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June 03, 2004

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 60/541,247

us/04/9387

FILING DATE: February 04, 2004

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH
RULE 17.1(a) OR (b)

**By Authority of the
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N. Williams
N. WILLIAMS
Certifying Officer

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U.S. DEPARTMENT OF COMMERCE
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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 C.F.R. § 1.53(c).

Docket Number		033935-005		Type a plus sign (+) inside this box		+	
INVENTOR(S)/APPLICANT(S)							
LAST NAME		FIRST NAME		MIDDLE INITIAL		RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)	
BODOR		Nicholas		S.		10101 Collins Avenue, #4A Bal Harbour, Florida 33154	
<input type="checkbox"/> Additional inventors are being named on the ___ separately numbered sheets attached hereto.							
TITLE OF THE INVENTION (500 characters max)							
ORAL FORMULATIONS OF CLADRIBINE							
CORRESPONDENCE ADDRESS							
Burns, Doane, Swecker & Mathis, L.L.P. Customer Number 2 1 8 3 9 Post Office Box 1404 Alexandria							
STATE		Virginia		ZIP CODE		22313-1404	
				COUNTRY		United States of America	
ENCLOSED APPLICATION PARTS (check all that apply)							
<input checked="" type="checkbox"/> Specification		Number of Pages 28		<input checked="" type="checkbox"/> Other (specify)		Claims 1-45 (7 pgs.), Abstract (1 pg.)	
<input checked="" type="checkbox"/> Drawing(s)		Number of Sheets 1					
<input type="checkbox"/> Application Data Sheet. See 37 CFR 1.76							
METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT (check one)							
<input type="checkbox"/> Applicant claims small entity status. See 37 C.F.R. § 1.27.				PROVISIONAL FILING FEE AMOUNT(S)		<input type="checkbox"/> \$80.00 (2005)	
<input checked="" type="checkbox"/> A check or money order is enclosed to cover the Provisional filing fees.						<input checked="" type="checkbox"/> \$160.00 (1005)	
<input checked="" type="checkbox"/> The Director is hereby authorized to charge any deficiency in filing fees or credit any overpayment to Deposit Account No. 02-4800. This paper is submitted in duplicate.							

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

No.

Yes, the name of the U.S. Government agency and the Government contract number are:

BURNS DOANE
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INTELLECTUAL PROPERTY LAW

PROVISIONAL APPLICATION FOR PATENT
COVER SHEET

Page 1

Respectfully submitted,

SIGNATURE Mary Katherine Baumeister DATE February 4, 2004
TYPED or PRINTED NAME Mary Katherine Baumeister Registration No. 26,254
(if appropriate)

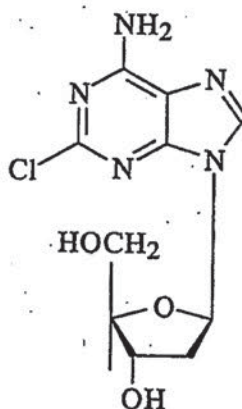
ORAL FORMULATIONS OF CLADRIBINE

FIELD OF THE INVENTION

The invention relates to a composition comprising a complex cladribine-cyclodextrin complex formulated into a solid oral dosage form and to a method for enhancing the oral bioavailability of cladribine.

BACKGROUND OF THE INVENTION

Cladribine, which is an acid-labile drug, has the chemical structure as set forth below:



It is also known as 2-chloro-2'-deoxyadenosine or 2-CdA. Cladribine exists as a white, nonhydroscopic, crystalline powder, consisting of individual crystals and of crystalline aggregates.

Cladribine is an antimetabolite which has use in the treatment of lymphoproliferative disorders. It has been used to treat experimental leukemias such as L1210 and clinically for hairy cell leukemia and chronic lymphocytic leukemia as well as Waldenstrom's macroglobulinaemia. It has also been used as an immunosuppressive agent and as a modality for the treatment of a variety of

autoimmune conditions including rheumatoid arthritis, inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis) and multiple sclerosis (see e.g., J. Liliemark, *Clin. Pharmacokinet*, 32(2): 120-131, 1997). It has also been investigated, either experimentally or clinically in, for example, lymphomas, 5 Langerhan's cell histiocytosis, lupus erythematosus, chronic plaque psoriasis, Sezary syndrome, Bing-Neel syndrome, recurrent glioma, and solid tumors.

Oral delivery of drugs is often preferred to parenteral delivery for a variety of reasons, foremost patient compliance, or for cost or therapeutic considerations. Patient compliance is enhanced insofar as oral dosage forms alleviate repeated 10 health care provider visits, or the discomfort of injections or prolonged infusion times associated with some active drugs. At a time of escalating health care costs, the reduced costs associated with oral or transmucosal administration versus parenteral administration costs gain importance. The cost of parenteral administration is much higher due to the requirement that a health care 15 professional administer the cladribine in the health care provider setting, which also includes all attendant costs associated with such administration. Furthermore, in certain instances, therapeutic considerations such as the need for a slow release of cladribine over a prolonged period of time may be practically met only by oral or transmucosal delivery.

20 However, to date the oral delivery of cladribine has been plagued by low bioavailability (see, e.g., J. Liliemark *et al.*, *J. Clin. Oncol.*, 10(10): 1514-1518, 1992), and suboptimal interpatient variation (see, e.g., J. Liliemark, *Clin. Pharmacokinet*, 32 (2): 120-131, 1997). See also, A. Tarasuik, *et al.* reporting poor absorption and pH dependent lability (*Arch. Immunol. et Therapiae Exper.*, 25 42: 13-15, 1994).

Cyclodextrins are cyclic oligosaccharides composed of cyclic α -(1-4) linked D-glucopyranose units. Cyclodextrins with six to eight units have been named α -, β - and γ -cyclodextrin, respectively. A number of derivatives of α -, β -

and γ -cyclodextrin are known in which one or more hydroxyl groups is/are replaced with ether groups or other radicals. These compounds are known complexing agents and have been previously used in the pharmaceutical field to form inclusion complexes with water-insoluble drugs and to thus solubilize them in aqueous media.

