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**(54) Title:** PHARMACEUTICAL PREPARATIONS OF CRYSTALLINE LAZABEMIDE

**(57) Abstract:** Pharmaceutical compositions of lazabemide HCl crystalline Form A are disclosed along with methods of their production.

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# PHARMACEUTICAL PREPARATIONS OF CRYSTALLINE LAZABEMIDE

## FIELD

[0001] The present invention relates to crystalline forms of lazabemide HCl and, more particularly, to processes for preparing crystalline forms of lazabemide HCl (N-(2-aminoethyl)-5-chloro-2-pyridinecarboxamide hydrochloride) and to pharmaceutical preparations thereof.

## INTRODUCTION

[0002] Crystalline forms of pharmaceutically active compounds are generally more stable than amorphous forms of the same compounds and as such the crystalline forms as well as the more stable of multiple crystalline forms or polymorphs are generally more suitable as drug candidates (*see* Gardner et al., *Nature Rev. Drug Disc. 3*: 926-934, 2004). Lazabemide HCl has been shown to be a monoamine oxidase inhibitor useful in the treatment of diseases such as Alzheimer's disease and Parkinson's disease (U.S. Patents Nos. 4,764,522 and 5,534,635; Cesura et al., *Adv. Neurol. 80*:521-528, 1999; LeWitt, *Neurology 63*:S23-S31, 2004). Pyridine-2-carboxamide compounds including lazabemide HCl and their synthesis have been described (U.S. Patents Nos. 4,764,522 and 5,534,635). Further, two crystalline forms of lazabemide HCl, Form A and Form B, have been identified (Suzuki et al., *Iyakuhin Kenkyu 25*:690-703, 1994). Nevertheless, pharmaceutical preparations of substantially pure crystalline form and methods for their preparation have not been reported.

## SUMMARY

[0003] Accordingly, the present invention is directed to pharmaceutical preparations of substantially pure crystalline forms of lazabemide HCl and to methods for the production of the pharmaceutical preparations. Further, the present invention provides new methods for the preparation crystalline forms of lazabemide HCl.

[0004] Thus, in various embodiments, the present invention includes pharmaceutical compositions of lazabemide HCl. The compositions can comprise lazabemide HCl, substantially all of which is in crystalline Form A; and one or more pharmaceutically acceptable excipients. In various aspects of the compositions, the lazabemide HCl has been selected as a component of the composition on the basis of substantially all of the lazabemide HCl being in crystalline Form A.

**[0005]** The present invention also includes methods of preparing a pharmaceutical composition. The methods can comprise combining lazabemide HCl substantially all of which is in crystalline Form A and one or more pharmaceutically acceptable excipients. In various embodiments, the methods can comprise selecting a composition of lazabemide HCl on the basis of the composition being substantially crystalline Form A of lazabemide and combining the composition with one or more pharmaceutically acceptable excipients. In various other embodiments the method can comprise (a) providing an amount of lazabemide HCl; (b) determining the crystalline form of the lazabemide HCl; and combining the lazabemide HCl with one or more pharmaceutically acceptable excipients if the crystalline form of the lazabemide HCl is substantially all Form A.

**[0006]** In various embodiments, the lazabemide HCl can be at least 99% w/w in crystalline form A, the composition can be formulated for oral administration such as in the form of a tablet and the one or more pharmaceutically acceptable excipients can be lactose.

## FIGURES

**[0007]** Figure 1 illustrates the infrared spectrum of polymorphic Form A produced by the process described below in Example 2.

**[0008]** Figure 2 illustrates the differential scanning calorimetry of polymorphic Form A produced by the process described below in Example 2.

**[0009]** Figure 3 illustrates the X-ray powder diffraction spectrum of polymorphic Form A produced by the process described below in Example 2.

## DETAILED DESCRIPTION

**[0010]** The present invention relates to pharmaceutical compositions of lazabemide HCl crystalline Form A and to processes for their preparation in which the lazabemide HCl in the composition is substantially all in the form of crystalline Form A.

**[0011]** Reference to “substantially all” of the lazabemide HCl being in crystalline Form A is intended to mean from about 80% to about 100% w/w or any percent therebetween, of the lazabemide HCl is in crystalline Form A, including at least about 80% w/w, at least about 85% w/w, at least about 90% w/w, at least about 95% w/w, at least 99% w/w or at least about 99.5% w/w.

**[0012]** Reference to percent "w/w" or "by weight" or "on a weight bases" is intended to represent the percent of a substance in a composition on the basis of the weight of the substance with respect to the total weight of the composition.

**[0013]** The lazabemide HCl for use in the pharmaceutical compositions of the present invention can be produced by any of a number of processes. In particular, lazabemide HCl can be produced by the process disclosed herein which can be generally characterized as involving the reaction of 2-cyano-5-chloropyridine with 1,2-diaminoethane to produce a 2-(5-chloropyridine-2-yl)-1H-imidazoline intermediate followed by hydrolyzing the 2-(5-chloropyridine-2-yl)-1H-imidazoline to produce lazabemide free base. Thereafter, lazabemide HCl can be formed by reacting the free base with HCl. Lazabemide HCl can be precipitated from the reaction mixture by adding an antisolvent. In embodiments in which the HCl salt is formed in an aqueous methanol solution as described in the examples, the Lazabemide HCl can be precipitated with methyl *tert*-butyl ether (MTBE). Recrystallization of the Lazabemide HCl by dissolving in methanol and precipitating the lazabemide HCl with MTBE produces crystalline Form A of lazabemide HCl in substantial polymorphic purity.

**[0014]** Lazabemide HCl, in crystalline Form A has an inhibitory activity on monoamine oxidase B. As a result, lazabemide is suitable for treatment of various neural conditions such as Parkinson's disease and Alzheimer's disease.

**[0015]** Crystalline Form A of lazabemide HCl can be used to prepare pharmaceutical compositions or pharmaceutical preparation. The pharmaceutical compositions or pharmaceutical preparations can comprise a therapeutically effective amount of lazabemide crystalline Form A and a pharmaceutically acceptable excipient.

**[0016]** The term "excipient" refers to a pharmaceutically acceptable, inactive substance used as a vehicle for a medicament or active ingredient in forming a pharmaceutical composition. Excipients can also aid the process by which a pharmaceutical composition is manufactured. Excipients can include vehicles, carriers, diluents, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors or colors and preservatives.

**[0017]** The pharmaceutical preparations of the crystalline form of lazabemide are in a pharmaceutically acceptable formulation. Such pharmaceutically acceptable formulations can comprise one or more pharmaceutically acceptable excipients and/or other active ingredients. Formulation of the compositions of the present invention can be achieved by various methods known in the art. A general discussion of these methods may be found in, for example, Hoover, John E., Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, PA: 1975) which is incorporated herein by reference. See also, Lachman, L., eds., Pharmaceutical Dosage Forms (Marcel Decker, New York, N.Y., 1980) which is incorporated herein by reference.

