultz et al. disclose weight ratios of from 1 to about 15 mg. of cladribine to about 100 to 500 mg. of a cyclodextrin; this can give a cladribine:cyclodextrin ratio of anywhere from 1:500 to 15:100, or from 1:500 to 1:6.67. If one took the lower limits of each in ratio to the upper limits of each, one would arrive at ratios from 1:100 to 15:500, or from 1:100 to 1:33.34. Most of the 1:500 to 1:6.67 ratio does not even

encompass applicants' ratio, while the 1:100 to 1:33.34 does not embrace it at all. Certainly no guidance in this respect is given by Schultz et al. Moreover, Claim 11 herein has been reworded to clarify that the point is on the curve, as described in the instant specification, and certainly this feature is not disclosed in any way by Schultz et al. Moreover, the instant claims no longer allow for the presence uncomplexed cladribine in either the composition or the complex.

The Examiner correctly states that the Schultz et al. patent incorporates by reference the method of making their solid oral dosage form by utilizing the melt-extrusion process of Baert et al. The Baert et al. process is carried out by mixing the cyclodextrin and the active ingredient, heating until melting one of the components, forcing the mixture through one or more nozzles, and cooling until the mixture solidifies (page 5, line 24-29). Milling may follow. The term "melting" is used broadly by Baert et al. and includes transition to a glass; in particular cases, one component melts and the other dissolves therein forming solid solutions (page 5, lines 8-12). The extruded material may contain amorphous material or a solid solution (page 7, line 35 to page 8, line 7). While amorphous products are of interest, those which are mainly a solid solution are preferred (page 8, lines 11-23). In Table 1, on page 30, several different mixtures of hydroxypropyl- β -cyclodextrin and selected drugs were subjected to the Baert et al. process. As noted on page 13, lines 5-6, in every case, the mixture using this cyclodextrin gave a solid solution. The Examiner will note from Table 1 that the temperatures used, regardless of the identity of the drug, went as high as 292°C., with the temperatures for the itraconazole/HPβCD mixtures reaching 279°C-280°C. According to *The Merck Index* (copy of excerpt enclosed), itraconazole melts at 166.2°C while HPβCD melts at 278°C according to *LookChem* (copy of excerpt also attached).

In addition to the teachings of Baert et al. noted above, applicants draw the Examiner's attention to three of Baert et al.'s teachings which are of particular importance here:

1. On page 4, lines 5-7, Baert et al state:

   > The compounds that are suitable to be used in this technique are compounds that show no appreciable decomposition at the temperatures needed to melt and extrude the mixture of said

one or more active ingredients with the cyclodextrin or cyclodextrins.

2. On page 6, lines 14-19, Baert et al. state:

> The possible formation of these solid solutions is one of the further advantages of the present invention. It will be appreciated by a person skilled in the art that mixing two or more solids, i.e., one or more cyclodextrins and the active ingredient or ingredients, and subsequently melting these solids together give rise to different products than when the said solids are first brought into contact with water or another solvent and then extruded.

3. While Baert et al. have general teachings regarding ratios of from 1:100 to 100:1, particularly 1:10 to 10:1, especially 1:5 to 5:1, 1:3 to 3:1, preferably 1:1, Table 1 therein uses ratios of active ingredient: HPβCD of 1:3 or 1:1. Table 2 utilizes 1:1 ratios.

The only solid dosage form envisioned by Schultz et al. is a melt-extrusion product of cladribine and cyclodextrin prepared according to Baert et al. There is no evidence that such a product was ever prepared. Indeed, cladribine melts at 220-235°C with decomposition; see the enclosed excerpt from *Linscott's Directory* (copy attached) as well as that from *The Merck Index* (also enclosed). Thus, cladribine decomposes well below the 278°C melting point of HPβCD and well below the temperature used by Baert et al. for their melt extrusion; cladribine is therefore not suitable for the Baert et al. process, according to Baert et al.'s teaching that suitable compounds show no appreciable decomposition at the temperature they use (point 1 above).

Furthermore, Baert et al.'s teaching on page 6 that their melt-extrusion process affords different products than when their solids are first brought into contact with water (point 2 above) militates against the Examiner's finding that a cladribine/cyclodextrin product prepared by Baert et al.'s process is the same as applicants' product, which is, in fact, prepared by first contacting cyclodextrin with water. Indeed, it is the use of water that enables the formation of cyclodextrin-drug complexes; it is by complex formation that the water solubility of many drugs has

been previously improved. There is no teaching by Baert et al. that would lead one of ordinary skill to conclude that Baert et al made solid complexes; indeed, Baert et al. specifically teach on page 6 that their products are different from products obtained by first dissolving cyclodextrin and drug in water. Thus, a melt-extrusion product of cladribine and cyclodextrin cannot anticipate applicants' product which comprises 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. Applicants' product is prepared by preparing the complex in water; Baert et al. teach they obtain a different product than one that can be obtained from water; moreover, applicants' process uses temperatures up to only about 80°C, far below the decomposition temperature for cladribine and far below the temperatures used by Baert et al. See Claims 82-89 herein.

Further, for an anticipation to be inherent, the reference must always provide applicants' product. There is no reason to assume that Schultz et al's solid product ever is the same as applicants'; indeed, Baert et al. clearly teach that it is different.

For at least the reasons set forth above, the anticipation rejection of Claims 1-5, 11, 56-60, 82-90 and 94-98 based on Schultz et al. as evidenced by Baert et al. is untenable and should be withdrawn.

CLAIM REJECTIONS - 35 U.S.C.§ 103

Claims 1, 6-10, 12, 56, 61-66, 82 and 91-93 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Schultz et al. in view of Baert et al. We respectfully disagree.

Both Schultz et al. and Baert et al. are fully discussed above. In referring to the ratios disclosed by Schultz et al. for their melt extrusion solid dosage form, the Examiner has chosen to ignore the 1 mg. dosage at which the amount of cladribine begins; therefore, the range disclosed by Schultz et al. for cladribine:cyclodextrin varies from about 1:500 to 1:6.67. This is not even in accord with Baert et al.'s ratio of from about 1:1 to about 1:3. And if one uses Schultz et al's ratios proportionately,

low:low and high:high, one arrives at from 1:100 to 15:500 (1:33.34). In the former case, there is absolutely nothing in Schultz et al. that would lead to a specific ratio of from about 1:10 to about 1:16 or about 1:11 or about 1:14; it is applicants' own teachings which lead to these ratios. Likewise, the features of the other claims rejected under 35 U.S.C. § 103 are not disclosed by Schultz et al. Certainly Baert et al doesn't teach these ratios and if one looks at Schultz et al.'s suggested amounts proportionately, applicants' ratios are not even broadly encompassed by the reference. Still further, as noted earlier, Baert et al. clearly teach that the drug-cyclodextrin solid products of their melt extrusion process are distinctly different from products prepared in water; since applicants' products are prepared in water, they cannot possibly be the same as those obtained by the Baert et al. process incorporated by reference by Schultz et al.

Baert et al.'s ratios of active ingredient have been interpreted as mole ratios by the Examiner. There is no good reason for such an interpretation. The Examiner reasons that the fact that the active ingredients have different molecular weights leads to this interpretation, yet there are cyclodextrins of different molecular weights contemplated by Schultz et al. and by the present inventors and the ratios of Schultz et al. are clearly by weight (col. 6, lines 23-31), just as applicants' ratios are clearly weight ratios, e.g., Claim 8. Absent a teaching to the contrary, one of ordinary skill would assume that the ratios of Baert et al. are also weight ratios. At any rate, the Baert et al. melt-extrusion product is not one obtained by complexation in water; Baert et al. teach their melt-extrusion product is different from a product whose preparation begins by dissolving the drug and cyclodextrin in water. Therefore, any product that Schultz et al. might produce from cladribine and cyclodextrin subjected to Baert et al.'s melt extrusion product cannot be the same as applicants' complex cladribine-cyclodextrin complex which must be obtained from an aqueous solution which is treated in a specific manner. Baert et al. never suggests that they obtain a complex by their melt-extrusion process, much less one meeting the requirements of applicants' claims. Indeed, Baert et al. emphasize that their process, which is different, affords a different product than that obtained by first dissolving the drug and cyclodextrin. Likewise, applicants emphasize that applicants' process is strikingly different from Baert et al.'s process and thus logically would not afford the

product which Schultz et al. would be expected to obtain by subjecting cladribine and cyclodextrin to Baert et al.'s process. Moreover, applicants have formed a very special complex which contains a large amount of cladribine as an amorphous inclusion complex and as amorphous free cladribine associated with the cyclodextrin as a non-inclusion complex. Note too that the free cladribine associated with the non-inclusion product is amorphous, in contrast to the cladribine starting material, which is crystalline. Note also that applicants produce their product by first complexing in water at temperatures of from about 45°C to about 80°C, far below the temperatures used by Baert et al. Cladribine actually decomposes at temperatures below that used by Baert et al.