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Recently, Schultz *et al.*, in U.S. Patent No. 6,194,395 B1, have described complexing and solubilizing cladribine with cyclodextrin. The Schultz *et al.* patent primarily addresses the problems inherent in previously described aqueous formulations of cladribine, particularly for subcutaneous and intramuscular injection. Schultz *et al.* have found that cladribine is not only significantly more soluble in aqueous media when formulated with cyclodextrin, but also is more stable against acid-catalyzed hydrolysis when combined with cyclodextrin. The latter finding is taught to be of particular benefit in the formulation of solid oral dosage forms, where the compound would normally undergo hydrolysis in the acid pH of the stomach contents. Schultz *et al.* do not appear to have described any actual work in connection with solid oral dosage forms. In fact, they describe only one method of preparing the solid dosage form, which is a melt extrusion process, in which the cladribine and cyclodextrin are mixed with other optional additives and then heated until melting occurs. Furthermore, the broad dosage ranges of 1 mg to 15 mg of cladribine and 100 mg to 500 mg of cyclodextrin listed in the patent suggest no criticality to the particular amount of cyclodextrin to be present with a given amount of cladribine in a solid oral dosage form. Indeed, these dosage ranges include many combinations which may be suitable as mixtures but not for complex formation. For example, a ratio of 1 mg of cladribine to 500 mg of cyclodextrin contains too much cyclodextrin, so that the drug would not readily leave the complex and achieve its therapeutic function. On the other hand, 15 mg of cladribine and only 100 mg of cyclodextrin would not be enough to complex that amount of cladribine.

The Schultz *et al.* patent does suggest improving the stability of cladribine in oral dosage forms by combining/complexing it with cyclodextrin, but does not suggest improving the drug's oral bioavailability by such means; in fact, the patent does not describe or suggest a method for enhancing or maximizing the
5 bioavailability of cladribine from a solid oral dosage form of cladribine and cyclodextrin, or a composition specially designed to do so.

Many workers have studied the solubility of specific drugs in water containing various concentrations of selected cyclodextrins in order to demonstrate that increasing concentrations of cyclodextrins increase the solubility of the drugs
10 at selected temperatures and pH levels, as for example reported in the Schultz *et al.* patent. Phase solubility studies have also been performed by various workers in order to elucidate the nature of the complex formation, for example; whether the cyclodextrin and drug form a 1:1 complex or a 1:2 complex; see, for example, Harada *et al.* U.S. Patent No. 4,497,803, relating to inclusion
15 complexes of lankacidin-group antibiotics with cyclodextrin, and Shinoda *et al.* U.S. Patent No. 4,478,995, relating to a complex of an acid addition salt of (2'-benzyloxycarbonyl)phenyl trans-4-guanidinomethylcyclohexanecarboxylate with a cyclodextrin.

While Schultz *et al.* teach that a cladribine-cyclodextrin complex improves
20 the water solubility and acid stability of cladribine, the art does not suggest how to maximize or enhance the benefits of the complexation in terms of bioavailability and interpatient variation when the complex is to be administered in a solid oral dosage form.

SUMMARY OF THE INVENTION

25 It has now been found that amorphous cyclodextrins can be combined with cladribine to form a particularly advantageous product which can be incorporated into a solid oral dosage form. This product is a complex cladribine-cyclodextrin

complex, and the solid oral dosage form containing it improves oral and/or transmucosal bioavailability and/or achieves lower interpatient and/or inpatient variation of the drug.

5 The present invention provides a pharmaceutical composition comprising a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture 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. Thus, the cyclodextrin itself is amorphous, the inclusion complex with cladribine
10 is amorphous (and is preferably saturated with cladribine) and the free cladribine which forms the non-inclusion complex is amorphous.

The invention also provides a method for increasing or enhancing the oral bioavailability of cladribine comprising orally administering to a subject in need thereof, a pharmaceutical composition comprising a complex cladribine-
15 cyclodextrin complex which is an intimate amorphous admixture 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 which maximizes the amount of cladribine in the inclusion and non-inclusion complexes.

20 The invention further provides for treatment of conditions responsive to administration of cladribine in mammals by administering thereto the composition of the invention. Use of cladribine in the preparation of the pharmaceutical compositions of the invention is also provided.

BRIEF DESCRIPTION OF THE DRAWING

25 A more complete appreciation of the invention and its many attendant advantages will be readily understood by reference to the following detailed description and the accompanying drawing, wherein the sole Figure is a graphical

representation of the results of a phase solubility study where various molar concentrations of hydroxypropyl- β -cyclodextrin (HP β CD) are plotted against various cladribine molar concentrations, with (●) representing the data points obtained for complexation under conditions specified in EXAMPLE 2 below.

5 DETAILED DESCRIPTION OF THE INVENTION

Throughout the instant specification and claims, the following definitions and general statements are applicable.

10 The patents, published applications, and scientific literature referred to herein establish the knowledge of those with skill in the art and are hereby incorporated by reference in their entirety to the same extent as if each was specifically and individually indicated to be incorporated by reference. Any conflict between any reference cited herein and the specific teachings of this specification shall be resolved in favor of the latter. Likewise, any conflict between an art-understood definition of a word or phrase and a definition of the word or phrase as specifically taught in this specification shall be resolved in favor of the latter.

15 The term "inclusion complex" as used herein refers to a complex of cladribine with the selected cyclodextrin wherein the hydrophobic portion of the cladribine molecule (the nitrogen-containing ring system) is inserted into the hydrophobic cavity of the cyclodextrin molecule. This is often referred to simply as a cyclodextrin complex of the drug.

20 The term "non-inclusion complex" refers to a complex which is not an inclusion complex; rather than the hydrophobic portion of cladribine being inserted in the cyclodextrin cavity, the non-inclusion complex is formed primarily by hydrogen-bonding of the hydroxyls and amino group on "free" cladribine, (*i.e.* cladribine not in the inclusion complex) to the hydroxyls on the exterior of the cyclodextrin torus (*e.g.* in the case of hydroxypropyl- β -cyclodextrin,

hydroxypropyl and hydroxy groups on the glucose rings). This is a more loosely-held association than an inclusion complex.

As used herein, whether in a transitional phrase or in the body of a claim, the terms "comprise(s)" and "comprising" are to be interpreted as having an open-ended meaning. That is, the terms are to be interpreted synonymously with the phrases "having at least" or "including at least". When used in the context of a process, the term "comprising" means that the process includes at least the recited steps, but may include additional steps. When used in the context of a composition, the term "comprising" means that the composition includes at least the recited features or components, but may also include additional features or components.

The terms "consists essentially of" or "consisting essentially of" have a partially closed meaning, that is, they do not permit inclusion of steps or features or components which would substantially change the essential characteristics of a process or composition; for example, steps or features or components which would significantly interfere with the desired properties of the compositions are described herein, *i.e.*, the process or composition is limited to the specified steps or materials and those which do not materially affect the basic and novel characteristics of the invention. The basic and novel features herein are the provision of a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture 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, so as to provide improved bioavailability and/or lower interpatient and/or inpatient variation following administration. Essential to the invention is the combination of the amorphous nature of the starting cyclodextrin, and the level of water solubility exhibited cladribine (about 5 mg/ml at room temperature), and consequently its capability for hydrogen bonding, which can be taken advantage of

under particular conditions described hereinafter, and which afford a special amorphous mixture uniquely well-suited for optimizing the oral bioavailability of cladribine.

5 The terms "consists of" and "consists" are closed terminology and allow only for the inclusion of the recited steps or features or components.

