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(74) Agent: **WHITE, John**; Cooper & Dunham LLP, 1185 Avenue of The Americas, New York, NY 10036 (US).

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(71) Applicant (*for all designated States except BB, US*):  
**TEVA PHARMACEUTICAL INDUSTRIES, LTD.**  
[IL/IL]; 5 Basel Street, P.o.box 3190, 49131 Petach-tikva (IL).

(71) Applicant (*for BB only*): **TEVA PHARMACEUTICALS USA, INC.** [US/US]; 1090 Horsham Road, North Wales, Pennsylvania 19454 (US).

(72) Inventors: **LIGHT, Daniella**; 1 Keren Ha Yesod, Ramat Ilan, 54051 Givat Shmuel (IL). **LOVINGER, Ioana**; 15/3 Tlamin Street, Ganei-Aviv, 71338 Lod (IL). **CACIULARU, Fanny**; 17 Shapira Street, 49491 Petach-Tikva (IL). **GILBERT, Adrian**; 60b Flat 5, Hankin Street, 43465 Ra'anana (IL).

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(54) Title: FORMULATIONS OF LADOSTIGIL TARTRATE

(57) Abstract: Disclosed are formulations of ladostigil tartrate, including pharmaceutical compositions, process for the manufacture, and use thereof.



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**FORMULATIONS OF LADOSTIGIL TARTRATE**

5 Throughout this application various publications, published  
patent applications, and published patents are referenced.  
The disclosures of these publications in their entireties  
are hereby incorporated by reference into this application  
in order to more fully describe the state of the art to  
10 which this invention pertains.

**Field of the Invention**

The present invention relates to formulations of tartrate  
salt of R(+)-6-(N-methyl, N-ethyl-carbamoyloxy)-N'-  
15 propargyl-1-aminoindan.

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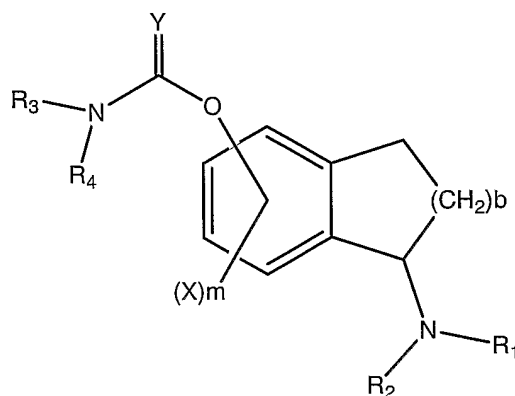
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**Background of the Invention**

PCT Application Publication No. WO98/27055 discloses indanylamine and aminotetralin derivative compounds, such as those of Formula I below, which are useful to treat depression, Attention Deficit Disorder (ADD), Attention Deficit and Hyperactivity Disorder (ADHD), Tourette's Syndrome, Alzheimer's Disease and other dementias. The indanylamine derivatives disclosed have been shown to have biological effects in animal models of neurological disease.

In addition, PCT Application Publication No. WO98/27055 discloses methods for preparation of the indanylamine derivative compounds.

Formula I:



wherein b is 1 or 2; m is 0-3; Y is O or S; X is halo; R<sub>1</sub> is hydrogen or C<sub>1-4</sub> alkyl; R<sub>2</sub> is hydrogen, C<sub>1-4</sub> alkyl, or optionally substituted propargyl; and R<sub>3</sub> and R<sub>4</sub> are each independently hydrogen, C<sub>1-8</sub> alkyl, C<sub>6-12</sub> aryl, C<sub>6-12</sub> aralkyl, each optionally halo substituted.

R(+)-6-(N-methyl,N-ethyl-carbamoyloxy)-N'-propargyl-1-aminoindan, also known as (3R)-3-(prop-2-ynylamino)-2,3,-dihydro-1H-inden-5-yl ethylmethylcarbamate, is disclosed in PCT Application Publication No. WO98/27055, specifically

compound 76 in Table 5. In addition, salts are disclosed, including the 1/2 L-tartrate salt. This salt has been given the nonproprietary name ladostigil tartrate. Its CAS registry number is 209394-46-7.

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Specific pharmaceutical compositions, i.e., formulations, comprising ladostigil tartrate suited for storage and desired pharmacokinetics have not been previously disclosed.