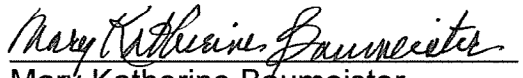
It is clear from the foregoing that a molecular inclusion complexation process, let alone the particular inclusion process utilized by applicants to form their unique complex cladribine-cyclodextrin complex, is not inherent in Baert et al.'s melt extrusion process and that Baert et al.'s process gives a different product. To hold otherwise would be to ignore Baert et al.'s own teachings.

In view of the foregoing, it is submitted that the present application is free of all record rejections and objections. Further, favorable action in the form of a Notice of Allowance is believed to be next in order and is earnestly solicited.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date:October 3, 2008

By: 
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Attachments:

"Cladribine", *The Merck Index,* (2001), pp. 407-408, Thirteenth Edition, Merck & Co., Inc., Whitehouse Station, NJ

"Itraconazole", *The Merck Index,* (2001), p. 938, Thirteen Edition, Merck & Co., Inc. Whitehouse Station, NJ

"Hydroxypropyl-beta-cyclodextrin, CAS No. 94035-02-6" *LookChem*, http://www.lookchem.com/cas-940/94035-02-6.html, September 23, 2008

"Non-antibody Products (Kits, Proteins, Microbial Antigens, Tissues, Services, etc.) *Linscott's Directory of Immunological & Biological Reagents*, http://www.linscottsdirectory.com/browse/products/page:36, Records 1,751-1,800 of 130,353, September 11, 2008

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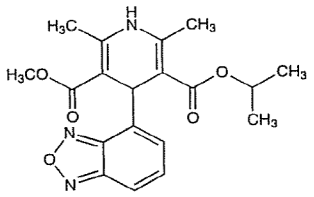
angina and coronary artery disease: C. E. Handler, E. Sowton, *ibid.* **27,** 415 (1984); in hypertension: E. B. Nelson *et al., Clin. Pharmacol. Ther.* **40,** 694 (1986). Comparison of hemodynamic effects of enantiomers: R. P. Hof *et al., J. Cardiovasc. Pharmacol.* **8,** 221 (1986). Series of articles on pharmacology and clinical use: *Am. J. Med.* **86,** 1-146 (1989).



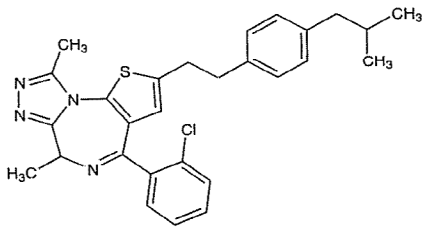
mp 168-170°.

***S*(+)-Form.** PN-205-033. Crystals from ether + hexane, mp 142°. $[\alpha]_D^{20}$ +6.7° (c = 1.5 in ethanol).

***R*(−)-Form.** PN-205-034. Crystals from ether + hexane, mp 140°. $[\alpha]_D^{20}$ −6.7° (c = 1.67 in ethanol).

THERAP CAT: Antihypertensive; antianginal.

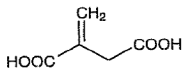
5263. Israpafant. [117279-73-9] 4-(2-Chlorophenyl)-6,-9-dimethyl-2-[2-[4-(2-methylpropyl)phenyl]ethyl]-6*H*-thieno-[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine; (±)-4-(*o*-chlorophenyl)-2-(*p*-isobutylphenethyl)-6,9-dimethyl-6*H*-thieno[3,2-*f*]-*s*-triazolo[4,3-*a*][1,4]diazepine; Y-24180; Pafnol. $C_{28}H_{29}ClN_4S$; mol wt 489.09. C 68.76%, H 5.98%, Cl 7.25%, N 11.46%, S 6.56%. Platelet activating factor (PAF) antagonist. Prepn: T. Tahara *et al.,* **EP 268242**; *eidem,* **US 4820703** (1988, 1989 both to Yoshitomi). Pharmacology: M. Terasawa *et al., Prostaglandins* **40,** 553 (1990). Receptor binding study: S. Takehara *et al., ibid.* 571. Clinical evaluation in asthma: S. Hozawa *et al., Am. J. Respir. Crit. Care Med.* **152,** 1198 (1995).



Colorless crystals from isopropyl ether, mp 129.5-131.5°. Sol in propylene glycol.

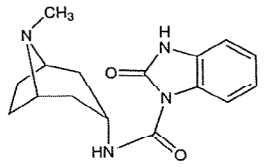
THERAP CAT: Antiasthmatic.

5264. Itaconic Acid. [97-65-4] Methylenesuccinic acid; propylenedicarboxylic acid. $C_5H_6O_4$; mol wt 130.10. C 46.16%, H 4.65%, O 49.19%. Obtained by dry distillation of citric acid and subsequent treatment of the anhydride with water. Produced on a large scale by submerged aerobic fermentation using *Aspergillus terreus* and low cost carbohydrates from beet or cane: Kane *et al.,* **US 2385283** (1945 to Pfizer). Synthesis from propargyl chloride, carbon monoxide, nickel carbonyl and water: Chiusoli, **US 3025320** (1962 to Montecatini).



Hygroscopic crystals; characteristic odor. d 1.63. mp 162-164° with decompn. Also reported as mp 172° [Kinoshita, *Acta Phytochem. (Japan)* **5,** 273 (1931)]. One gram dissolves in 12 ml water, 5 ml alcohol; very slightly sol in benzene, chloroform, ether, carbon disulfide, petr ether. *Keep well closed.*

5265. Itasetron. [123258-84-4] 2,3-Dihydro-*N*-[(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]-2-oxo-1*H*-benzimidazole-1-carboxamide; 2-oxo-*N*-1α*H*,5α*H*-tropan-3α-yl-1-benzimidazoline-1-carboxamide. $C_{16}H_{20}N_4O_2$; mol wt 300.35. C 63.98%, H 6.71%, N 18.65%, O 10.65%. Serotonin ($5\text{-}HT_3$) receptor antagonist. Prepn: M. Turconi *et al.,* **EP 309423** (1989 to Istituto De Angeli); *eidem,* **US 5223511** (1993 to Boehringer, Ing.); M. Turconi *et al., J. Med. Chem.* **33,** 2101 (1990). Pharmacology: *idem et al., Eur. J. Pharmacol.* **203,** 203 (1991). Mode of action: M. B. Passani *et al., Brit. J. Pharmacol.* **112,** 695 (1994). Clinical efficacy and tolerability: H. Goldschmidt *et al., Anti-Cancer Drugs* **8,** 436 (1997). Review of therapeutic potential: M. B. Passani, R. Corradetti, *CNS Drug Reviews* **2,** 195-213 (1996).

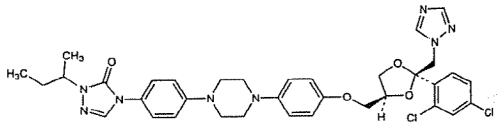


Crystals from acetonitrile, mp 205-207°. LD_{50} in mice, rats (mg/kg): 56, 62 i.v. (Passani).

Hydrochloride. [127618-28-4] DAU 6215. $C_{16}H_{20}N_4O_2$·HCl; mol wt 336.82. Colorless crystals, mp 270°.

THERAP CAT: Antiemetic.