As used herein, the singular forms "a," "an" and "the" specifically also encompass the plural forms of the terms to which they refer, unless the content clearly dictates otherwise.

10 The term "about" is used herein to mean approximately, in the region of, roughly, or around. When the term "about" is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term "about" or "approximately" is used herein to modify a numerical value above and below the stated value by a variance of 20%.

15 The term "amorphous" is used herein to refer to a noncrystalline solid. The cyclodextrins encompassed herein themselves are amorphous because they are each composed of a multitude of individual isomers, and their complexes with cladribine are also amorphous. Further, conditions for complexation can be selected (elevated temperature and prolonged complexation times, as described
20 hereinafter) so that a supersaturated cladribine solution will be formed. When cooled, because of the amorphous nature of the complex and the cyclodextrin, some excess free cladribine does not precipitate but rather is trapped in amorphous form in intimate admixture with the (preferably saturated) amorphous cladribine-cyclodextrin inclusion complex. This excess cladribine forms a loosely-held
25 association, or non-inclusion complex, with the cyclodextrin through hydrogen bonding. This, then, further increases the amount of cladribine in the product; this additional cladribine, because it is amorphous and also because it is in intimate admixture with the amorphous inclusion complex, is expected to be

somewhat protected from degradation by stomach acid (although it may not be as protected as the cladribine which is in the form of the inclusion complex).

The term "saturated" when used in conjunction with a complex of cladribine in amorphous cyclodextrin means that the complex is saturated with cladribine, that is, the complex contains the maximum amount of cladribine which can be complexed (by means of both inclusion and non-inclusion complexes) with a given amount of cyclodextrin under the conditions of complexation used. A phase solubility study can be used to provide this information, as described in more detail hereinafter. (Conditions for the complexation are also described in more detail below.) Alternatively, a saturated complex may be arrived at empirically by simply adding cladribine to an aqueous solution of the selected cyclodextrin until no more cladribine goes into solution; ultimately, excess cladribine is removed (by filtration or centrifugation) and the solution lyophilized to provide the dry saturated complex.

The expression "substantially", as in "substantially free" means within 20% of the exact calculated amount, preferably within 10%, most preferably within 5%.

The term "interpatient variability" refers to variation among patients to which a drug is administered. The term "intrapatient variability" refers to variation experienced by a single patient when dosed at different times.

As used herein, the recitation of a numerical range for a variable is intended to convey that the invention may be practiced with the variable equal to any of the values within that range. Thus, for a variable which is inherently discrete, the variable can be equal to any integer value of the numerical range, including the end-points of the range. Similarly, for a variable which is inherently continuous, the variable can be equal to any real value of the numerical range, including the end-points of the range. As an example, a variable which is described as having values between 0 and 2, can be 0, 1 or 2 for variables which

are inherently discrete, and can be 0.0, 0.1, 0.01, 0.001, or any other real value for variables which are inherently continuous.

In the specification and claims, the singular forms include plural referents unless the context clearly dictates otherwise. As used herein, unless specifically indicated otherwise, the word "or" is used in the "inclusive" sense of "and/or" and not the "exclusive" sense of "either/or."

Technical and scientific terms used herein have the meaning commonly understood by one of skill in the art to which the present invention pertains, unless otherwise defined. Reference is made herein to various methodologies and materials known to those of skill in the art. Standard reference works setting forth the general principles of pharmacology include Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, 10th Ed., McGraw Hill Companies Inc., New York (2001).

Reference is made hereinafter in detail to specific embodiments of the invention. While the invention will be described in conjunction with these specific embodiments, it will be understood that it is not intended to limit the invention to such specific embodiments. On the contrary, it is intended to cover alternatives, modifications, and equivalents as may be included within the spirit and scope of the invention as defined by the appended claims. In the following description, numerous specific details are set forth in order to provide a thorough understanding of the present invention. The present invention may be practiced without some or all of these specific details. In other instances, well-known process operations have not been described in detail, in order not to unnecessarily obscure the present invention.

There is provided by the present invention compositions, as well as methods of making and of using pharmaceutical compositions, useful to achieve desirable pharmacokinetic properties. Such compositions stem from the discovery that solutions of cyclodextrin and cladribine in which cladribine is in a high

thermodynamic state, when presented to the gastric mucosa through which they are absorbed are associated with improved cladribine absorption, as reflected by higher bioavailability and/or lower interpatient variation.

5 It is postulated, without wishing to so limit the invention, that upon dissolution (*e.g.*, by contact with a fluid, such as a bodily fluid), dry compositions according to the invention form a locally saturated cladribine solution in which cladribine is in the state of highest thermodynamic activity (HTA), thus favoring absorption. Cladribine has a fairly low, although not insignificant, intrinsic aqueous solubility; it is in fact somewhat water soluble. The free cladribine
10 formed from dissociation of the inclusion and non-inclusion complexes in a saturated aqueous solution seeks a more stable activity level by being absorbed through the gastric musoca.

In view of the foregoing, it is apparent that to produce optimal pharmaceutical compositions, in a solid oral dosage form, these dosage forms
15 should be formulated to release a localized saturated cladribine solution, upon contact of the solid dosage forms with body fluid at the mucosa, in which cladribine is in its HTA state. To provide such a localized saturated solution *in vivo*, it is important to first identify the optimal ratio of cladribine to amorphous cyclodextrin, which ratio is referred to herein as the HTA ratio, to be used in the
20 solid dosage form.

The HTA ratio is empirically determined and is identified as the ratio of cladribine to amorphous cyclodextrin which corresponds to the maximum amount of cladribine that can be complexed with a given amount of the cyclodextrin. The HTA ratio may be determined using an empirical method such as a phase
25 solubility study to determine the saturation concentration of cladribine that can be solubilized with different concentrations of amorphous cyclodextrin solutions. Hence, the method identifies the concentrations at which a saturated cladribine-cyclodextrin complex is formed. It is noted that the molar ratio represented by a

point on the phase solubility graph shows how many moles of amorphous cyclodextrin are the minimum needed to maintain the drug in the complex, under given conditions; this may then be converted to a weight ratio. For example, if a phase solubility diagram shows that 9 moles of a given cyclodextrin are needed to maintain the cladribine in a saturated complex, then multiplying the number of moles of cladribine by its molecular weight and multiplying the number of moles of the selected cyclodextrin by its molecular weight, one can arrive at the ratio of the products as an appropriate optimized weight ratio. A phase solubility study also provides information about the nature of the cladribine-cyclodextrin inclusion complex formed, for example whether the inclusion complex is a 1:1 complex (1 molecule of drug complexed with 1 molecule of cyclodextrin) or a 1:2 complex (1 molecule of drug complexed with 2 molecules of cyclodextrin).