**[0018]** The preferred pharmaceutical preparation depends on the route of administration. Any route of administration may be used as long as the lazabemide is available *via* that route. Often suitable routes of administration include, for example, oral, parenteral, inhalation, rectal, nasal, topical (e.g., transdermal and intraocular), intravesical, intrathecal, enteral, pulmonary, intralymphatic, intracavital, vaginal, transurethral, intradermal, aural, intramammary, buccal, orthotopic, intratracheal, intralesional, percutaneous, endoscopical, transmucosal, sublingual, and intestinal administration.

**[0019]** Pharmaceutically acceptable excipients that may be used in conjunction with lazabemide HCl are well known to those of ordinary skill in the art. Excipients can be selected based on a number of factors including, for example, the lazabemide HCl crystalline From A itself; the compound's concentration, stability, and intended bioavailability; the condition being treated; the subject's age, size, and general condition; the route of administration; etc. A general discussion related to carriers may be found in, for example, J.G. Nairn, Remington's Pharmaceutical Science, pp. 1492 1517 (A. Gennaro, ed., Mack Publishing Co., Easton, Pa. (1985), which is incorporated herein by reference.

**[0020]** Solid dosage forms for oral administration include, for example, capsules, tablets, gelcaps, pills, dragees, troches, powders, granules, and lozenges. In such solid dosage forms, the lazabemide HCl can be combined with one or more excipients. If administered *per os*, the lazabemide HCl can be mixed with excipients such as lactose, sucrose, starch powder, corn starch, potato starch, magnesium carbonate, microcrystalline cellulose, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, sodium carbonate, agar, mannitol, sorbitol, sodium saccharin, gelatin, acacia gum, alginic acid, sodium alginate, tragacanth, colloidal silicon dioxide, croscarmellose sodium, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets can contain a controlled release formulation, as can be provided in a dispersion of the compound or salt in hydroxypropylmethyl cellulose. In the case of capsules, tablets, and pills, the dosage forms also can comprise buffering agents, such as sodium citrate, or magnesium or calcium carbonate or bicarbonate. Tablets and pills additionally can, for example, include a coating (e.g., an enteric coating) to delay disintegration and absorption.

**[0021]** The concentration of lazabemide HCl Form A in a solid oral dosage form can be from about 5 and about 50%, from about 8 to about 40 % or from about 10 to about 30% by weight based on the total weight of the composition.

**[0022]** The dosage form is prepared in unit doses of from about 10 mg to about 400 mg, from about 20 mg to about 200 mg and from about 50 mg to about 100 mg of lazabemide HCl Form A. In particular, tablets or capsules can be prepared to contain about 50 mg, about 100 mg, about 200 mg or about 400 mg of lazabemide HCl Form A.

**[0023]** Liquid dosage forms for oral administration include, for example, pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art (e.g., water). Such compositions also can comprise adjuvants, such as wetting, emulsifying, suspending, flavoring (e.g., sweetening), and/or perfuming agents. The concentration of the compound preferably can be from about 0.01 to about 10 mg per ml of the composition. In certain embodiments, the oral compositions can be formulated in solid form for addition of water or other aqueous or non-aqueous liquid prior to use.

**[0024]** Techniques for making oral dosage forms useful in the present invention are generally described in, for example, Modern Pharmaceutics, Chapters 9 and 10 (Banker & Rhodes, Editors (1979)); Lieberman et al., Pharmaceutical Dosage Forms: Tablets (1981); Ansel, Introduction to Pharmaceutical Dosage Forms (2nd Edition (1976)) and R.C. Rowe, "An Expert System for the Formulation of Pharmaceutical Tablets", Manufacturing Intelligence, No. 14, Spring 1993, all of which are incorporated herein in their entireties by reference.

**[0025]** Additional components can be included in the compositions of this invention for various purposes generally known in the pharmaceutical industry. These components tend to impart properties that, for example, enhance retention of lazabemide HCl at the site of administration, protect the stability of the composition, control the pH, facilitate processing of the lazabemide HCl into pharmaceutical formulations, and the like. Specific examples of such components include cryoprotective agents; agents for preventing reprecipitation of the compound or salt surface; active, wetting, or emulsifying agents (e.g., lecithin, polysorbate 80, TWEEN 80, pluronic 60, and polyoxyethylene stearate); preservatives (e.g., ethyl p-hydroxybenzoate); microbial preservatives (e.g., benzyl alcohol, phenol, m cresol, chlorobutanol, sorbic acid, thimerosal, and paraben); agents for adjusting pH or buffering agents (e.g., acids, bases, sodium acetate, sorbitan monolaurate, etc.); agents for adjusting osmolarity (e.g., glycerin); thickeners (e.g., aluminum monostearate, stearic acid, cetyl alcohol, stearyl alcohol, guar gum, methyl cellulose, hydroxypropylcellulose, tristearin, cetyl wax esters, polyethylene glycol, etc.); colorants; dyes; flow aids; non volatile silicones (e.g., cyclomethicone); clays (e.g., bentonites); adhesives; bulking agents; flavorings; sweeteners; adsorbents; fillers (e.g., sugars such as lactose, sucrose, mannitol, sorbitol, cellulose, calcium phosphate, etc.); binders (e.g., gelatin; gum tragacanth; methyl cellulose; hydroxypropyl methylcellulose; sodium carboxymethyl cellulose; polyvinylpyrrolidone; sugars; polymers; acacia; starches, such as maize starch, wheat starch, rice starch, and potato starch; etc.); disintegrating agents (e.g., starches, such as maize starch, wheat starch, rice starch, potato starch, and carboxymethyl starch; cross linked polyvinyl pyrrolidone; agar; alginic acid or a salt thereof, such as sodium alginate; croscarmellose sodium; crospovidone; etc); lubricants (e.g., silica; talc; stearic acid and salts thereof, such as magnesium stearate; polyethylene glycol; etc.); coating agents (e.g., concentrated sugar solutions including gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, titanium dioxide, etc.); and antioxidants (e.g., sodium metabisulfite, sodium bisulfite, sodium sulfite, dextrose, phenols, thiophenols, etc.).

**[0026]** Suppositories for rectal administration can be prepared by, for example, mixing the drug with a suitable nonirritating excipient that is solid at ordinary temperatures, but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, such as cocoa butter; synthetic mono , di , or triglycerides; fatty acids; and/or polyethylene glycols.

**[0027]** Compositions for transdermal administration are also contemplated. In various embodiments, the compositions can comprise a semi-solid formulation base containing solid micronized drug.