5266. Itraconazole. [84625-61-6] 4-[4-[4-[4-[[2-(2,4-Dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one; (±)-1-*sec*-butyl-4-[*p*-[4-[*p*-[[(2*R**,4*S**)-2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ²-1,2,4-triazolin-5-one; oriconazole; R-51211; Itrizole; Sporanox; Triasporin. $C_{35}H_{38}Cl_2N_8O_4$; mol wt 705.65. C 59.57%, H 5.43%, Cl 10.05%, N 15.88%, O 9.07%. Orally active antimycotic structurally related to ketoconazole, *q.v.* Prepn: J. Heeres, L. J. J. Backx, **EP 6711**; *eidem,* **US 4267179** (1980, 1981 both to Janssen); J. Heeres *et al., J. Med. Chem.* **27,** 894 (1984). *In vitro* activity: A. Espinel-Ingroff *et al., Antimicrob. Ag. Chemother.* **26,** 5 (1984). HPLC determn in biological samples: R. Woestenborghs *et al., J. Chromatog.* **413,** 332 (1987). Symposium on pharmacology and clinical efficacy: *Rev. Infect. Dis.* **9,** Suppl 1, S1-S152 (1987). Toxicity data: H. Van Cauteren *et al., ibid.* S43. Review of clinical pharmacokinetics: J. Heykants *et al., Mycoses* **32,** Suppl 1, 67-87 (1989); of clinical efficacy in dermatophytosis: P. De Doncker, G. Cauwenbergh, *Brit. J. Clin. Pract.* **Suppl. 71,** 118-122 (1990). *Review:* A. M. Sugar, *Curr. Clin. Topics Inf. Dis.* **13,** 74-98 (1993).



Crystals from toluene, mp 166.2°. pKa 3.7. Lipophilic; partition coefficient (*n*-octanol/aq buffer of pH 8.1): 5.66. Practically insol in water and dil acidic solns. LD_{50} (14 day) in mice, rats, dogs (mg/kg): >320, >320, >200 orally (Van Cauteren).

THERAP CAT: Antifungal.

5267. Itramin Tosylate. [13445-63-1] 2-Aminoethanol nitrate mono(4-methylbenzenesulfonate); 2-aminoethanol nitrate mono-*p*-toluenesulfonate; 2-nitratoethylaminotoluene-*p*-sulfonate; Cardisan; Tostram; Nilatil. $C_9H_{14}N_2O_6S$; mol wt 278.28. C 38.85%, H 5.07%, N 10.07%, O 34.50%, S 11.52%. Prepn: **SE 168308** (1959 to Aktiebolaget Pharmacia), *C.A.* **54,** 24405d (1960).

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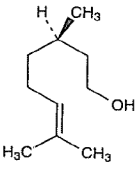
α-citronellal. [141-26-4] 3,7-Dimethyl-7-octenal; rhodinal. Liquid. bp_{14} 51°. n_D^{20} 1.4410. $[\alpha]_D^{20}$ +9.75°.
USE: In soap perfumes; insect repellent.

2354. β-Citronellol. [106-22-9] 3,7-Dimethyl-6-octen-1-ol; 2,6-dimethyl-2-octen-8-ol; citronellol; eephrol. $C_{10}H_{20}O$; mol wt 156.26. C 76.86%, H 12.90%, O 10.24%. *l*-Form is a constituent of rose and geranium oils. *d*-Form occurs in Ceylon and Java citronella oils. History: J. L. Simonsen, L. N. Owen, *The Terpenes* **vol. I** (University Press, Cambridge, 2nd ed, 1947). Prepn of (±)-form: Adams, Garvey, *J. Am. Chem. Soc.* **48,** 477 (1926); Ofner *et al., Helv. Chim. Acta* **42,** 2577 (1959). Prepn of (+)-form: Rienäcker, Ohloff, *Angew. Chem.* **73,** 240 (1961); Naves, Tullen, *Helv. Chim. Acta* **44,** 1867 (1961); Eschinazi, *J. Org. Chem.* **26,** 3072 (1961); Rienäcker, *Chimia* **27,** 97 (1973); C. G. Overberger, J. L. Weise, *J. Am. Chem. Soc.* **90,** 3525 (1968); T. Sato *et al., Tetrahedron Letters* **1980,** 3377. Prepn of (−)-form: Ohloff, *loc. cit.;* Rienäcker, *loc. cit.;* Shono *et al., Tetrahedron Letters* **1974,** 1295; K. Mori, T. Sugai, *Synthesis* **1982,** 752. Synthesis of (+) or (−)-form from isoprene: Hidai *et al., Chem. Commun.* **1975,** 170. Stereospecific prepn via microbiological *(Saccharomyces cerevisiae)* reduction: P. Gramatica *et al., Experientia* **38,** 775 (1982). Manuf: Woroch *et al.;* Bain; Webb, **US 2990422**; **US 3005845**; **US 3028431** (1961, 1961, 1962, all to Glidden); Eschinasi, **US 3052730** (1962 to Givaudan). Abs config of the (+)-form: Freudenberg, Hohmann, *Ann.* **584,** 54 (1953); Freudenberg, Lwowski, *ibid.* **587,** 213 (1954). NMR, HPLC determn of *R/S* enantiomer ratios: D. Valentine *et al., J. Org. Chem.* **41,** 62 (1976). *See also* Rhodinol.



R-(+)-β-Citronellol

(+)-Form. Oily liquid, bp 224.5°, bp_{10} 108.4°, d_4^{20} 0.8550. n_D^{20} 1.4559. $[\alpha]_D^{20}$ +5.22°. Very slightly sol in water, miscible with with alcohol, ether.

(−)-Form. β-Rhodinol; Levocitrol. bp_{10} 108-109°. d_4^{18} 1.4576. $[\alpha]_D^{20}$ −4.76°.

(±)-Form. Dihydrogeraniol. $d_4^{23.5}$ 0.851. $n_D^{23.5}$ 1.454.
USE: In perfumery.

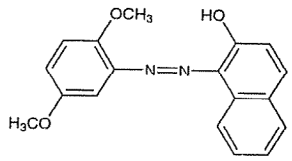
2355. Citrulline. [372-75-8] N^5-(Aminocarbonyl)-L-ornithine; δ-ureidonorvaline; α-amino-δ-ureidovaleric acid; N^5-carbamylornithine. $C_6H_{13}N_3O_3$; mol wt 175.19. C 41.13%, H 7.48%, N 23.99%, O 27.40%. $H_2NCONH(CH_2)_3CH(NH_2)$-COOH. An amino acid, first isolated from the juice of watermelon, *Citrullus vulgaris* Schrad., *Cucurbitaceae:* Wada, *Biochem. Z.* **224,** 420 (1930); isoln from casein: Wada, *ibid.* **257,** 1 (1933). Synthesis from ornithine through copper complexes: Kurtz, *J. Biol. Chem.* **122,** 477 (1938); by alkaline hydrolysis of arginine: Fox, *ibid.* **123,** 687 (1938); from cyclopentanone oxime: Fox *et al., J. Org. Chem.* **6,** 410 (1941). Crystallization: Matsuda *et al.,* **JP 71 174** (1971 to Ajinomoto), *C.A.* **74,** 126056u (1971). Crystal and molecular structure: Naganathan, Venkatesan, *Acta Crystallogr.* **27B,** 1079 (1971); Ashida *et al., ibid.* **28B,** 1367 (1972). Use in asthenia and hepatic insufficiency: **FR 2198739** (1974 to Hublot & Vallet), *C.A.* **82,** 144952c (1975). Clinical trial in treatment of lysinuric protein intolerance: J. Rajantie *et al., J. Pediatr.* **97,** 927 (1980); T. O. Carpenter *et al., N. Engl. J. Med.* **312,** 290 (1985).
Prisms from methanol + water, mp 222°. $[\alpha]_D^{20}$ +3.7° (c = 2). pK_1 2.43; pK_2 9.41. Sol in water. Insol in methanol, ethanol.

Hydrochloride. [34312-10-2] $C_6H_{13}N_3O_3$ HCl. Crystals, dec 185°. $[\alpha]_D^{22}$ +17.9° (c = 2).

Malate (salt). [54940-97-5] Stimol. $C_6H_{13}N_3O_3.C_4H_6O_5$; mol wt 309.27.
THERAP CAT: Treatment of asthenia.

2356. Citrullol. [1390-93-8] $C_{22}H_{38}O_4$; mol wt 366.53. C 72.09%, H 10.45%, O 17.46%. From fruit pulp of *Citrullus colocynthis* Schrad., *Cucurbitaceae:* Power, Moore, *J. Chem. Soc.* **97,** 99 (1910); Power, Salway, *ibid.* **103,** 399, 1022 (1913); Khadem, Rahman, *Tetrahedron Letters* **1962,** 1137.
Crystals, mp 282-283°. uv max: 242, 272, 282 nm (log ε 2.85, 2.68, 2.68). Sol in pyridine; practically insol in usual organic solvents.
Diacetate. $C_{26}H_{42}O_6$. Crystals, mp 162°.