In accordance with the present invention, one can start using either the selected amorphous cyclodextrin, such as hydroxypropyl- β -cyclodextrin (HP β CD) or hydroxypropyl- γ -cyclodextrin, or cladribine as the fixed variable to which an excess of the other is added to identify various solubility data points (indicating saturated cladribine-cyclodextrin complexes) and draw the resultant line. Typically, cladribine is added to an aqueous solution having a known concentration of amorphous cyclodextrin under conditions empirically found to promote complex formation. Generally, the complexation is conducted with heating, for example at 45 to 60°C for a significant period of time, *e.g.* at least 6-9 hours; it is believed that even better results can be obtained by heating at up to about 80°C for up to 24 hours. Excess precipitated cladribine is then removed and the cladribine concentration is subsequently measured. This concentration represents the amount of cladribine solubilized for a given amorphous cyclodextrin concentration. This process is repeated for a different known concentration of cyclodextrin until several data points are obtained. Each data point represents the concentration of the cladribine dissolved in a known concentration of the selected

amorphous cyclodextrin. The data points are then plotted to show the concentration of cladribine against the various cyclodextrin concentrations used. The graph is a phase solubility diagram which can be used to determine the amount of cladribine for any specific concentration of cyclodextrin used to form the solution under a given set of complexation conditions. It will be appreciated that the aqueous solubility of cladribine is about 5 mg/ml at room temperature and would be higher at elevated temperature. Consequently, the data points correspond to the amount of cladribine dissolved in aqueous HP β CD or other amorphous cyclodextrin under the selected conditions; when later lyophilized, the solution yields a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture 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. If equilibrium conditions are reached during the complexation, the amorphous cladribine-cyclodextrin complex will be saturated with cladribine.

One of skill in the art will appreciate that concentrations at which saturated complexes of cladribine with amorphous cyclodextrins are formed (and thus HTA ratios as well) may be identified by a variety of alternative methodologies. Accordingly, any method known in the field suitable to identify these concentrations is within the scope of the invention.

Using intrinsically amorphous cyclodextrins, for example hydroxypropyl- β -cyclodextrin, hydroxypropyl- γ -cyclodextrin, randomly methylated cyclodextrins, and the like, with cladribine, which is a somewhat water soluble compound (capable of H-bonding through its free hydroxy and amino groups), the cladribine provides increased solubility in solutions of these cyclodextrins. Not only is there increased water solubility but also H-bonded association of the cladribine with the cyclodextrin, separately from the actually inclusion complexed material. Consequently, it is possible to maximize the cladribine in solid

amorphous mixtures, by forcing additional cladribine into solution (using more dilute solutions of cyclodextrin, higher temperatures and longer complexation times, as indicated above). When the solution is cooled off, the extensively amorphous nature of these cyclodextrins does not allow crystallization of an excess amount of cladribine beyond that which forms an inclusion complex with the cyclodextrin; and upon freeze-drying/lyophilization, one obtains an amorphous mixture of cladribine-cyclodextrin inclusion complex (which is amorphous) and amorphous free cladribine, loosely associated with uncomplexed cyclodextrin (and even with complexed cyclodextrin) by hydrogen-bonding, that is the non-inclusion complex. This is done by maximizing solubilization by elevating the temperature (for example, to about 50° to 80°C), and stirring for many hours (up to 24 hours) before freeze-drying. The apparent optimum weight/weight ratio is about 1:14 of cladribine:cyclodextrin. If too much excess cladribine is added to the complexation medium, then crystallization of some of the cladribine takes place, which would in turn result in some crystalline cladribine in the product; this undesired excess cladribine is not in solution and is not H-bonded to the amorphous cyclodextrin and lowers the weight ratio. Therefore, it is desirable to carefully control the amount of excess cladribine beyond that which will form the inclusion complex to only the amount which will dissolve in the solution. The desired amorphous mixture of amorphous inclusion complex and amorphous free cladribine can be termed a "complex cladribine-cyclodextrin complex," which includes both inclusion and non-inclusion/H-bonded complexes. The inclusion complex is a complex of cladribine inserted into the hydrophobic cavity of the selected amorphous cyclodextrin, while the non-inclusion/H-bonded complex is amorphous free cladribine loosely hydrogen-bonded to the cyclodextrin. In the case of a representative amorphous cyclodextrin, hydroxypropyl- β -cyclodextrin (HP β CD), a cladribine:cyclodextrin weight ratio of from about 1:10 to about 1:16 is appropriate; the ratio is expected to be the same for hydroxypropyl- γ -

cyclodextrin. The material obtained is characterized by rapid dissolution of the cladribine in aqueous media.

5 The above-described method requires amorphous cyclodextrins rather than originally crystalline cyclodextrins which have relatively low water solubilities, such as α -, β - or γ -cyclodextrin, 2,6-dimethyl- β -cyclodextrin and the like, because these cyclodextrins would allow crystallization of cladribine in excess of that forming an inclusion complex and therefore would not afford the desired amorphous mixture. The method also would not be useful if cladribine were highly hydrophobic/lipophilic, because in such a situation the drug would not
10 have intrinsic aqueous solubility/H-bonding capability and could not provide the unique mixture obtained herein. However, in point of fact, cladribine has an aqueous solubility of 5 mg/ml at room temperature, thus a significant amount of the drug will be simply soluble in the water phase especially at higher than room temperature; also, as in the case of HP β CD, for example, some of the cladribine
15 will be associated by hydrogen-bonding to the 2-hydroxypropyl and free glucose-OH groups in the cyclodextrin via the two hydroxy functions found in the deoxyadenosine moiety of the cladribine.

The cyclodextrins within the scope of this invention are amorphous derivatives of the natural cyclodextrins α -, β , and γ -cyclodextrin wherein one or
20 more of the hydroxy groups are substituted, for example, by alkyl, hydroxyalkyl, carboxyalkyl, alkylcarbonyl, carboxyalkoxyalkyl, alkylcarbonyloxyalkyl, alkoxyalkyl or hydroxy-(mono or polyalkoxy)alkyl groups; and wherein each alkyl or alkylene moiety preferably contains up to six carbons. Although commonly referred to as a single entity, an amorphous cyclodextrin is actually a
25 mixture of many different entities, since the substituent groups can be located on various hydroxyls of the basic cyclodextrin structure. This in turn results in the amorphous nature of these cyclodextrins, which is indeed well-known. Substituted amorphous cyclodextrins which can be used in the invention include polyethers,