**[0028]** It is also contemplated that parenteral compositions such as, for example, compositions for intravenous or subcutaneous administration, can be formulated in a solid form. Such solid dosage forms can be prepared in a container such as a sealed ampoule for addition of a liquid vehicle prior to use. The liquid vehicle can, in certain embodiments, accompany the solid dosage form in a separate container from that of the solid dosage form and together the solid dosage form and the vehicle can comprise a kit for preparation of the final formulation for parenteral administration.

**[0029]** Injectable parenteral preparations (e.g., sterile injectable aqueous or oleaginous suspensions) can be formulated according to the known art using suitable dispersing, wetting agents, and/or suspending agents. Acceptable vehicles for parenteral use include both aqueous and nonaqueous pharmaceutically acceptable solvents

**[0030]** Suitable pharmaceutically acceptable aqueous solvents include, for example, water, saline solutions, dextrose solutions (e.g., such as DW5), electrolyte solutions, etc.

**[0031]** Suitable pharmaceutically-acceptable nonaqueous solvents include, for example, the following (as well as mixtures thereof): alcohols (these include, for example, α-glycerol formal, β-glycerol formal, 1, 3-butyleneglycol, aliphatic or aromatic alcohols having from 2 to about 30 carbons (*e.g.*, methanol, ethanol, propanol, isopropanol, butanol, t-butanol, hexanol, octanol, amylene hydrate, benzyl alcohol, glycerin (glycerol), glycol, hexylene glycol, tetrahydrofurfuranyl alcohol, lauryl alcohol, cetyl alcohol, and stearyl alcohol), fatty acid esters of fatty alcohols (*e.g.*, polyalkylene glycols, such as polypropylene glycol and polyethylene glycol), sorbitan, sucrose, and cholesterol); amides (these include, for example, dimethylacetamide (DMA), benzyl benzoate DMA, dimethylformamide, N-(β-hydroxyethyl)-lactamide, N,N-dimethylacetamide-amides, 2-pyrrolidinone, 1-methyl-2-pyrrolidinone, and polyvinylpyrrolidone); esters (these include, for example, acetate esters (*e.g.*, monoacetin, diacetin, and triacetin), aliphatic and aromatic esters (*e.g.*, ethyl caprylate or octanoate, alkyl oleate, benzyl benzoate, or benzyl acetate), dimethylsulfoxide (DMSO), esters of glycerin (*e.g.*, mono, di, and tri-glyceryl citrates and tartrates), ethyl benzoate, ethyl acetate, ethyl carbonate, ethyl lactate, ethyl oleate, fatty acid esters of sorbitan, glyceryl monostearate, glyceride esters (*e.g.*, mono, di, or tri-glycerides), fatty acid esters (*e.g.*, isopropyl myristrate), fatty acid derived PEG esters (*e.g.*, PEG-hydroxyoleate and PEG-hydroxystearate), N-methyl pyrrolidinone, pluronic 60, polyoxyethylene sorbitol oleic polyesters (*e.g.*, poly(ethoxylated)$_{30\text{-}60}$ sorbitol poly(oleate)$_{2\text{-}4}$, poly(oxyethylene)$_{15\text{-}20}$ monooleate, poly(oxyethylene)$_{15\text{-}20}$ mono 12-hydroxystearate, and poly(oxyethylene)$_{15\text{-}20}$ mono ricinoleate), polyoxyethylene sorbitan esters (*e.g.*, polyoxyethylene-sorbitan monooleate, polyoxyethylene-sorbitan monopalmitate, polyoxyethylene-sorbitan monolaurate, polyoxyethylene-sorbitan monostearate, and POLYSORBATE 20, 40, 60, and 80 (from ICI Americas, Wilmington, DE)), polyvinylpyrrolidone, alkyleneoxy modified fatty acid esters (*e.g.*, polyoxyl 40 hydrogenated castor oil and polyoxyethylated castor oils, such as CREMOPHOR EL solution or CREMOPHOR RH 40 solution), saccharide fatty acid esters (*i.e.*, the condensation product of a monosaccharide (*e.g.*, pentoses, such as, ribose, ribulose, arabinose, xylose, lyxose, and xylulose; hexoses, such as glucose, fructose, galactose, mannose, and sorbose; trioses; tetroses; heptoses; and octoses), disaccharide (*e.g.*, sucrose, maltose, lactose, and trehalose), oligosaccharide, or a mixture thereof with one or more $C_4$-$C_{22}$ fatty acids (*e.g.*, saturated fatty acids, such as caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, and stearic acid; and unsaturated fatty acids, such as palmitoleic acid, oleic acid, elaidic acid, erucic acid, and linoleic acid), and steroidal esters); ethers (these are typically alkyl, aryl, and cyclic ethers having from 2 to about 30 carbons. Examples include diethyl ether, tetrahydrofuran, dimethyl isosorbide, diethylene glycol monoethyl ether), and glycofurol (tetrahydrofurfuranyl alcohol polyethylene glycol ether); ketones (these typically have from about 3 to about 30 carbons. Examples include acetone, methyl ethyl ketone, methyl isobutyl ketone); hydrocarbons (these are typically aliphatic, cycloaliphatic, and aromatic hydrocarbons having from about 4 to about 30 carbons. Examples include benzene, cyclohexane, dichloromethane, dioxolanes, hexane, n-decane, n-dodecane, n-hexane, sulfolane, tetramethylenesulfon, tetramethylenesulfoxide, toluene, dimethylsulfoxide (DMSO), and tetramethylenesulfoxide); oils (these include oils of mineral, vegetable, animal, essential, or synthetic origin. These include mineral oils, such as aliphatic and wax-based hydrocarbons, aromatic hydrocarbons, mixed aliphatic and aromatic based hydrocarbons, and refined paraffin oil; vegetable oils, such as linseed, tung, safflower, soybean, castor, cottonseed, groundnut, rapeseed, coconut, palm, olive, corn, corn germ, sesame, persic, and peanut oil; glycerides, such as mono-, di-, and triglycerides; animal oils, such as fish, marine, sperm, cod-liver, haliver, squalene, squalane, and shark liver oil; oleic oils; and polyoxyethylated castor oil); alkyl, alkenyl, or aryl halides (these include alkyl or aryl halides having from 1 to about 30 carbons and one or more halogen substituent. Examples include methylene chloride); monoethanolamine; petroleum benzin; trolamine; omega-3 polyunsaturated fatty acids (*e.g.*, alpha-linolenic acid, eicosapentaenoic acid, docosapentaenoic acid, or docosahexaenoic acid); polyglycol ester of 12-hydroxystearic acid and polyethylene glycol (SOLUTOL HS-15, from BASF, Ludwigshafen, Germany); polyoxyethylene glycerol; sodium laurate; sodium oleate; and sorbitan monooleate. Other pharmaceutically acceptable solvents for use in the invention are well known to those of ordinary skill in the art. General discussion relating to such solvents may be found in, for example, *The Chemotherapy Source Book* (Williams & Wilkens Publishing), *The Handbook of Pharmaceutical Excipients*, (American Pharmaceutical Association, Washington, D.C., and The Pharmaceutical Society of Great Britain, London, England, 1968), *Modern Pharmaceutics 3d ed.*, (G. Banker *et al.*, eds., Marcel Dekker, Inc., New York, New York (1995)), *The Pharmacological Basis of Therapeutics*, (Goodman & Gilman, McGraw Hill Publishing), *Pharmaceutical Dosage Forms*, (H. Lieberman *et al.*, eds., Marcel Dekker, Inc., New York, New York (1980)), *Remington's Pharmaceutical Sciences, 19th ed.*, (A. Gennaro, ed., Mack Publishing, Easton, PA, (1995)), *The United States Pharmacopeia 24, The National Formulary 19*, (National Publishing, Philadelphia, PA (2000)); Spiegel, A.J., *et al.*, "Use of Nonaqueous Solvents in Parenteral Products," *J. Pharma. Sciences*, Vol. 52, No. 10, pp. 917-927 (1963).