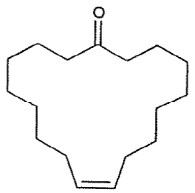
2357. Citrus Red 2. [6358-53-8] 1-[(2,5-Dimethoxyphenyl)azo]-2-naphthalenol; C.I. Solvent Red 80; C.I. 12156. $C_{18}H_{16}N_2O_3$; mol wt 308.33. C 70.12%, H 5.23%, N 9.09%, O 15.57%. Prepn: H. W. Elley, H. W. Daudt, **US 2224904** (1940 to Du Pont). Metabolism: J. L. Radomski, *J. Pharmacol. Exp. Ther.* **134,** 100 (1961); **136,** 378 (1962). Toxicology: M. Sharratt *et al., Food Cosmet. Toxicol.* **4,** 493 (1966). Review of carcinogenicity studies: *IARC Monographs* **8,** 101-106. *See also Colour Index* **vol. 4** (3rd ed., 1971) p 4033.



Crystals, mp 155-157°. Slightly sol in water; partially sol in ethanol and vegetable oils.
USE: To color orange skins.

2358. Civet. Zibeth. Unctuous secretion from receptacles between the anus and genitalia of both male and female civet cat. *Constit.* Civetone and similar compds.
Semi-solid, yellowish to brown unctuous substance; unpleasant, subacrid, bitter taste; fusible and burns without leaving much residue. Insol in water; partly sol in hot alcohol or in ether.
USE: As a fixative in perfumery.

2359. Civetone. [542-46-1] (*Z*)-9-Cycloheptadecen-1-one. $C_{17}H_{30}O$; mol wt 250.42. C 81.54%, H 12.07%, O 6.39%. 17-Membered macrocyclic musk, constituent of civet: Ruzicka, *Helv. Chim. Acta* **9,** 230 (1926); Ruzicka *et al., ibid.* **10,** 695 (1927). Occurs in nature as *cis*-form. Synthesis of *cis*-civetone: Stoll *et al., ibid.* **31,** 543 (1948); J. Tsuji, T. Mondai, *Tetrahedron Letters* **1977,** 3285; E. Seoane *et al., Chem. & Ind. (London)* **1978,** 165. Synthesis of *trans*-form: H. Hunsdiecker, *Ber.* **77,** 185 (1944); H. H. Mathur, S. C. Bhattacharyya, *J. Chem. Soc.* **1968,** 114. Crystal and molecular structure of *cis*-civetone: G. Bernardinelli, R. Gerdil, *Helv. Chim. Acta* **65,** 558 (1982).

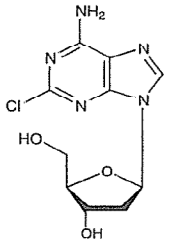


(cis)-form

Crystals, mp 31-32°. Musky odor becoming pleasant in extreme dilns. d_4^{33} 0.917. bp_{742} 342°; bp_2 59°. $n_D^{33.4}$ 1.4830.
USE: In perfumery.

2360. Cladribine. [4291-63-8] 2-Chloro-2′-deoxyadenosine; 2-chloro-6-amino-9-(2-deoxy-β-D-*erythro*-pentofuran-

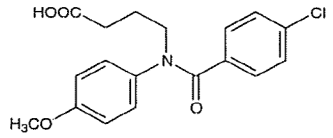
osyl)purine; 2-chlorodeoxyadenosine; 2-CdA; CldAdo; NSC-105014-F; Leustatin. $C_{10}H_{12}ClN_5O_3$; mol wt 285.69. C 42.04%, H 4.23%, Cl 12.41%, N 24.51%, O 16.80%. Substituted purine nucleoside with antileukemic activity. Prepn as intermediate in synthesis of 2-deoxynucleosides: H. Venner, *Ber.* **93,** 140 (1960); M. Ikehara, H. Tada, *J. Am. Chem. Soc.* **85,** 2344 (1963); *eidem, ibid.* **87,** 606 (1965). Synthesis and biological activity: L. F. Christensen *et al., J. Med. Chem.* **15,** 735 (1972). Stereospecific synthesis: Z. Kazimierczuk *et al., J. Am. Chem. Soc.* **106,** 6379 (1984); R. K. Robins, G. R. Revankar, **EP 173059**; *eidem,* **US 4760137** (1986, 1988 both to Brigham Young Univ.). Specific toxicity to lymphocytes: D. A. Carson *et al., Proc. Nat. Acad. Sci. USA* **77,** 6865 (1980); *eidem, Blood* **62,** 737 (1983). Mechanism of action: S. Seto *et al., J. Clin. Invest.* **75,** 377 (1985). Clinical evaluation in chronic lymphocytic leukemia: L. D. Piro *et al., Blood* **72,** 1069 (1988); in hairy cell leukemia: *eidem, N. Engl. J. Med.* **322,** 1117 (1990).



Crystals from water, softens at 210-215°, solidifies and turns brown (Christensen). Also reported as crystals from ethanol, mp 220° (softens), resolidifies, turns brown and does not melt below 300° (Kazimierczuk). $[\alpha]_D^{25}$ −18.8° (c = 1 in DMF). uv max in 0.1*N* NaOH: 265 nm; in 0.1*N* HCl: 265 nm.

THERAP CAT: Antineoplastic.

2361. Clanobutin. [30544-61-7] 4-[(4-Chlorobenzoyl)-(4-methoxyphenyl)amino]butanoic acid; 4-[*p*-chloro-*N*-(*p*-methoxyphenyl)benzamido]butyric acid; *N*-(*p*-chlorobenzoyl)-γ-(*p*-anisidino)butyric acid; Bykahepar. $C_{18}H_{18}ClNO_4$; mol wt 347.80. C 62.16%, H 5.22%, Cl 10.19%, N 4.03%, O 18.40%. Prepn: K. Klemm *et al.,* **DE 1917036** corresp to **US 3780095** (1971, 1973 both to Byk-Gulden). Series of articles on synthesis, physical and pharmacological properties: *Arzneimittel-Forsch.* **29,** 1-15 (1979). *In vitro* biochemical study: H. Wolf *et al., Biochem. Pharmacol.* **29,** 1649 (1980). Effect on bile excretion in rats, dogs: P. Berchtold *et al., Arzneimittel-Forsch.* **30,** 1878 (1980).

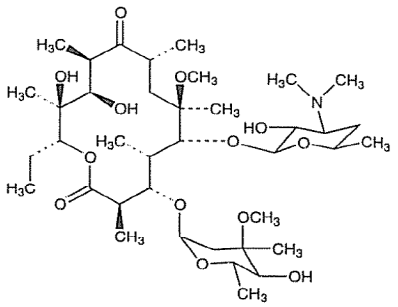


Cryst from ethyl acetate, mp 115-116°. pKa 5.04. Soly in water at 37°: 4.02×10^{-2} mol/l at pH 7. LD_{50} in rats (mg/kg): >2000 orally; 570 i.v. (Klemm).

THERAP CAT: Choleretic.

THERAP CAT (VET): Choleretic; in treatment of piroplasmosis and anaplasmosis.

2362. Clarithromycin. [81103-11-9] 6-*O*-Methylerythromycin; A-56268; TE-031; Biaxin; Clathromycin; Cyllind; Klacid; Klaricid; Macladin; Naxy; Veclam; Zeclar. $C_{38}H_{69}NO_{13}$; mol wt 747.95. C 61.02%, H 9.30%, N 1.87%, O 27.81%. Semisynthetic macrolide antibiotic; derivative of erythromycin, *q.v.* Prepn: Y. Watanabe *et al.,* **EP 41355**; *eidem,* **US 4331803** (1981, 1982 both to Taisho); and *in vitro* antibacterial activity: S. Morimoto *et al., J. Antibiot.* **37,** 187 (1984). *In vitro* and *in vivo* antibacterial activity: P. B. Fernandes *et al., Antimicrob. Ag. Chemother.* **30,** 865 (1986). Comparative antibacterial spectrum *in vitro:* C. Benson *et al., Eur. J. Clin. Microbiol.* **6,** 173 (1987); H. M. Wexler, S. M. Finegold, *ibid.* 492. HPLC determn in biological fluids: D. Croteau *et al., J. Chromatog.* **419,** 205 (1987). Acute toxicity study: S. Abe *et al., Chemotherapy (Tokyo)* **36,** Suppl. 3, 274 (1988). Symposium on pharmacology and comparative clinical studies: *J. Antimicrob. Chemother.* **27,** Suppl. A, 1-124 (1991). Comprehensive description: I. I. Salem, *Anal. Profiles Drug Subs. Excip.,* **24,** 45-85, (1996).