for example, as described in U.S. Patent No. 3,459,731. Further examples of substituted cyclodextrins include ethers wherein the hydrogen of one or more cyclodextrin hydroxy groups is replaced by C₁₋₆-alkyl, hydroxy-C₁₋₆ alkyl, carboxy-C₁₋₆ alkyl or C₁₋₆ alkyloxycarbonyl-C₁₋₆ alkyl groups or mixed ethers thereof. In particular, such substituted cyclodextrins are ethers wherein the hydrogen of one or more cyclodextrin hydroxy groups is replaced by C₁₋₃ alkyl, hydroxy-C₂₋₄ alkyl or carboxy-C₁₋₂ alkyl or more particularly by methyl, ethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, carboxymethyl or carboxyethyl. The term "C₁₋₆ alkyl" is meant to include straight and branched saturated hydrocarbon radicals, having from 1 to 6 carbon atoms such as methyl, ethyl, 1-methylethyl, 1,1-dimethylethyl, propyl, 2-methylpropyl, butyl, pentyl, hexyl and the like. Other cyclodextrins contemplated for use herein include glucosyl-β-cyclodextrin and maltosyl-β-cyclodextrin. Of particular utility in the present invention are randomly methylated β-cyclodextrin and polyethers such as hydroxypropyl-β-cyclodextrin, hydroxyethyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, and hydroxyethyl-γ-cyclodextrin, as well as sulfobutyl ethers, especially β-cyclodextrin sulfobutyl ether. In addition to simple cyclodextrins, branched cyclodextrins and cyclodextrin polymers may also be used. Other cyclodextrins are described, for example, in *Chemical and Pharmaceutical Bulletin* 28: 1552-1558 (1980); *Yakugyo Jiho* No. 6452 (28 March 1983); *Angew. Chem. Int. Ed. Engl.* 19: 344-362 (1980); U.S. Patent. Nos. 3,459,731 and 4,535,152; European Patent Nos. EP 0 149 197A and EP 0 197 571A; PCT International Patent Publication No. WO90/12035; and UK Patent Publication GB 2,189,245.

References describing cyclodextrins for use in the compositions according to the present invention, and/or which provide a guide for the preparation, purification and analysis of cyclodextrins include the following: *Cyclodextrin Technology* by Jozsef Szejtli, Kluwer Academic Publishers (1988) in the chapter Cyclodextrins in Pharmaceuticals; *Cyclodextrin Chemistry* by M. L. Bender *et.*

al., Springer-Verlag, Berlin (1978); *Advances in Carbohydrate Chemistry*, Vol. 12, Ed. by M. L. Wolfrom, Academic Press, New York in the chapter "The Schardinger Dextrins" by Dexter French, pp. 189-260; *Cyclodextrins and their Inclusion Complexes* by J. Szejtli, Akademiai Kiado, Budapest, Hungary (1982);
5 I. Tabushi, *Acc. Chem. Research*, 1982, 15, pp. 66-72; W. Sanger, *Angewandte Chemie*, 92, p. 343-361 (1981); A. P. Croft *et. al.*, *Tetrahedron*, 39, pp. 1417-1474 (1983); Irie *et. al.*, *Pharmaceutical Research*, 5, pp. 713-716 (1988); Pitha *et. al.*, *Int. J. Pharm.* 29, 73 (1986); U.S. Patent Nos. 4,659,696 and 4,383,992; German Patent Nos. DE 3,118,218 and DE-3,317,064; and European Patent No.
10 EP 0 094 157A. Patents describing hydroxyalkylated derivative of β - and γ -cyclodextrin include Pitha U.S. Patent Nos. 4,596,795 and 4,727,064 and Müller U.S. Patent Nos. 4,764,604, 4,870,060 and 6,407,079.

Amorphous cyclodextrins of particular interest for complexation with cladribine include hydroxyalkyl, *e.g.* hydroxyethyl or hydroxypropyl, derivatives
15 of β - and γ -cyclodextrin, carboxyalkyl, *e.g.* carboxymethyl or carboxyethyl, derivatives of β - or γ -cyclodextrin, β -cyclodextrin sulfobutyl ether and randomly methylated β -cyclodextrin. 2-Hydroxypropyl- β -cyclodextrin (HP β CD), 2-hydroxypropyl- γ -cyclodextrin (HP γ CD), randomly methylated β -cyclodextrin, β -cyclodextrin sulfobutyl ether, carboxymethyl- β -cyclodextrin (CMBCD) and
20 carboxymethyl- γ -cyclodextrin (CM γ CD) are of special interest, especially hydroxypropyl- β -cyclodextrin and hydroxypropyl- γ -cyclodextrin.

Compositions of an amorphous mixture of amorphous free cladribine and an amorphous, preferably saturated, cladribine-cyclodextrin inclusion complex for
25 use in the present invention can be prepared under conditions favoring complex formation in a liquid environment as described and as exemplified herein. The resultant liquid preparations can be subsequently converted to a dry form suitable for administration as a solid oral or transmucosal dosage form.

One of skill will appreciate that a variety of approaches are available in the field to prepare compositions as described herein. One available method exemplified herein includes the steps of mixing the cladribine in an aqueous solution of an amorphous cyclodextrin, separating un-dissolved cladribine (e.g.,
5 by filtering or centrifugation), and lyophilizing or freeze-drying the saturated solution to form a solid amorphous mixture.

Pharmaceutical compositions according to the invention may optionally include one or more excipients or other pharmaceutically inert components. One of the advantages of the invention, however, is that cladribine drug forms as
10 described herein are prepared with the minimal amount of excipients necessary for shaping and producing the particular form, such as a tablet or patch. Excipients may be chosen from those that do not interfere with cladribine, with cyclodextrin or with complex formation.

Dosage forms are optionally formulated in a pharmaceutically acceptable
15 vehicle with any of the well-known pharmaceutically acceptable carriers, diluents, binders, lubricants, disintegrants, scavengers, flavoring agents, coloring agents, and excipients (see *Handbook of Pharmaceutical Excipients*, Marcel Dekker Inc., New York and Basel (1998); Lachman *et al.* Eds., *The Theory and Practice of Industrial Pharmacy*, 3rd Ed., (1986); Lieberman *et al.*, Eds. *Pharmaceutical Dosage Forms*, Marcel Dekker Inc., New York and Basel (1989); and *The Handbook of Pharmaceutical Excipients*, 3rd Ed., American Pharmaceutical Association and Pharmaceutical Press, 2000); see also *Remington's Pharmaceutical Sciences*, 18th Ed., Gennaro, Mack Publishing Co., Easton, PA
20 (1990) and *Remington: The Science and Practice of Pharmacy*, Lippincott, Williams & Wilkins, (1995)). A simple solid oral dosage form consists of the
25 amorphous mixture of amorphous free cladribine and amorphous cladribine-cyclodextrin complex (preferably saturated) as described above, *i.e.* the complex

cladribine-cyclodextrin complex, compressed with a small amount (*e.g.* about 1% by weight) of a suitable binder or lubricant such as magnesium stearate.

In certain instances, oral absorption may be further facilitated by the addition of various excipients and additives to increase solubility or to enhance
5 penetration, such as by the modification of the microenvironment.

The methods and pharmaceutical compositions described herein offer novel therapeutic modalities for the treatment of patients in need of treatment with cladribine. As shown herein, the invention addresses the problems of poor bioavailability traditionally associated with oral cladribine.