**[0032]** Preferred solvents include those known to stabilize the compound(s) or salt(s) of interest. These typically include, for example, oils rich in triglycerides, such as safflower oil, soybean oil, and mixtures thereof; and alkyleneoxy modified fatty acid esters, such as polyoxyl 40 hydrogenated castor oil and polyoxyethylated castor oils (e.g., CREMOPHOR EL solution or CREMOPHOR RH 40 solution). Commercially available triglycerides include INTRALIPID emulsified soybean oil (Kabi Pharmacia Inc., Stockholm, Sweden), NUTRALIPID emulsion (McGaw, Irvine, California), LIPOSYN II 20% emulsion (a 20% fat emulsion solution containing 100 mg safflower oil, 100 mg soybean oil, 12 mg egg phosphatides, and 25 mg glycerin per ml of solution; Abbott Laboratories, Chicago, IL), LIPOSYN III 2% emulsion (a 2% fat emulsion solution containing 100 mg safflower oil, 100 mg soybean oil, 12 mg egg phosphatides, and 25 mg glycerin per ml of solution; Abbott Laboratories, Chicago, IL), natural or synthetic glycerol derivatives containing the docosahexaenoyl group at levels of from about 25 to about 100% (by weight based on the total fatty acid content) (DHASCO from Martek Biosciences Corp., Columbia, MD; DHA MAGURO from Daito Enterprises, Los Angeles, CA; SOYACAL; and TRAVEMULSION. Ethanol is an often preferred solvent for dissolving the compound or salt to form solutions, emulsions, and the like.

**[0033]** Other excipients and modes of administration well known in the pharmaceutical art can also be used.

**[0034]** The pharmaceutical compositions of the present invention can be used to treat various diseases and conditions including Alzheimer's disease, Parkinson's disease and smoking cessation.

**[0035]** It is also contemplated that the pharmaceutical formulations of the present invention can contain at least one additional active pharmaceutical agent. Such additional active agents can be selected based upon combined actions of the lazabemide HCl and the additional agents and/or based upon the disease intended for treatment.

**[0036]** In various embodiments the pharmaceutical composition of the present invention can comprise (a) lazabemide HCl, substantially all of which is in crystalline Form A; (b) one or more pharmaceutically acceptable excipients and (c) at least one additional active pharmaceutical agent. The additional agent can be a cholinesterase inhibitor such as donepezil hydrochloride (ARICEPT®), rivastigmine (EXELON®) or galantamine (RAZADYNE®), an N-methyl-D-aspartate (NMDA) receptor antagonist such as, for example, memantine (NAMENDA®) or remacemide hydrochloride a dopamine receptor agonist such as, for example ropinirole hydrochloride or levadopa or another active pharmaceutical agent.

## EXAMPLES

**[0037]** It is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following specific examples are offered by way of illustration and not by way of limiting the remaining disclosure.

### Example 1

**[0038]** This example illustrates the preparation of lazabemide HCl crystalline form A.

### A. Preparation of 2-(5-chloropyridine-2-yl)-1-H-imidazoline.

**[0039]** A reactor equipped with external cooler was charged under nitrogen flow with 1800 grams (12.99 moles) of 5-chloro-2-cyanopyridine, 46.8 grams (0.2 moles) of *p*-toluenesulfonic acid monohydrate and 6600 grams of toluene. The mixture was heated to 95°-100°C. Over a period of 2-3 hours, 858.2 grams (14.28 moles) of ethylenediamine were added. Formation and evolution of ammonia occurred during the addition which was controlled by the addition rate. The mixture was maintained at 95-100°C for 2 hours and then heated to reflux at 110-114°C for 4 hours. Upon completion of the reaction, the mixture was cooled to about 70°C and thereafter maintained at a temperature greater than 55°C. 3600 grams of diethyl acetate and subsequently, 350 grams of demineralized water were added. The mixture was heated to 65 ± 2°C and vigorously stirred for 15-30 minutes. Stirring was stopped and after 15-30 minutes, the lower aqueous layer was discarded. 350 grams of demineralized water was then added and the mixture was heated again to 65 ± 2°C with vigorous stirring for 15-30 minutes. Stirring was stopped and after 15-30 minutes, the lower aqueous layer was again discarded. The mixture was then cooled to 53-55°C and the temperature maintained until a precipitate was formed. The material was then cooled to 0 ± 2°C in about 2 hours. Thereafter, a temperature of 0 ± 2°C was maintained for about 30 minutes and the solids were filtered and washed twice with a mixture of 1440 grams of toluene and 720 grams of ethyl acetate cooled to 0 ± 2°C. About 2400 grams of wet solid were obtained. The product was then vacuum dried at 45°C to constant weight and 2075 grams of 2-(5-chloropyridine-2-yl)-1-H-imidazoline were obtained (88% yield).

### B. Hydrolysis of 2-(5-chloropyridine-2-yl)-1-H-imidazoline to produce lazabemide free base.

**[0040]** A reactor was charged with 6225 grams of demineralized water and 33.2 grams (0.25 moles) of sodium hydroxide. After a few minutes under stirring, 2075 grams (11.43 moles) of 2-(5-chloropyridine-2-yl)-1H-imidazoline were added and the mixture was heated to reflux under vigorous stirring for 4 hours. Upon completion of the reaction, the mixture was cooled to 65 - 70°C and 17.5 grams (0.29 moles) of acetic acid were added. Water was vacuum distilled until internal temperature reached 70 - 80°C. The reactor was then vented with nitrogen and 3458 grams of ethanol denatured with cyclohexane/methanol (hereinafter referenced as denatured ethanol) were added. The distillation was then repeated until an internal temperature of 70 - 80°C was again reached. The temperature was then maintained for an additional 30 minutes. 3458 grams of denatured ethanol were then added and the distillation was repeated until an internal temperature of 70 - 80°C was again reached. This temperature was maintained for an additional 30 minutes and, then the reactor was vented with nitrogen.