Colorless needles from chloroform + diisopropyl ether (1:2), mp 217-220° (dec). Also reported as crystals from ethanol, mp 222-225° (Morimoto). uv max ($CHCl_3$): 288 nm (ε 27.9). uv max ($CHCl_3$): 240, 288 nm; (methanol): 211, 288 nm. $[\alpha]_D^{24}$ −90.4° (c = 1 in $CHCl_3$). Stable at acidic pH. LD_{50} in male, female mice, male, female rats (mg/kg): 2740, 2700, 3470, 2700 orally, 1030, 850, 669, 753 i.p., >5000 all s.c. (Abe).

THERAP CAT: Antibacterial.

2363. Clathrates. Compounds that are capable of trapping other substances within their own crystal lattices. The cavities of the host molecules are classified as cages, tunnels, or layered types, depending on the way they include guest molecules. The geometry of the cavities limits the guest molecules by size and shape, rather than by chemical similarity with the host molecules. Among common clathrates are ***molecular sieves***, ***cyclotriphosphazenes***, and ***Dianin's compound***, as well as hydroquinone, cyclodextrins, *o*-thymotide, and deoxycholic acid, *q.q.v.* ***Cavitands*** are organic hosts with enforced (rigid) cavities: D. J. Cram, *Science* **219,** 1177 (1983); R. C. Helgeson *et al., Chem. Commun.* **1983,** 101. Comprehensive book: *Clathrate Compounds,* V. M. Bhatnagar, Ed. (Chemical Pub. Co., New York, 1970) 244 pp. *Reviews:* D. D. MacNicol *et al., Chem. Soc. Rev.* **7,** 65-87 (1978); E. C. Makin, "Clathration" in *Kirk-Othmer Encyclopedia of Chemical Technology* **Vol. 6** (Wiley-Interscience, New York, 3rd ed., 1979) pp 178-189.

USE: As complexing agent; stabilizing agent. In analytical separations.

2364. Clavulanic Acid. [58001-44-8] [2*R*-(2α,3*Z*,5α)]-3-(2-Hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo-[3.2.0]heptane-2-carboxylic acid; MM 14151. $C_8H_9NO_5$; mol wt 199.16. C 48.25%, H 4.55%, N 7.03%, O 40.17%. β-Lactamase inhibitor. Antibiotic produced by *Streptomyces clavuligerus;* first reported naturally occurring fused β-lactam containing oxygen. Isoln: M. Cole *et al.,* **DE 2517316** (1975 to Beecham), *C.A.* **84,** 72635t (1976); A. G. Brown *et al., J. Antibiot.* **29,** 668 (1976). Structure, x-ray crystallography: T. T. Howarth *et al., Chem. Commun.* **1976,** 266. Total synthesis of (±)-form: P. H. Bentley *et al., ibid.* **1977,** 748, 905; *eidem, Tetrahedron Letters* **1979,** 1889. β-Lactamase inhibition and antibacterial spectrum: C. Reading, M. Cole, *Antimicrob. Ag. Chemother.* **11,** 852 (1977). Mechanism of action: B. G. Spratt *et al., ibid.* **12,** 406 (1977). Antibacterial activity, pharmacology and clinical efficacy of combination with amoxicillin: A. P. Ball *et al., Lancet* **1,** 620 (1980); R. N. Brogden *et al., Drugs* **22,** 337-362 (1981). *In vitro* and *in vivo* synergism with ticarcillin: R. Sutherland *et al., Am. J. Med.* **79,** Suppl. 5B, 13 (1985).

Hydroxypropyl-beta-cyclodextrin
CAS No:94035-02-6

Name: Hydroxypropyl-beta-cyclodextrin

Synonyms: beta-Hydroxypropylcyclodextrin
beta-Cyclodextrin, 2-hydroxypropyl ether
HPB
2-Hydroxypropyl-beta-cyclodextrin
128446-35-5

CAS Number: 94035-02-6

Molecular Formula: $C_{42}(H)_{70-n}O_{35}(C_3H_7)_n$

Melting Point: 278 °C

Safety Description: S24/25 Details

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Yiming Fine Chemicals Co., Ltd.
Introduction:mp : 267 °C (dec.)
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storage temp. : 2-8°C

solubility : H2O: 45 % (w/v)

form : solution (clear, colorless)

[Hangzhou]86-571-85889139 85459303 85459719 ext.8015

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Name	Description	Size	Catalog #	Supplier	
CKBB	Recombinant Human Creatine Kinase BB Isoenzyme	10µg, 50µg, 1mg	CKI- 268	PROSPEC-TANY TECHNOGENE LTD.	More In
Ckdk6	The RP-39008 Ckdk6 protein is a partial length (aa 1-327) bacterially expressed recombinant protein.RP-39008 is suitable for use as a control in ELISA and Western blot applications.The RP-39008 protein is GST-tagged.	10 ug	RP-39008	ABR - AFFINITY BIOREAGENTS INC.	More In
CKMM	Human Creatine Kinase MM	200µg, 1mg, 10mg	CKI- 273	PROSPEC-TANY TECHNOGENE LTD.	More In
CKS-17	Sequence: Leu-Gln-Asn-Arg-Arg-Gly-L eu-Asp-Leu-Leu-Phe-Leu-Ly s-Glu-Gly-Gly-LeuStorage and Stability: Lyophilized powder may be stored at 4?C for short-term only. Reconstitute to nominal volume by adding sterile 40-50% glycerol and store at -20?C. R...	1mg	C5818-05	UNITED STATES BIOLOGICAL	More In
CKS-17 (7-12)	Sequence: Leu-Asp-Leu-Leu-Phe-LeuSt orage and Stability: Lyophilized powder may be stored at 4?C for short-term only. Reconstitute to nominal volume by adding sterile 40-50% glycerol and store at -20?C. Reconstituted product is stable for 12 months...	25mg	C5818-05A	UNITED STATES BIOLOGICAL	More In

CKS-17	This Peptide CKS-17 is considered as the major immunosuppressive site of retroviral TM protein. It can suppress T effector cell function in vitro. It has been shown that CKS-17 causes an imbalance of human types 1 and 2 cytokines and inhibition of...	0.5 mg	06-271-83162	GENWAY BIOTECH INC.	**More In**
CKS-17	This Peptide CKS-17 is considered as the major immunosuppressive site of retroviral TM protein. It can suppress T effector cell function in vitro. It has been shown that CKS-17 causes an imbalance of human types 1 and 2 cytokines and inhibition of...	1 mg	06-271-83162	GENWAY BIOTECH INC.	**More In**
CARCINOEMBRYONIC ANTIGEN (CL)	testing/assay service	n/a	n/a	RDL REFERENCE LABORATORY INC.	**More In**
CASPASE-3/7 (CL)	n/a	n/a	n/a	PROMEGA CORPORATION	**More In**
CASPASE-8 (CL)	n/a	n/a	n/a	PROMEGA CORPORATION	**More In**
CASPASE-9 (CL)	n/a	n/a	n/a	PROMEGA CORPORATION	**More In**
CASPASE (CL)	n/a	n/a	n/a	PROMEGA CORPORATION	**More In**
CL 218872	Benzodiazepine agonist displaying selectivity for α1 subunit-containing GABAA receptors (Ki values are 130, 1820, 1530, > 10000, 490 and > 10000 nM for α1, α2, α3, α4, α5 and α6-subunit containing re...	10mg, 50mg	1709	TOCRIS BIOSCIENCE	**More In**
CL-387,785	Irreversibly inhibits EGF-receptor (EGFR) kinase activity in vivo (IC50 = 250-490 pM) as well as EGF-stimulated autophosphorylation of tyrosine residues in the EGFR in vivo (IC50 = 5 nM). Blocks EGF-mediated growth in A431 cells. Inhibits prolifer...	n/a	233100	CALBIOCHEM/EMD BIOSCIENCES	**More In**
	A selective inhibitor of MMP-13 (IC50 = 10 μM).				