10 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 complex, *i.e.* the amorphous mixture of the optimized amorphous saturated
15 cladribine-amorphous cyclodextrin complex with amorphous free cladribine as described above is used (*e.g.*, an amount effective for the treatment of multiple sclerosis, rheumatoid arthritis, or leukemia).

The term "therapeutically effective amount" or "effective amount" is used to denote treatments at dosages effective to achieve the therapeutic result sought.
20 Therapeutically effective dosages described in the literature include those for hairy cell leukemia (0.09 mg/kg/day for 7 days), for multiple sclerosis (from about 0.04 to about 1.0 mg/kg/day (*see* U.S. Patent No. 5,506,214)); for other diseases, *see* also U.S. Patent Nos. 5,106,837 (autohemolytic anemia); 5,310,732 (inflammatory bowel disease); 5,401,724 (rheumatoid arthritis); 5,424,296
25 (malignant astrocytoma); 5,510,336 (histiocytosis); 5,401,724 (chronic myelogenous leukemia); and 6,239,118 (atherosclerosis). 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 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
5 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 one week in the first month, repeated for another
10 week 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 one week per month for a total of six months, followed by eighteen months of no treatment.

15 Furthermore, one of skill will appreciate that the therapeutically effective amount of cladribine administered herein may be lowered or increased by fine tuning and/or by administering cladribine according to the invention with another active ingredient. The invention therefore provides a method to tailor the administration/treatment to the particular exigencies specific to a given mammal.
20 Therapeutically effective amounts may be easily determined, for example, empirically by starting at relatively low amounts and by step-wise increments with concurrent evaluation of beneficial effect.

As used herein, "treating" means reducing, preventing, hindering the development of, controlling, alleviating and/or reversing the symptoms in the
25 individual to which a compound of the invention has been administered, as compared to the symptoms of an individual not being treated according to the invention. A practitioner will appreciate that the complexes, compositions, dosage forms and methods described herein are to be used in concomitance with

continuous clinical evaluations by a skilled practitioner (physician or veterinarian) to determine subsequent therapy. Such evaluation will aid and inform in evaluating whether to increase, reduce or continue a particular treatment dose, and/or to alter the mode of administration.

5 The methods of the present invention are intended for use with any subject/patient that may experience the benefits of the methods of the invention. Thus, in accordance with the invention, the terms "subjects" as well as "patients" include humans as well as non-human subjects, particularly domesticated animals.

10 Any suitable materials and/or methods known to those of skill can be utilized in carrying out the present invention. However, preferred materials and methods are described. Materials, reagents and the like to which reference are made in the following description and examples are obtainable from commercial sources, unless otherwise noted.

15 The following examples are intended to further illustrate certain preferred embodiments of the invention and are not limiting in nature. Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, numerous equivalents to the specific substances and procedures described herein.

EXAMPLES

20

EXAMPLE 1 PHASE SOLUBILITY STUDY

25 A phase solubility study can be carried out as follows. Excess cladribine is added to cyclodextrin solutions of various concentrations of hydroxypropyl- β -cyclodextrin (HP β CD) and allowed to complex as described in EXAMPLE 2 below. The excess, undissolved cladribine is removed by filtration. The amount of cladribine in the complexation solution is measured to obtain a data point. This process is repeated with different known concentrations of HP β CD until several

data points are obtained. These data points are then plotted graphically, each data point representing the amount of cladribine that can be dissolved in water with a specific concentration of cyclodextrin. Points on the line generated by the data points represent ratios for the product. One of skill in the art will realize the same results will be generated if excess cyclodextrin is added to cladribine solutions of known concentration.

The molar concentrations of cladribine to cyclodextrin obtained are plotted and presented graphically. A representative phase solubility diagram is shown in the Figure. The plotted lines for cladribine-HP β CD represent cladribine solubilization for the conditions tested, that is, the ratio of the concentration of cladribine to the concentration of cyclodextrin. The area above each of the plotted lines represents conditions where excess insoluble cladribine is present. The area below each of the plotted lines represents the conditions where cyclodextrin is in excess.

The plot for cladribine-HP β CD shown in the Figure is approximately linear; this is indicative of a 1:1 complex, in which one molecule of the drug is complexed with one molecule of cyclodextrin. The Figure also shows that additional cyclodextrin is needed to maintain the cladribine in the complex. For example, about 0.14 mole of HP β CD is needed to maintain about 0.049 mole of cladribine dissolved under the selected conditions, which will ultimately provide the amorphous mixture of the amorphous, preferably saturated, cladribine-HP β CD inclusion complex and amorphous free cladribine (as a non-inclusion complex). Under the conditions of EXAMPLE 2 below, a significant portion of the cladribine in the product can be expected to be not in the inclusion complex but rather in amorphous form loosely held in intimate admixture therewith by hydrogen bonding as a non-inclusion complex.

EXAMPLE 2

PREPARATION OF CLADRIBINE-CYCLODEXTRIN COMPLEX
FOR HUMAN TRIALS

Cladribine is complexed with HP β CD by the following method.

5 In 825 mL of distilled water, 172.5 mg of hydroxypropyl- β -cyclodextrin are dissolved (forming an approximately 17% solution), then cladribine is added and the mixture is stirred at about 48°C for about nine hours. Stirring is continued for an additional 7 hours at room temperature. Any undissolved cladribine is removed by filtration and the solution is cooled to room temperature.
10 To form the amorphous mixture of amorphous cladribine-cyclodextrin complex and amorphous free cladribine, the aqueous cladribine-cyclodextrin solution is dried by lyophilization prior to incorporation into solid oral tablets. The lyophilization procedure consists of rapidly bringing the complexation solution to -45°C for approximately 200 minutes, followed by lyophilization at -25°C for
15 approximately 80-90 hours.

Two batches of cladribine/cyclodextrin product made by the foregoing general procedure were calculated to have the following characteristics:

TABLE I

Lot No.	Cladribine:HP β CD w/w	Cladribine:HP β CD Weight Ratio
20 FD04	12.00g:172.50g	1:14.38
FD05	15.91g:172.50g	1:10.84

The products are amorphous mixtures of amorphous cladribine-HP β CD inclusion complex and amorphous free cladribine hydrogen-bonded to the cyclodextrin as a non-inclusion complex.

25 Generally speaking, amorphous mixtures within the scope of the present invention have cladribine:HP β CD weight ratios of from about 1:10 to 1:16.

EXAMPLE 3

PREPARATION OF ORAL TABLETS

Tablets were manufactured using batches of amorphous mixtures FD04 and FD05 described in EXAMPLE 2 for use in a clinical study.