[0041] The reactor was then charged with 6225 grams of denatured ethanol and the mixture was heated and refluxed for 30 minutes. The mixture was then cooled to 20 - 25°C and 20.7 grams of charcoal were added. The mixture was stirred and maintained at 20 - 25°C for 30 minutes. The solution containing the lazabemide free base was then filtered through a cake formed by 48.5 grams of celite. The reactor and cake were washed with 1038 grams of denatured ethanol and the filtered solutions combined.

### C. Reaction with HCl to produce lazabemide HCl crystalline Form A.

[0042] The combined filtered solutions were assayed using HPLC/MS (Agilent Technologies, Palo Alto CA) with ESI source (positive mode) ion trap analyzer (ID R-HMS-01); column: polarity dC18, 5 µm, 4.6 x 150 mm; mobile phase A: water + 0.05% trifluoroacetic acid; and mobile phase B: acetonitrile + 0.05% trifluoroacetic acid. The combined solutions were determined to contain 2167 grams (10.86 moles) of lazabemide free base and this was added to a reactor. 6225 grams of denatured ethanol were added and the mixture was heated to about 40 ± 2°C. 1087 grams (10.74 moles) of 36.1% hydrochloric acid was added and the line washed with 1153 grams of denatured anhydrous ethanol. The mixture was then heated to 52 - 55°C and maintained within that temperature range until a solution was obtained. The mixture was then cooled to 47 ± 2°C, optionally seeded with crystals of Form A and maintained within that temperature range until a precipitate formed and 30 minutes thereafter. The mixture was then cooled to 0 ± 2°C in 2 hours and maintained at 0 ± 2°C for at least 30 minutes. The product was then filtered and washed twice with a total of 4150 grams of denatured ethanol cooled to 0°C. About 3140g of wet product were obtained and this was dried under vacuum at 50 - 60°C for 15 hours. 2160 grams of dry lazabemide HCl hydrochloride crystalline Form A was obtained (80% yield calculated based upon imidazoline).

## Example 2

**[0043]** This example illustrates an alternative method for the production of crystalline Form A of lazabemide HCl.

**[0044]** Lazabemide free base can be produced by processes performed as described below. Hydrolysis of 2-(5-chloropyridine-2-yl)-1H-imidazoline was carried in water (7.5g per g of substrate) with a catalytic amount of sodium hydroxide (0.04 moles per mole of substrate). The reaction mixture was heated to reflux for two hours, cooled to room temperature and, after addition of sodium chloride aqueous saturated solution, the product was extracted with dichloromethane. The organic phase was dehydrated with sodium sulphate and then vacuum distilled. A waxy solid was obtained, having 99% assay with a yield of about 96%.

**[0045]** Alternatively, the reaction can be performed as follows using 3 g of water per g substrate and 0.02 moles sodium hydroxide per g substrate and vacuum distillation which is possible because lazabemide free base is liquid at temperatures higher than 35°C. At the end of the reaction, sodium hydroxide was neutralized with an equimolar quantity of hydrochloric acid or acetic acid. Thereafter, the aqueous phase was distilled under reduced pressure. An azeotrope-forming solvent was added and the mixture was vacuum distilled again. Ethanol solvent was added to the crude solid, inorganic salts were filtered off and crude lazabemide HCl free base was recovered. Yield was 89% based upon lazabemide free base.

**[0046]** A four-necked jacketed 3.5 liter reactor, equipped with condenser and nitrogen inlet, thermometer and mechanical stirrer, was charged with a solution of lazabemide free base (175.3 g, 98.6%, 0.87 mol obtained from alternative process above) in methanol (900 ml). While maintaining the temperature at 20°C, a solution of 37% hydrochloric acid in methanol, 4.48N (195 ml, 0.87 mol) was added over a period of 30 min. After 20 min from the end of the addition precipitation occurred. The temperature was then raised to 50°C to effect complete dissolution. While maintaining the temperature at 50-55°C, methyl *tert*-butyl ether (1700 ml) was added over a period of about 1.5 hours. The suspension obtained was then cooled to 5°C over a period of 2 hrs, maintained at that temperature for an additional hour and then filtered. The cake was washed with methyl *tert*-butyl ether and the light pink solid thus formed was dried at 45°C, under vacuum to constant weight (181.6 g). Yield was 89% based upon lazabemide free base.

**[0047]** The crude product was dissolved in methanol (890 ml) at 50°C. The solution was then treated for one hour at reflux temperatures with decolorizing charcoal (8.0 g) and then filtered. While maintaining the temperature at 50-55°C, methyl *tert*-butyl ether (1500 ml) was added to the filtrate liquid over a period of one hour. The suspension was then cooled to 2°C over a period of 3 hours and maintained at this temperature overnight. The suspension was then filtered and the cake rinsed with methyl *tert*-butyl ether (600 ml). The white solid was dried at 45-50°C, under vacuum, to constant weight (162.4 g). Recrystallization yield was 79% based upon the free base starting material above and 89.5% based upon lazabemide HCl starting material for the recrystallization step.

**[0048]** This material was then characterized by IR powder spectrum, differential scanning calorimetry, and X-ray powder diffraction as described below.

## Example 3

**[0049]** This example illustrates the characterization of lazabemide HCl crystalline Form A using infrared spectroscopy, differential scanning calorimetry and X-ray powder diffractometry.

**[0050]** Infrared spectroscopy was performed using a ReactIR 4000 system equipped with an DiComp ATR diamond sensor (Mettler-Toledo, Inc., 1900 Polaris Parkway, Columbus, OH, 43240). The infrared spectral analysis performed on powder samples of crystalline Form A from Example 2 above, is shown in Figure 1.

**[0051]** Differential scanning calorimetry was performed using a Q100 differential scanning calorimeter (TA Instruments, Inc., 109 Lukens Drive, New Castle, DE 19720). Tests were performed from 20° to 220°C at 10°C/min in a sealed aluminum crucible. Thermal analysis of crystalline Form A from Example 2 above, is shown in Figure 2. As shown in the figure, the differential scanning calorimetry spectrum of Form A is well defined with an endothermic peak at about 200°C.

**[0052]** The endothermic peak of Form A was further characterized in samples of Form A from different synthetic batches as shown below in Table 1.