CL-82198	Binds to the S1' pocket of MMP-13 with its morpholine ring adjacent to the catalytic zinc atom. Does not inhibit MMP-1, MMP-9, and TACE.	n/a	233105	CALBIOCHEM/EMD BIOSCIENCES	**More In**
Calphostin C, Cladosporium cladosporioides	A cell permeable, highly specific inhibitor of protein kinase C (IC50 = 50 nM) that interacts with the protein's regulatory domain by competing at the binding site of diacylglycerol and phorbol esters. Does not compete with Ca2+ or phospholi...	n/a	208725	CALBIOCHEM/EMD BIOSCIENCES	**More In**
Cladribine	It is a substituted purine nucleoside with antileukemic activity.Melting Point: 220-235?C dec.Solubility: Methanol, Water	50mg	C5819-75	UNITED STATES BIOLOGICAL	**More In**
Clarithromycin	A semi-synthetic macrolide antibiotic. A derivative of erythromycin.Melting Point: 217-220?C dec.Solubility: Chloroform, Ethanol	50mg	C5829	UNITED STATES BIOLOGICAL	**More In**
Clavulanic Acid	A B-Lactamase inhibitor.	10mg	C5836	UNITED STATES BIOLOGICAL	**More In**
CLIC3	The RP-39009 CLIC3 protein is a full length bacterially expressed recombinant protein.RP-39009 is suitable for use as a control in ELISA and Western blot applications.The RP-39009 amino acid sequence corresponds to the NCBI accession number NP_004...	10 ug	RP-39009	ABR - AFFINITY BIOREAGENTS INC.	**More In**
Clidinium Bromide	An anticholinergic. Used as an antispasmodic.Melting Point: 240-241?C	5g	C5840-75	UNITED STATES BIOLOGICAL	**More In**
	A metal ion chelator that crosses the blood brain barrier and acts as a neurotoxic antibiotic. Reported to dissolve				

Clioquinol	senile plaques and reduce amyloid's ability to clump together, apparently by trapping the Cu2+ and Zn2+ that stud these depos...	n/a	233165	CALBIOCHEM/EMD BIOSCIENCES	**More In**
CLK3, active	n/a	10 ug	14-724	MILLIPORE	**More In**
CLK2, active	n/a	10 ug	14-774	MILLIPORE	**More In**
Clofarabine	ISecond generation purine nucleoside analog; antimetabolite that inhibits DNA synthesis and resists deamination by adenosine deaminase. Antineoplastic.Melting Point: 225-227?C	10mg	C5843-55	UNITED STATES BIOLOGICAL	**More In**
Clofarabine	Deoxycytidine kinase (dCK) substrate. Phosphorylated to form clofarabine triphosphate, which competes with dATP for DNA polymerase- α and - ε and potently inhibits ribonucleotide reductase (IC50 = 65 nM). Induces apoptosis by directl...	10mg, 50mg	2600	TOCRIS BIOSCIENCE	**More In**
CLOFIBRATE	n/a	n/a	n/a	CAYMAN CHEMICAL CO.	**More In**
Clofibrate	PPAR agonist (EC50 values are 50, 500 and > 100 μM at PPAR α, PPAR γ and PPAR δ respectively). Antihyperlipoproteinemic.	1g	0824	TOCRIS BIOSCIENCE	**More In**
Clofibric acid	PPAR agonist. Antihyperlipoproteinemic.	1g	0825	TOCRIS BIOSCIENCE	**More In**
Clofibrate	An anti-hyperlipoproteinemic agent believed to act by inhibiting cholesterol biosynthesis. Activates PPARα and induces cytochrome P450 4A1 and 4A3. Imparts protection against acetaminophen toxicity and increases hepatic glutathione levels.	n/a	231405	CALBIOCHEM/EMD BIOSCIENCES	**More In**
Clofulbicyne	n/a	1 mg.	TXL9001-1	ACCURATE CHEMICAL & SCIENTIFIC CO.	**More In**

Clofulbicyne	n/a	5x1 mg.	TXL9001-5	ACCURATE CHEMICAL & SCIENTIFIC CO.	**More In**
Clomifene citrate	International Chemical Reference Substances are established upon the advice of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. They are supplied primarily for use in physical and chemical tests and assays described in t...	100 mg	9930259	W.H.O. COLLABORATING CENTRE	**More In**
Clomiphene, Citrate	An unducer of ovulation. A gonad-stimulating principle.Melting Point: 116.5-118?CSolubility: Methanol	10g	C5843-65	UNITED STATES BIOLOGICAL	**More In**
Cloning	>1500 bp into 3 different expression vectors	n/a	PE05-0003	HYPEROMICS FARMA INC.	**More In**
Cloning	<1500 bp into 3 different expression vectors	n/a	PE05-0002	HYPEROMICS FARMA INC.	**More In**
Clopidogrel Carboxylic Acid	A metabolite of the drug Clopidogrel.Solubility: Methanol, Water	5mg	C5849-01	UNITED STATES BIOLOGICAL	**More In**
CLOSTRIPAIN Clostridium	n/a	n/a	n/a	PROMEGA CORPORATION	**More In**
Clotrimazole	An antifungal agent that acts as a potent and specific inhibitor of the Ca2+-activated K+ channel (Gardos channel; IC50 = 650 nM). Prevents K+ loss and dehydration of sickled erythrocytes.	n/a	233230	CALBIOCHEM/EMD BIOSCIENCES	**More In**
Clozapine	An antipsychotic.Melting Point: 183-184? CSolubility: Acetone, Ether	250mg	C5866	UNITED STATES BIOLOGICAL	**More In**
Clozapine	Atypical antipsychotic drug, with a much lower tendency to cause extrapyramidal side effects than conventional neuroleptics. Displays a broad range of pharmacological actions; the antipsychotic effects are thought to be mediated principally by 5-H...	50mg, 500mg	0444	TOCRIS BIOSCIENCE	**More In**

CLTB	The RP-39010 CLTB protein is a full length bacterially expressed recombinant protein.RP-39010 is suitable for use as a control in ELISA and Western blot applications.The RP-39010 amino acid sequence corresponds to the NCBI accession number NP_0018...	10 ug	RP-39010	ABR - AFFINITY BIOREAGENTS INC.	**More In**
Aldosterone-3 CMO (BSA)	The major mineralcorticoid, which is secreted almost independently of ACTH from the pitutitary, is aldosterone. Aldosterone secretion is controlled mostly by the levels of potassium and sodium in serum and a blood pressure control system called th...	5mg	A1350-04	UNITED STATES BIOLOGICAL	**More In**
Androstenedione-3 (CMO)	Androstenedione was discovered in 1935. It is naturally produced in men and women. It is a direct precursor to the hormone testosterone. The liver converts androstenedione to testosterone.Precursor:4-Androsten-3,17-dione-3Sto rage and Stability:Lyo...	10mg	A2292-02	UNITED STATES BIOLOGICAL	**More In**
CMPD-1	Non-ATP-competitive, selective inhibitor of p38 α-mediated MK2a (mitogen-activated protein kinase-activated protein kinase 2a) phosphorylation (apparent Ki = 330 nM). Does not inhibit p38 α-mediated phosphorylation of the two other kno...	10mg, 50mg	2186	TOCRIS BIOSCIENCE	**More In**
CMV	Glycine Extract	mL	0810003GE	ZEPTOMETRIX CORP.	**More In**
CMV	Cytomegalovirus (AD169) Infected Cell Extract. Used for IgG assays - Control is NHDF AV043	n/a	CV001	EASTCOAST BIO INC.	**More In**
	Cytomegalovirus				

CMV	Gradient Purified. Used for IgM assays.	n/a	CV046	EASTCOAST BIO INC.	More In
CMV	Cytomegalovirus Ag slides for FA. Made to Order	n/a	CG015	EASTCOAST BIO INC.	More In
CMV	Part Pure	n/a	J43010	BIOSPACIFIC INC.	More In