5 Batch N0120 was manufactured using cladribine-2-HP β CD complex mixture FD05 to a batch size of 3,000 tablets and batch N0126 was manufactured using cladribine-HP β CD complex mixture FD04, to a batch size of 800 tablets. The master formulations for the two batches are shown in TABLE II. Batch N0120 represented 3.0 mg tablets and Batch N0126 represented 10 mg tablets for
10 clinical study.

TABLE II

Constituent	Lot Number	mg/tablet	mg/tablet
		3.0 mg Batch N0120	10.0 mg Batch N0126
Cladribine-HP β CD complex mix	FD05	30.60*	
Cladribine-HP β CD complex mix	FD04		153.75**
15 Sorbitol powder NF	1007403	68.4	44.25
Magnesium stearate NF	1006280	1.00	2.00
Total		100.00	200.00

*Equivalent to 3.0 mg cladribine per tablet.

**Equivalent to 10.0 mg cladribine per tablet.

20 The following table sets forth the method of manufacture of the Batch N0120 and N0126 tablets.

TABLE III

5	1. Pre-mix the magnesium stearate with an approximately equal quantity of sorbitol powder.
	2. Pass the cladribine-HP β CD complex and the remainder of the sorbitol powder into a one-liter glass jar via a 40-mesh screen.
	3. Blend the contents for 10 minutes at 12 rpm.
	4. Pass the magnesium stearate/sorbitol powder pre-mix into the glass jar via the 40-mesh screen.
	5. Blend the final mixture for 5 minutes at 12 rpm.
10	6. Compress into 3.0 mg and 10.0 mg tablets at a target compression weight of 100 mg and 200 mg, respectively.

The Batch N0120 3.0 mg and N0126 10.0 mg tablets were used in the clinical study summarized in EXAMPLE 4 below.

EXAMPLE 4
CLINICAL STUDY

15

The objective of this study was to assess the systemic availability of cladribine after oral administration in two different fixed oral doses, in comparison with one fixed intravenous administration (reference formulation) in patients with MS (multiple sclerosis), and to evaluate the safety and tolerability of cladribine in this population.

20

This study was a 3 center, open-label, randomized, 3-way crossover single dose study using twenty-six patients with MS. Patients received randomly two different fixed oral doses (3.0 mg and 10.0 mg) and a fixed intravenous dose of 3.0 mg (administered as a 1 hour infusion). The three treatment days were separated by a drug-free interval of at least 5 days. In each treatment period blood samples were collected over a 24-hour period for evaluation of plasma cladribine.

25

The plasma concentrations of cladribine were measured by a HPLC/MS/MS method. Using this method the relationship between

concentrations versus peak area ratios was found to be linear within the range of 100 pg/ml to 50000 pg/ml for cladribine. The limit of quantification was 100 pg/ml. Analysis of samples was carried out in 16 runs. Except the first run (which had to be rejected because of equipment failure), all other runs could be
5 accepted. No calibrator had to be excluded from fitting of the calibration curve and accuracy of each quality control sample met the GLP requirements.

858 clinical plasma samples were analyzed and concentration values of cladribine were determined. The results were compiled and are summarized in the tables below [TABLES IV through VII]. In these tables, the following definitions
10 are applicable: T_{\max} is the time to reach maximum concentration in the plasma; $T_{1/2}$ is the half-life of cladribine in the plasma; C_{\max} is the maximum concentration of cladribine in the plasma; AUC_{inf} is the area under the curve for the measured data from zero extrapolated to infinity; AUC_t is the area under the curve for the measured data (from zero to the last time point); Geom Mean is the geometric
15 mean; CV is the coefficient of variation (relative standard deviation); LL is the lower limit; UL is the upper limit; σ^2 is the mean variance; σ_B^2 is the mean variance between subjects; σ_W^2 is the mean variance within subjects; CV_T is the total coefficient of variation; and CV_W is the coefficient of variation within subjects.

TABLE IV

Summary Statistics for Pharmacokinetic Parameters for Cladribine Study Obtained via Non-Compartmental Analyses (n=26)

Pharmacokinetic Parameter	3.0 mg IV infusion			Oral Administration					
				3.0 mg			10.0 mg		
	Geom Mean	Mean \pm SD	CV** (%)	Geom Mean	Mean \pm SD	CV** (%)	Geom Mean	Mean \pm SD	CV** (%)
T _{max} (hr)	N/A	.817 \pm .397	48.6	N/A	.548 \pm .300	54.8	N/A	.558 \pm .204	36.5
T _{1/2} (hr)	N/A	6.50 \pm 1.27	19.5	N/A	5.85 \pm 1.18	20.2	N/A	5.60 \pm 0.75	13.3
C _{max} (pg/ml)	21425	N/A	27.6	5608	N/A	49.5	21242	N/A	50.5
AUC _{inf} (hr*pg/ml)	58528	N/A	24.0	20159	N/A	35.0	76690	N/A	30.3
AUC _t (hr*pg/ml)	56396	N/A	24.0	19166	N/A	36.9	74532	N/A	30.3

**CV=SD/mean for T_{max} and T_{1/2} and CV% geometric mean for C_{max}, AUC_{inf} and AUC_t.

TABLE V

Ratios of Oral to I.V. Pharmacokinetic Parameters and Corresponding Lower Limit (LL) for the one-sided 95% Confidence Interval for Cladribine Study (n=26)

Pharmacokinetic Parameter	Oral Administration			
	3.0 mg		10.0 mg	
	Ratio*	LL	Ratio*	LL
AUC _{inf}	34.5	31.7	39.1	35.9
AUC _t	34.0	31.2	39.4	36.1

*Ratios (dose normalized) and Corresponding 95% LL obtained via inverse transformation of log-transformed data.

TABLE VI

Ratios and Corresponding two-sided 90% Confidence Intervals for Cladribine Study (n=26)

Pharmacokinetic Parameter	10.0 mg/3.0 mg		
	Ratio*	LL	UL
C _{max}	112.6	95.1	133.3
AUC _{inf}	113.3	104.2	123.3
AUC _t	115.8	106.1	126.5

*Ratios (dose normalized) and Corresponding 90% CI obtained via inverse transformation of log-transformed data.