Table 1

| Batch No. | Differential Scanning Calorimetry Data | |
|---|---|---|
| | Onset (°C) | Peak (°C) |
| 1 | 190.77 | 193.15 |
| 2 | 186.63 | 194.30 |
| 3 | 189.92 | 191.97 |
| 4 | 193.86 | 197.93 |
| 5 | 192.03 | 196.18 |
| 6 | 192.19 | 195.93 |
| 7 | 197.81 | 200.03 |
| 8 | 197.59 | 199.58 |
| 9 | 197.57 | 199.22 |
| 10 | 198.43 | 199.99 |
| Mean | 193.58 | 196.73 |

**[0053]** X-ray diffraction spectra were obtained using a Brucker D8 Advance with LynxEye Detector (BRUKER AXS Inc., 5465 East Cheryl Parkway, Madison, WI 53711-5373). The spectrum for crystalline Form A of Example 2 above, is shown in Figure 3.

### Example 4

**[0054]** This example illustrates methods that could be used to produce formulations of lazabemide crystalline Form A.

## Formulation 1

[0055] One thousand gelatin capsules containing 100 mg of lazabemide HCl crystalline Form A could be manufactured, for example, as follows:

lazabemide HCl crystalline Form A: 100 g

lactose: 100 g

[0056] The lazabemide HCl crystalline Form A and the lactose (very finely ground) are mixed together well. The resulting powder is sieved and introduced into gelatin capsules in portions of 0.20 g.

## Formulation 2

[0057] One thousand tablets containing 50 mg of lazabemide HCl crystalline Form A could be produced from the following components:

Lazabemide HCl crystalline Form A: 50.0 g

lactose: 200 g

wheat starch: 15 g

polyethylene glycol 6000: 10 g

talc: 10 g

magnesium stearate: 3.6 g

demineralized water: q.s.

[0058] All the solid ingredients are first forced through a sieve of about 0.6 mm mesh width. Then the lazabemide HCl, the lactose, the talc, the magnesium stearate and half the starch are mixed. The other half of the starch is suspended in 80 ml of water and this suspension is added to a boiling solution of the polyethylene glycol in 200 ml of water and the mixture, if necessary with the addition of water, is granulated. The granulate is dried overnight at 35°C, forced through a sieve of 1.2 mm mesh width and compressed to form tablets having a diameter of about 6 mm.

[0059] The detailed description set-forth above is provided to aid those skilled in the art in practicing the present invention. However, the invention described and claimed herein is not to be limited in scope by the specific embodiments herein disclosed because these embodiments are intended as illustration of several aspects of the invention. Any equivalent embodiments are intended to be within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description which do not depart from the spirit or scope of the present inventive discovery. Such modifications are also intended to fall within the scope of the appended claims.

**[0060]** All publications, patents, patent applications, and other references cited in this application are incorporated herein by reference in their entirety for all purposes to the same extent as if each individual publication, patent, patent application or other reference was specifically and individually indicated to be incorporated by reference in its entirety for all purposes. Citation of a reference herein shall not be construed as an admission that such is prior art relevant to the present invention.

## CLAIMS

**WHAT IS CLAIMED IS:**

1. A pharmaceutical composition comprising:

(a) lazabemide HCl, substantially all of which is in crystalline Form A; and

(b) one or more pharmaceutically acceptable excipients.

2. A composition according to claim 1, wherein at least 99% of the lazabemide is in crystalline Form A.

3. A composition according to claim 1 which is formulated for oral, transdermal, intravenous or subcutaneous administration.

4. A composition according to claim 3 which is formulated for oral administration.

5. A composition according to claim 4 which is formulated as a tablet.

6. A composition according to claim 1, wherein the composition comprises from about 20% to about 80% w/w lazabemide HCl crystalline Form A and from about 20% to about 80% w/w lactose.

7. A composition according to claim 1, which further comprises at least one additional active pharmaceutical agent.

8. A composition according to claim 7, wherein the at least one additional active pharmaceutical agent is selected from the group consisting of donepezil hydrochloride, rivastigmine galantamine, memantine, remacemide hydrochloride, ropinirole hydrochloride and levadopa.

9. A composition according to claim 8, wherein the at least one additional active pharmaceutical agent is donepezil hydrochloride.

10. A pharmaceutical composition comprising:

(a) lazabemide HCl which has been selected on the basis of substantially all of the lazabemide HCl being crystalline Form A; and

(b) one or more pharmaceutically acceptable excipients.

11. A composition according to claim 10, wherein at least 99% of the lazabemide is in crystalline Form A.

12. A composition according to claim 10 which is formulated for oral, transdermal, intravenous or subcutaneous administration.

13. A composition according to claim 12 which is formulated for oral administration.

14. A composition according to claim 13 which is formulated as a tablet.

15. A composition according to claim 10, wherein the composition comprises from about 20% to about 80% w/w lazabemide HCl crystalline Form A and from about 20% to about 80% w/w lactose.

16. A composition according to claim 10, which further comprises at least one additional active pharmaceutical agent.

17. A composition according to claim 16, wherein the at least one additional active pharmaceutical agent is selected from the group consisting of donepezil hydrochloride, rivastigmine galantamine, memantine, remacemide hydrochloride, ropinirole hydrochloride and levadopa.

18. A composition according to claim 17, wherein the at least one additional active pharmaceutical agent is donepezil hydrochloride.

19. A method of preparing a pharmaceutical composition, the method comprising combining:

(a) lazabemide HCl substantially all of which is in crystalline Form A and

(b) one or more pharmaceutically acceptable excipients.

20. A method according to claim 19, wherein at least 99% of the lazabemide is in crystalline Form A.

21. A method according to claim 19, wherein the composition is formulated for oral, transdermal, intravenous or subcutaneous administration.

22. A method according to claim 21, wherein the composition is formulated for oral administration.

23. A method according to claim 21, wherein the composition is formulated as a tablet.

24. A method according to claim 19, wherein the composition comprises from about 20% to about 80% w/w lazabemide HCl crystalline Form A and from about 20% to about 80% w/w lactose.

25. A method according to claim 19 further comprising combining with the lazabemide HCl and the one ore more pharmaceutically acceptable excipients, at least one additional active pharmaceutical agent.

26. A method according to claim 25, wherein the at least one additional active pharmaceutical agent is selected from the group consisting of donepezil hydrochloride, rivastigmine galantamine, memantine, remacemide hydrochloride, ropinirole hydrochloride and levadopa.

27. A method according to claim 26, wherein the at least one additional active pharmaceutical agent is donepezil hydrochloride.

28. A method of preparing a pharmaceutical composition, the method comprising:

(a) selecting a composition of lazabemide HCl on the basis of the composition being substantially crystalline Form A of lazabemide and

(b) combining the composition with one or more pharmaceutically acceptable excipients.