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Name	Description	Size	Catalog #	Supplier	
CKBB	Recombinant Human Creatine Kinase BB Isoenzyme	10µg, 50µg, 1mg	CKI- 268	PROSPEC-TANY TECHNOGENE LTD.	More In
Ckdk6	The RP-39008 Ckdk6 protein is a partial length (aa 1-327) bacterially expressed recombinant protein.RP-39008 is suitable for use as a control in ELISA and Western blot applications.The RP-39008 protein is GST-tagged.	10 ug	RP-39008	ABR - AFFINITY BIOREAGENTS INC.	More In
CKMM	Human Creatine Kinase MM	200µg, 1mg, 10mg	CKI- 273	PROSPEC-TANY TECHNOGENE LTD.	More In
CKS-17	Sequence: Leu-Gln-Asn-Arg-Arg-Gly-L eu-Asp-Leu-Leu-Phe-Leu-Ly s-Glu-Gly-Gly-LeuStorage and Stability: Lyophilized powder may be stored at 4?C for short-term only. Reconstitute to nominal volume by adding sterile 40-50% glycerol and store at -20?C. R...	1mg	C5818-05	UNITED STATES BIOLOGICAL	More In
CKS-17 (7-12)	Sequence: Leu-Asp-Leu-Leu-Phe-LeuSt orage and Stability: Lyophilized powder may be stored at 4?C for short-term only. Reconstitute to nominal volume by adding sterile 40-50% glycerol and store at -20?C. Reconstituted product is stable for 12 months...	25mg	C5818-05A	UNITED STATES BIOLOGICAL	More In

CKS-17	This Peptide CKS-17 is considered as the major immunosuppressive site of retroviral TM protein. It can suppress T effector cell function in vitro. It has been shown that CKS-17 causes an imbalance of human types 1 and 2 cytokines and inhibition of...	0.5 mg	06-271-83162	GENWAY BIOTECH INC.	**More In**
CKS-17	This Peptide CKS-17 is considered as the major immunosuppressive site of retroviral TM protein. It can suppress T effector cell function in vitro. It has been shown that CKS-17 causes an imbalance of human types 1 and 2 cytokines and inhibition of...	1 mg	06-271-83162	GENWAY BIOTECH INC.	**More In**
CARCINOEMBRYONIC ANTIGEN (CL)	testing/assay service	n/a	n/a	RDL REFERENCE LABORATORY INC.	**More In**
CASPASE-3/7 (CL)	n/a	n/a	n/a	PROMEGA CORPORATION	**More In**
CASPASE-8 (CL)	n/a	n/a	n/a	PROMEGA CORPORATION	**More In**
CASPASE-9 (CL)	n/a	n/a	n/a	PROMEGA CORPORATION	**More In**
CASPASE (CL)	n/a	n/a	n/a	PROMEGA CORPORATION	**More In**
CL 218872	Benzodiazepine agonist displaying selectivity for α1 subunit-containing GABAA receptors (Ki values are 130, 1820, 1530, > 10000, 490 and > 10000 nM for α1, α2, α3, α4, α5 and α6-subunit containing re...	10mg, 50mg	1709	TOCRIS BIOSCIENCE	**More In**
CL-387,785	Irreversibly inhibits EGF-receptor (EGFR) kinase activity in vivo (IC50 = 250-490 pM) as well as EGF-stimulated autophosphorylation of tyrosine residues in the EGFR in vivo (IC50 = 5 nM). Blocks EGF-mediated growth in A431 cells. Inhibits prolifer...	n/a	233100	CALBIOCHEM/EMD BIOSCIENCES	**More In**
	A selective inhibitor of MMP-13 (IC50 = 10 μM).				

CL-82198	Binds to the S1' pocket of MMP-13 with its morpholine ring adjacent to the catalytic zinc atom. Does not inhibit MMP-1, MMP-9, and TACE.	n/a	233105	CALBIOCHEM/EMD BIOSCIENCES	**More In**
Calphostin C, Cladosporium cladosporioides	A cell permeable, highly specific inhibitor of protein kinase C (IC50 = 50 nM) that interacts with the protein's regulatory domain by competing at the binding site of diacylglycerol and phorbol esters. Does not compete with Ca2+ or phospholi...	n/a	208725	CALBIOCHEM/EMD BIOSCIENCES	**More In**
Cladribine	It is a substituted purine nucleoside with antileukemic activity.Melting Point: 220-235?C dec.Solubility: Methanol, Water	50mg	C5819-75	UNITED STATES BIOLOGICAL	**More In**
Clarithromycin	A semi-synthetic macrolide antibiotic. A derivative of erythromycin.Melting Point: 217-220?C dec.Solubility: Chloroform, Ethanol	50mg	C5829	UNITED STATES BIOLOGICAL	**More In**
Clavulanic Acid	A B-Lactamase inhibitor.	10mg	C5836	UNITED STATES BIOLOGICAL	**More In**
CLIC3	The RP-39009 CLIC3 protein is a full length bacterially expressed recombinant protein.RP-39009 is suitable for use as a control in ELISA and Western blot applications.The RP-39009 amino acid sequence corresponds to the NCBI accession number NP_004...	10 ug	RP-39009	ABR - AFFINITY BIOREAGENTS INC.	**More In**
Clidinium Bromide	An anticholinergic. Used as an antispasmodic.Melting Point: 240-241?C	5g	C5840-75	UNITED STATES BIOLOGICAL	**More In**
	A metal ion chelator that crosses the blood brain barrier and acts as a neurotoxic antibiotic. Reported to dissolve				

Clioquinol	senile plaques and reduce amyloid's ability to clump together, apparently by trapping the Cu2+ and Zn2+ that stud these depos...	n/a	233165	CALBIOCHEM/EMD BIOSCIENCES	**More In**
CLK3, active	n/a	10 ug	14-724	MILLIPORE	**More In**
CLK2, active	n/a	10 ug	14-774	MILLIPORE	**More In**
Clofarabine	ISecond generation purine nucleoside analog; antimetabolite that inhibits DNA synthesis and resists deamination by adenosine deaminase. Antineoplastic.Melting Point: 225-227?C	10mg	C5843-55	UNITED STATES BIOLOGICAL	**More In**
Clofarabine	Deoxycytidine kinase (dCK) substrate. Phosphorylated to form clofarabine triphosphate, which competes with dATP for DNA polymerase- α and - ε and potently inhibits ribonucleotide reductase (IC50 = 65 nM). Induces apoptosis by directl...	10mg, 50mg	2600	TOCRIS BIOSCIENCE	**More In**
CLOFIBRATE	n/a	n/a	n/a	CAYMAN CHEMICAL CO.	**More In**
Clofibrate	PPAR agonist (EC50 values are 50, 500 and > 100 µM at PPAR α, PPAR γ and PPAR δ respectively). Antihyperlipoproteinemic.	1g	0824	TOCRIS BIOSCIENCE	**More In**
Clofibric acid	PPAR agonist. Antihyperlipoproteinemic.	1g	0825	TOCRIS BIOSCIENCE	**More In**
Clofibrate	An anti-hyperlipoproteinemic agent believed to act by inhibiting cholesterol biosynthesis. Activates PPARα and induces cytochrome P450 4A1 and 4A3. Imparts protection against acetaminophen toxicity and increases hepatic glutathione levels.	n/a	231405	CALBIOCHEM/EMD BIOSCIENCES	**More In**
Clofulbicyne	n/a	1 mg.	TXL9001-1	ACCURATE CHEMICAL & SCIENTIFIC CO.	**More In**

Clofulbicyne	n/a	5x1 mg.	TXL9001-5	ACCURATE CHEMICAL & SCIENTIFIC CO.	**More In**
Clomifene citrate	International Chemical Reference Substances are established upon the advice of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. They are supplied primarily for use in physical and chemical tests and assays described in t...	100 mg	9930259	W.H.O. COLLABORATING CENTRE	**More In**
Clomiphene, Citrate	An unducer of ovulation. Λ gonad-stimulating principle.Melting Point: 116.5-118?CSolubility: Methanol	10g	C5843-65	UNITED STATES BIOLOGICAL	**More In**
Cloning	>1500 bp into 3 different expression vectors	n/a	PE05-0003	HYPEROMICS FARMA INC.	**More In**
Cloning	<1500 bp into 3 different expression vectors	n/a	PE05-0002	HYPEROMICS FARMA INC.	**More In**
Clopidogrel Carboxylic Acid	A metabolite of the drug Clopidogrel.Solubility: Methanol, Water	5mg	C5849-01	UNITED STATES BIOLOGICAL	**More In**
CLOSTRIPAIN Clostridium	n/a	n/a	n/a	PROMEGA CORPORATION	**More In**
Clotrimazole	An antifungal agent that acts as a potent and specific inhibitor of the Ca2+-activated K+ channel (Gardos channel; IC50 = 650 nM). Prevents K+ loss and dehydration of sickled erythrocytes.	n/a	233230	CALBIOCHEM/EMD BIOSCIENCES	**More In**
Clozapine	An antipsychotic.Melting Point: 183-184? CSolubility: Acetone, Ether	250mg	C5866	UNITED STATES BIOLOGICAL	**More In**
Clozapine	Atypical antipsychotic drug, with a much lower tendency to cause extrapyramidal side effects than conventional neuroleptics. Displays a broad range of pharmacological actions; the antipsychotic effects are thought to be mediated principally by 5-H...	50mg, 500mg	0444	TOCRIS BIOSCIENCE	**More In**