TABLE VII

Variance components for Cladribine Study (n=26)

Source of variation	C _{max}	AUC _{inf}	AUC _t
Between (σ_B^2)	.0380	.0487	.0492
With (σ_W^2)	.1315	.0330	.0357
TOTAL ($\sigma_B^2 + \sigma_W^2$)	.1695	.0816	.0849
CV _T (%)	43.0	29.2	29.8
CV _W (%)	37.5	18.3	19.1

Where PK parameters are dose-adjusted and $CV = \sqrt{\exp(\sigma^2) - 1}$

The foregoing is considered as illustrative only of the principles of the invention. Further, since numerous modifications and changes will readily occur to those skilled in the art, it is not desired to limit the invention to the exact construction and operation shown and described, and accordingly, all suitable modifications and equivalence thereof may be resorted to, falling within the scope of the invention claimed.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and
5 (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form.
2. The pharmaceutical composition according to Claim 1, wherein the complex is saturated with cladribine.
3. The composition according to Claim 1 or 2, wherein the amorphous
10 cyclodextrin is hydroxypropyl- β -cyclodextrin, hydroxypropyl- γ -cyclodextrin, randomly methylated β -cyclodextrin, carboxymethyl- β -cyclodextrin or sulfobutyl- β -cyclodextrin.
4. The composition according to Claim 1 or 2, wherein the amorphous cyclodextrin is hydroxypropyl- β -cyclodextrin.
- 15 5. The composition according to Claim 1 or 2, wherein the amorphous cyclodextrin is hydroxypropyl- γ -cyclodextrin.
6. The composition according to any one of Claims 1 to 3, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.
- 20 7. The composition according to Claim 6, wherein the amorphous cyclodextrin is hydroxypropyl- β -cyclodextrin.

8. The composition according to Claim 6, wherein the amorphous cyclodextrin is hydroxypropyl- γ -cyclodextrin.

9. The composition according to any one of Claims 1 to 5, wherein the approximate molar ratio of cladribine to amorphous cyclodextrin corresponds to a point located on a phase solubility diagram for saturated complexes of cladribine in varying concentrations of the cyclodextrin.

10. 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 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.

11. The method according to Claim 10, wherein the complex is saturated with cladribine.

12. The method according to Claim 10 or 11, wherein the amorphous cyclodextrin is hydroxypropyl- β -cyclodextrin, hydroxypropyl- γ -cyclodextrin, randomly methylated β -cyclodextrin, carboxymethyl- β -cyclodextrin or sulfobutyl- β -cyclodextrin.

13. The method according to Claim 10 or 11, wherein the amorphous cyclodextrin is hydroxypropyl- β -cyclodextrin.

14. The method according to Claim 10 or 11, wherein the amorphous cyclodextrin is hydroxypropyl- γ -cyclodextrin.

15. The method according to any one of Claims 10 to 12, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about
5 1:16.

16. The method according to Claim 15, wherein the amorphous cyclodextrin is hydroxypropyl- β -cyclodextrin.

17. The method according to Claim 15, wherein the amorphous cyclodextrin is hydroxypropyl- γ -cyclodextrin.

18. The method according to any one of Claims 10 to 14, wherein the approximate molar ratio of cladribine to amorphous cyclodextrin corresponds to a point located on a phase solubility diagram for saturated complexes of cladribine in varying concentrations of the cyclodextrin.
10

19. A method for the treatment of symptoms of a cladribine-responsive condition in a subject suffering from said symptoms comprising orally
15 administering to said subject a pharmaceutical composition comprising a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a
20 non-inclusion complex, formulated into a solid oral dosage form.

20. The method according to Claim 19, wherein the complex is saturated with cladribine.

21. The method according to Claim 19 or 20, wherein the cladribine-responsive condition is selected from the group consisting of multiple sclerosis, rheumatoid arthritis and leukemia.

5 22. The method according to Claim 21, wherein the cladribine-responsive condition is multiple sclerosis.

23. The method according to Claim 19, 20, 21 or 22, wherein the amorphous cyclodextrin is hydroxypropyl- β -cyclodextrin, hydroxypropyl- γ -cyclodextrin, randomly methylated β -cyclodextrin, carboxymethyl- β -cyclodextrin or sulfobutyl- β -cyclodextrin.

10 24. The method according to Claim 19, 20, 21 or 22, wherein the amorphous cyclodextrin is hydroxypropyl- β -cyclodextrin.

25. The method according to Claim 19, 20, 21 or 22, wherein the amorphous cyclodextrin is hydropropyl- γ -cyclodextrin.

15 26. Use of a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, in the formulation of a solid oral dosage form, for administration in the treatment of symptoms of a cladribine-responsive condition.

20 27. Use according to Claim 26, wherein the complex is saturated with cladribine.

28. Use according to Claim 26 or 27, wherein the cladribine-responsive condition is selected from the group consisting of multiple sclerosis, rheumatoid arthritis and leukemia.

5 29. Use according to Claim 28, wherein the cladribine-responsive condition is multiple sclerosis.

30. Use according to Claim 26, 27, 28 or 29, wherein the amorphous cyclodextrin is hydroxypropyl- β -cyclodextrin, hydroxypropyl- γ -cyclodextrin, randomly methylated β -cyclodextrin, carboxymethyl- β -cyclodextrin or sulfobutyl- β -cyclodextrin.

10 31. Use according to any one of Claims 26 to 29, wherein the amorphous cyclodextrin is hydroxypropyl- β -cyclodextrin.

32. Use according to any one of Claims 26 to 29, wherein the amorphous cyclodextrin is hydroxypropyl- γ -cyclodextrin.

15 33. Use of a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture 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, in the formulation of a solid oral dosage form, for enhancing the oral or transmucosal bioavailability of cladribine.

20 34. Use according to Claim 33, wherein the complex is saturated with cladribine.

35. Use according to Claim 33 or 34, wherein the amorphous cyclodextrin is hydroxypropyl- β -cyclodextrin, hydroxypropyl- γ -cyclodextrin, randomly methylated β -cyclodextrin, carboxymethyl- β -cyclodextrin or sulfobutyl- β -cyclodextrin.

5 36. Use according to Claim 33 or 34, wherein the amorphous cyclodextrin is hydroxypropyl- β -cyclodextrin.

37. Use according to Claim 33 or 34, wherein the amorphous cyclodextrin is hydroxypropyl- γ -cyclodextrin.

10 38. A complex cladribine-cyclodextrin complex which is an intimate amorphous admixture 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.

39. The complex according to Claim 38, saturated with cladribine.

15 40. The complex according to Claim 38 or 39, wherein the amorphous cyclodextrin is hydroxypropyl- β -cyclodextrin, hydroxypropyl- γ -cyclodextrin, randomly methylated β -cyclodextrin, carboxymethyl- β -cyclodextrin or sulfobutyl- β -cyclodextrin.

41. The complex according to Claim 38 or 39, wherein the amorphous cyclodextrin is hydroxypropyl- β -cyclodextrin.

20 42. The complex according to Claim 38 or 39, wherein the amorphous cyclodextrin is hydroxypropyl- γ -cyclodextrin.

43. The complex according to any one of Claims 38 to 40, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.

5 44. The complex according to Claim 43, wherein the amorphous cyclodextrin is hydroxypropyl- β -cyclodextrin.

45. The complex according to Claim 43, wherein the amorphous cyclodextrin is hydroxypropyl- γ -cyclodextrin.

ABSTRACT OF THE DISCLOSURE

Provided are compositions of cladribine and cyclodextrin which are especially suited for the oral administration of cladribine.