29. A method according to claim 28, wherein at least 99% of the lazabemide is in crystalline Form A.

30. A method according to claim 28, wherein the composition is formulated for oral, transdermal, intravenous or subcutaneous administration.

31. A method according to claim 30, wherein the composition is formulated for oral administration.

32. A method according to claim 28, wherein the composition is formulated as a tablet.

33. A method according to claim 28, wherein the composition comprises from about 20% to about 80% w/w lazabemide HCl crystalline Form A and from about 20% to about 80% w/w lactose.

34. A method according to claim 28 further comprising combining with the composition of lazabemide HCl and the one or more pharmaceutically acceptable excipients, at least one additional active pharmaceutical agent.

35. A method according to claim 34, wherein the at least one additional active pharmaceutical agent is selected from the group consisting of donepezil hydrochloride, rivastigmine galantamine, memantine, remacemide hydrochloride, ropinirole hydrochloride and levadopa.

36. A method according to claim 35, wherein the at least one additional active pharmaceutical agent is donepezil hydrochloride.

37. A method of preparing a pharmaceutical composition, the method comprising:

(a) providing lazabemide HCl;

(b) determining crystalline form of the lazabemide HCl; and

(c) combining the lazabemide HCl with one or more pharmaceutically acceptable excipients if the crystalline form of the lazabemide HCl is substantially all Form A.

38. A method according to claim 37, wherein substantially all Form A comprises 99% Form A.

39. A method according to claim 37, wherein the composition is formulated for oral, transdermal, intravenous or subcutaneous administration.

40. A method according to claim 39, wherein the composition is formulated for oral administration.

41. A method according to claim 40, wherein the composition is formulated as a tablet.

42. A method according to claim 37, wherein the composition comprises from about 20% to about 80% w/w lazabemide HCl crystalline Form A and from about 20% to about 80% w/w lactose.

43. A method according to claim 37 further comprising combining with the lazabemide HCl and one or more pharmaceutically acceptable excipients, at least one additional active pharmaceutical agent.

44. A method according to claim 43, wherein the at least one additional active pharmaceutical agent is selected from the group consisting of donepezil hydrochloride, rivastigmine galantamine, memantine, remacemide hydrochloride, ropinirole hydrochloride and levadopa.

45. A method according to claim 44, wherein the at least one additional active pharmaceutical agent is donepezil hydrochloride.

46. A method of treating a subject for Alzheimer's disease, Parkinson's disease or smoking cessation, the method comprising administering to a subject in need thereof, a therapeutically effective amount of a pharmaceutical composition of claims 1-18 or a pharmaceutical composition prepared by a method of claims 19-45.

47. A method according to claim 46 wherein the subject suffers from Alzheimer's disease.

48. A method according to claim 46, wherein the subject suffers from Parkinson's disease.

49. A method according to claim 46, wherein the treatment assists in smoking cessation.

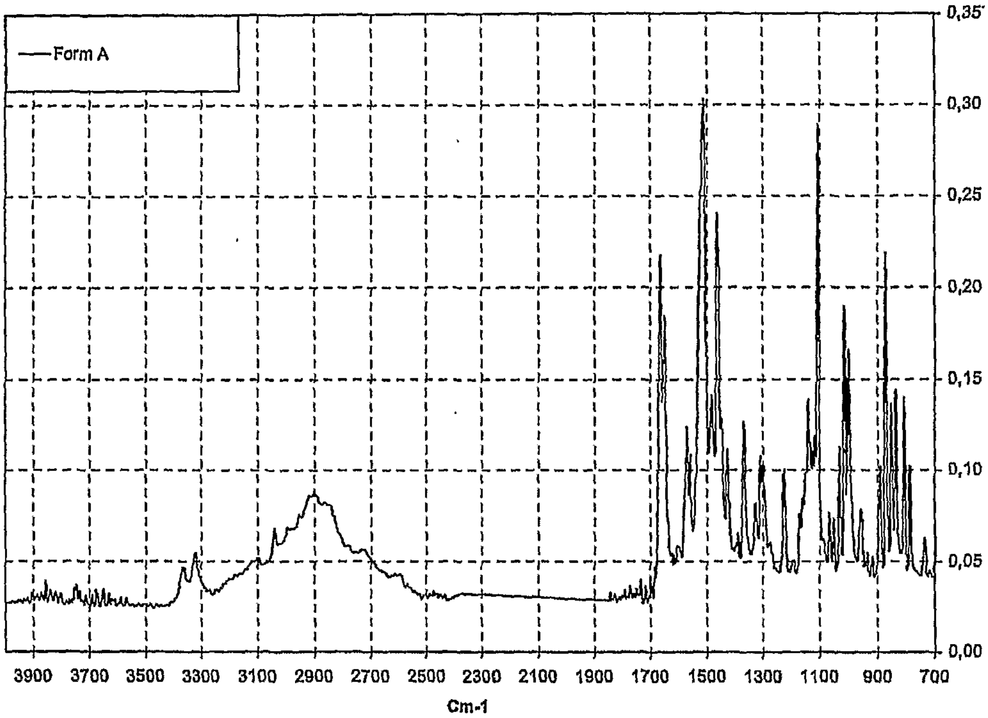

Figure 1.

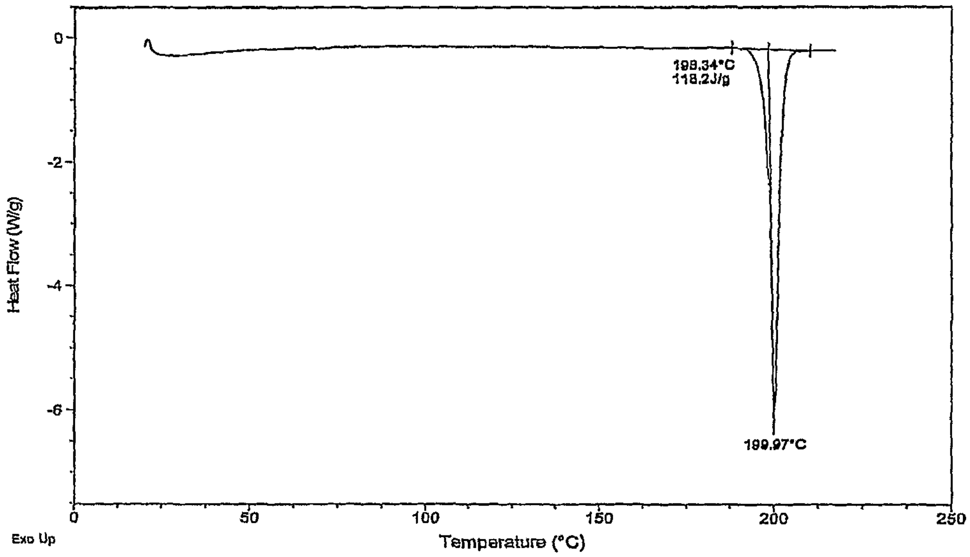

Figure 2.