CLTB	The RP-39010 CLTB protein is a full length bacterially expressed recombinant protein.RP-39010 is suitable for use as a control in ELISA and Western blot applications.The RP-39010 amino acid sequence corresponds to the NCBI accession number NP_0018...	10 ug	RP-39010	ABR - AFFINITY BIOREAGENTS INC.	**More In**
Aldosterone-3 CMO (BSA)	The major mineralcorticoid, which is secreted almost independently of ACTH from the pitutitary, is aldosterone. Aldosterone secretion is controlled mostly by the levels of potassium and sodium in serum and a blood pressure control system called th...	5mg	A1350-04	UNITED STATES BIOLOGICAL	**More In**
Androstenedione-3 (CMO)	Androstenedione was discovered in 1935. It is naturally produced in men and women. It is a direct precursor to the hormone testosterone. The liver converts androstenedione to testosterone.Precursor:4-Androsten-3,17-dione-3Sto rage and Stability:Lyo...	10mg	A2292-02	UNITED STATES BIOLOGICAL	**More In**
CMPD-1	Non-ATP-competitive, selective inhibitor of p38 α-mediated MK2a (mitogen-activated protein kinase-activated protein kinase 2a) phosphorylation (apparent Ki = 330 nM). Does not inhibit p38 α-mediated phosphorylation of the two other kno...	10mg, 50mg	2186	TOCRIS BIOSCIENCE	**More In**
CMV	Glycine Extract	mL	0810003GE	ZEPTOMETRIX CORP.	**More In**
CMV	Cytomegalovirus (AD169) Infected Cell Extract. Used for IgG assays - Control is NHDF AV043	n/a	CV001	EASTCOAST BIO INC.	**More In**
	Cytomegalovirus				

CMV	Gradient Purified. Used for IgM assays.	n/a	CV046	EASTCOAST BIO INC.	**More In**
CMV	Cytomegalovirus Ag slides for FA. Made to Order	n/a	CG015	EASTCOAST BIO INC.	**More In**
CMV	Part Pure	n/a	J43010	BIOSPACIFIC INC.	**More In**

Page 36 of 2,608 **Records 1,751 - 1,800 of 130,353**

[1] « 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 |

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Electronic Patent Application Fee Transmittal

Application Number:	10551205
Filing Date:	14-Nov-2006
Title of Invention:	Oral formulations of cladribine
First Named Inventor/Applicant Name:	Nicholas S. Bodor
Filer:	Mary Katherine Baumeister/Diana Francis
Attorney Docket Number:	0056192-000024

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 3 months with $0 paid	1253	1	1110	1110

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**1110**

Electronic Acknowledgement Receipt

EFS ID:	4054303
Application Number:	10551205
International Application Number:	
Confirmation Number:	4092
Title of Invention:	Oral formulations of cladribine
First Named Inventor/Applicant Name:	Nicholas S. Bodor
Customer Number:	21839
Filer:	Mary Katherine Baumeister/Diana Francis
Filer Authorized By:	Mary Katherine Baumeister
Attorney Docket Number:	0056192-000024
Receipt Date:	03-OCT-2008
Filing Date:	14-NOV-2006
Time Stamp:	10:37:12
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1110
RAM confirmation Number	5296
Deposit Account	024800
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. 1.492 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	005619224TL.pdf	106535 802ec79ff5c0d1ec5dba3514562c642abd4a9181	no	2
Warnings:					
Information:					
2	Extension of Time	005619224EOT.pdf	46723 dc7eb25d6272e05224cf13c539e286ac0a2e3259	no	1
Warnings:					
Information:					
3	Amendment/Req. Reconsideration-After Non-Final Reject	005619224AMEND.pdf	4488479 b527124e797383c9425f8fece79d8cd57c4ee563	no	48
Warnings:					
Information:					
4	Fee Worksheet (PTO-06)	fee-info.pdf	30075 a665357a4ed17d1ebac948c63e3acee571ae5f56	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	4671812		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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
	)	
Filing Date: November 14, 2006	)	Confirmation No.: 4092
	)	
Title: ORAL FORMULATIONS OF CLADRIBINE	)	
	)	
	)	
	)	

AMENDMENT/REPLY TRANSMITTAL LETTER

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

Sir:

Enclosed is a reply for the above-identified patent application.

☒ A Petition for Extension of Time is enclosed.

☐ _____ Terminal Disclaimer(s) and the ☐ $ 65 ☐ $ 130 fee per Disclaimer due under 37 C.F.R. § 1.20(d) are enclosed.

☒ Also enclosed is/are: copies of the attachments listed on page 26 of Reply and Amendment.

☐ Small entity status is hereby claimed.

☐ Applicant(s) requests continued examination under 37 C.F.R. § 1.114 and enclose the ☐ $ 405 ☐ $ 810 fee due under 37 C.F.R. § 1.17(e).

☐ Applicant(s) requests that any previously unentered after final amendments not be entered. Continued examination is requested based on the enclosed documents identified above.

☐ Applicant(s) previously submitted _____ on _____ for which continued examination is requested.

☐ Applicant(s) requests suspension of action by the Office until at least _____, which does not exceed three months from the filing of this RCE, in accordance with 37 C.F.R. § 1.103(c). The required fee under 37 C.F.R. § 1.17(i) is enclosed.

☐ A Request for Entry and Consideration of Submission under 37 C.F.R. § 1.129(a) (1809/2809) is also enclosed.

☒ No additional claim fee is required.

☐ An additional claim fee is required, and is calculated as shown below:

AMENDED CLAIMS					
	No. of Claims	**Highest No. of Claims Previously Paid For**	**Extra Claims**	**Rate**	**Additional Fee**
Total Claims	78	78	0	x $ 50 (1202)	$ 0
Independent Claims	5	5	0	x $ 210 (1201)	0
☐ If Amendment adds multiple dependent claims, add $ 370 (1203)					$ 0
Total Claim Amendment Fee					**$ 0**
☐ Small Entity Status claimed - subtract 50% of Total Claim Amendment Fee					0
TOTAL ADDITIONAL CLAIM FEE DUE FOR THIS AMENDMENT					**$ 0**

☐ Charge _____ to Deposit Account No. 02-4800 for the fee due.

☐ A check in the amount of _____ is enclosed for the fee due.

☐ Charge_____ to credit card for the fee due. Form PTO-2038 is attached.

☒ The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§ 1.16, 1.17 and 1.20(d) and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date October 3, 2008

By: Mary Katherine Baumeister
Mary Katherine Baumeister
Registration No. 26254

P.O. Box 1404
Alexandria, VA 22313-1404
703 836 6620

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
Filing Date: November 14, 2006	)	Confirmation No.: 4092
Title: ORAL FORMULATIONS OF CLADRIBINE	)	

PETITION FOR EXTENSION OF TIME

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

Sir:

The following extension of time is requested to: extend the period for response to the Office Action dated April 4, 2008 for

Three Months to October 6, 2008 ☒ $ 1110 ☐ $ 525

☐ The shortened statutory period has been reset by an Advisory Action dated _____.

☐ An Extension fee in the amount of _____ is enclosed.

☒ Charge $ 1110 to Deposit Account No. 02-4800.

☐ Charge _____ to credit card. Form PTO-2038 is attached.

The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17 and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date: October 3, 2008

By: Mary Katherine Baumeister
Mary Katherine Baumeister
Registration No. 26254

P.O. Box 1404
Alexandria, VA 22313-1404
703 836 6620

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
10/551,205	11/14/2006	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 10/03/2008

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 78	Minus	** 78	= 0	X $ =		OR	X $52=	0
Independent (37 CFR 1.16(h))	* 4	Minus	***6	= 0	X $ =		OR	X $220=	0
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/SHERRY A. DAVIS/