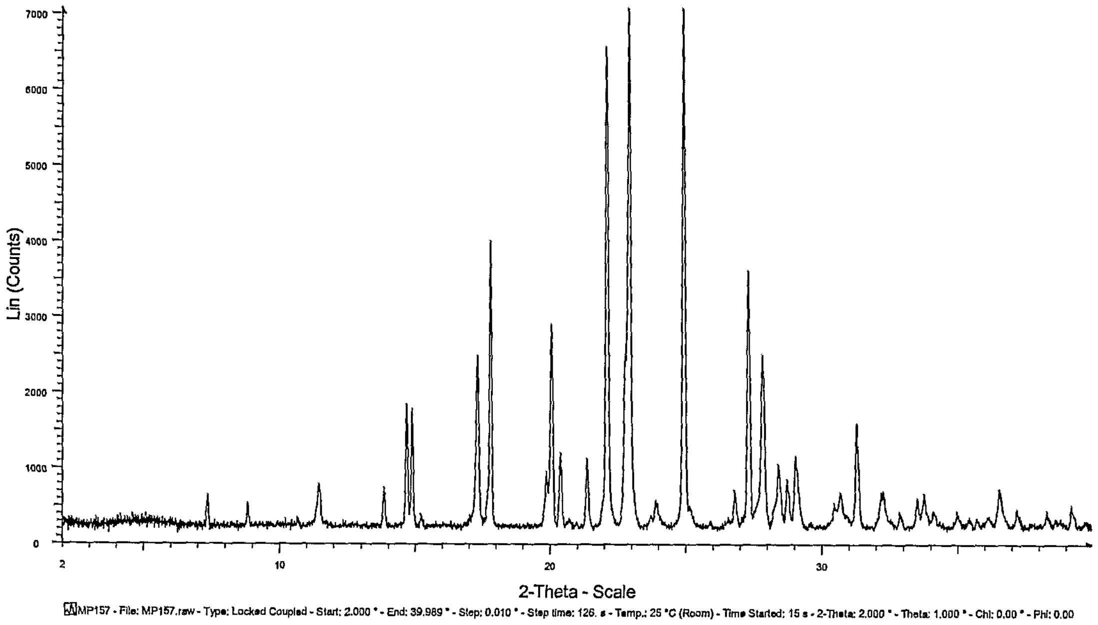
7000
6000
5000
4000
3000
2000
1000
0
Lin (Counts)
2
10
20
30
2-Theta - Scale
MP157 - File: MP157.raw - Type: Locked Coupled - Start: 2.000 ° - End: 39.989 ° - Step: 0.010 ° - Step time: 126. s - Temp.: 25 °C (Room) - Time Started: 15 s - 2-Theta: 2.000 ° - Theta: 1.000 ° - Chi: 0.00 ° - Phi: 0.00

Figure 3

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US06/27930

A. CLASSIFICATION OF SUBJECT MATTER

IPC: **A01N 43/40**( 2006.01);**A61K 31/44**( 2006.01)

USPC: 514/354

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/354

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | US 4,764,522 (IMHOF et al) 16 August 1998 (16.08.1998), see entire document. | 1-6 and 10-15 |
| A | US 5,534,635 A (SCALONE et al) 09 July 1996 (09.07.1996), see entire document. | 1-6 and 10-15 |
| A | LEWITT P.A. "Clinical Trials of Neuroprotection for Parkinson's Disease". Neurology (Supplement), October 2004. Vol.63, Suppl. No. 2, pages S23-S31, see entire document. | 1-6 and 10-15 |
| A | MASON R.P. et al. "Antioxidant Activity of the Monoamine Oxidase B Inhibitor Lazabemide". Biochemical Pharmacology, 2000, Vol.60, No. 5, pages 709-716, see entire document. | 1-6 and 10-15 |
| A | DAVIS P.P. et al. "Determination of Ro 19-6327 (Lazabemide) in Human Plasma and Urine by Gas Chromatography-Negative Chemical Ionization Mass Spectrometry." Journal of Chromatography B: Biomedical Applications, 1995, Vol.665, pages 327-335, see entire document. | 1-6 and 10-15 |

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

04 September 2007 (04.09.2007)

Date of mailing of the international search report

26 SEP 2007

Name and mailing address of the ISA/US

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| International application No. |
|---|
| PCT/US06/27930 |

## C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | Database on STN (Iyakuhin Kenkyu) Accession No: 1994:708127, "Physicochemical Properties and Stability of Lazabemide Hydrochloride, 1994, Vol.25, No. 8, pages 690-703, Suzuki, et al, abstract only. | 1-6 and 10-15 |

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US06/27930

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-6 and 10-15

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING
This International Search Authority has found 5 inventions claims in the International Application convered by the claims indicated below: This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. *In order for all inventions to be examined, the appropriate additional examination fees must be paid.*

Group I, claim(s) 1-18 (in part), drawn to a composition comprising lazabemide HCl.

Group II, claim(s) 1-18 (in part), drawn to a composition comprising lazabemide HCl and an additional agent.

Group III, claim(s) 19-45 (in part), drawn to a method of preparing a composition comprising lazabemide.

Group IV, claim(s) 19-45 (in part), drawn to a method of preparing a composition comprising lazabemide and an additional agent.

Group V, claim(s) 46-49, drawn to a method for treating a subject comprising lazabemide.

This International Searching Authority considers that the international application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated below:

The inventions listed as Groups I-V do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCR Rule 13.2, they lack the same or corresponding special technical features for the following reasons: a composition comprising lazabemide HCl is not novel (See EP 1 078 632). Moreover, the claims directed to a single active agent and a combination of active agents do not have the same or corresponding technical feature since one has a single active and others comprise multiple active agents.

Continuation of B. FIELDS SEARCHED Item 3:
WEST Search and STN Online (Registry, HCAPlus, Medline, Embase, Biosis, WPIDS); Search Terms Used: lazabemide, lazabemide hydrochloride, lazabemide HCl, tempium, Ro 19-6327, Ro 19-6327/001, lazabemide Form A, lazabemide HCl Form A, lazabemide hydrochloride Form A, crystalline lazabemide, lazabemide crystal(s), "2-pyridinecarboxamide, N-(2-aminoethyl)-5-chloro-, hydrochloride", "2-pyridinecarboxamide, N-(2-aminoethyl)-5-chloro-, monohydrochloride", etc.