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**Summary of the Invention**

The subject invention provides a formulation comprising tartrate salt crystals of R(+)-6-(N-methyl, N-ethyl-carbamoyloxy)-N'-propargyl-1-aminoindan.

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The subject invention also provides a pharmaceutical composition comprising R(+)-6-(N-methyl, N-ethyl-carbamoyloxy)-N'-propargyl-1-aminoindan  $\frac{1}{2}$  tartrate, at least one pharmaceutically acceptable excipient and up to 5% by weight of the composition of water.

10

The subject invention also provides a pharmaceutical composition comprising R(+)-6-(N-methyl, N-ethyl-carbamoyloxy)-N'-propargyl-1-aminoindan  $\frac{1}{2}$  tartrate, at least one pharmaceutically acceptable excipient and no more than 0.5% by weight of the composition of magnesium stearate.

15

The subject invention also provides a pharmaceutical composition comprising R(+)-6-(N-methyl, N-ethyl-carbamoyloxy)-N'-propargyl-1-aminoindan  $\frac{1}{2}$  tartrate, at least one pharmaceutically acceptable excipient and no more than 1.5% by weight of the composition of sodium stearyl fumarate.

20

The subject invention also provides a pharmaceutical composition comprising R(+)-6-(N-methyl, N-ethyl-carbamoyloxy)-N'-propargyl-1-aminoindan  $\frac{1}{2}$  tartrate and a pharmaceutically acceptable carrier, formulated so as to provide upon administration to a human subject a maximum blood plasma concentration of R(+)-6-(N-methyl, N-ethyl-carbamoyloxy)-N'-propargyl-1-aminoindan of at least 0.7 nmol/mL.

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The subject invention also provides a method for inducing in a human subject a maximum blood plasma concentration of R(+)-6-(N-methyl, N-ethyl-carbamoyloxy)-N'-propargyl-1-aminoindan of at least 0.7 nmol/mL after one administration, comprising administering orally to the human subject a solid pharmaceutical composition comprising R(+)-6-(N-methyl, N-ethyl-carbamoyloxy)-N'-propargyl-1-aminoindan ½ tartrate and a pharmaceutically acceptable carrier so as to induce in the subject the blood plasma concentration.

**Detailed Description of the Invention**

The subject invention provides a pharmaceutical composition comprising R(+)-6-(N-methyl, N-ethyl-carbamoyloxy)-N'-  
5 propargyl-1-aminoindan  $\frac{1}{2}$  tartrate, at least one  
pharmaceutically acceptable excipient and up to 5% by weight  
of the composition of water.

In an embodiment, the pharmaceutical composition comprises  
10 2-5% water.

In a further embodiment, the pharmaceutical composition  
comprises 1-5% water.

15 In a further embodiment, the pharmaceutical composition  
comprises 1.5-4% water.

In yet a further embodiment, the pharmaceutical composition  
comprises 2-3.5% water.  
20

In yet a further embodiment, the pharmaceutical composition  
comprises 2-3.5% water.

The subject invention also provides a pharmaceutical  
25 composition comprising R(+)-6-(N-methyl, N-ethyl-  
carbamoyloxy)-N'-propargyl-1-aminoindan  $\frac{1}{2}$  tartrate, at least  
one pharmaceutically acceptable excipient and no more than  
0.5% by weight of the composition of magnesium stearate.

30 In an embodiment, the pharmaceutical composition is free of  
magnesium stearate.

The subject invention also provides a pharmaceutical composition comprising R(+)-6-(N-methyl, N-ethyl-carbamoyloxy)-N'-propargyl-1-aminoindan ½ tartrate, at least one pharmaceutically acceptable excipient and no more than 1.5% by weight of the composition of sodium stearyl fumarate.

In an embodiment, the composition comprises no more than 0.5% by weight of the composition of sodium stearyl fumarate.

In another embodiment, the pharmaceutical composition is free of sodium stearyl fumarate.

In another embodiment, no more than 0.5% by weight of the composition is magnesium stearate.

In another embodiment, the pharmaceutical composition is free of magnesium stearate and of stearic acid.

In another embodiment, no more than 0.5% by weight of the composition is sodium stearyl fumarate.

In another embodiment, the pharmaceutical composition is free of sodium stearyl fumarate.

In another embodiment, no more than 0.5% by weight of the composition is stearic acid.

In another embodiment, the pharmaceutical composition is free of stearic acid.



In yet another embodiment, at least one pharmaceutically acceptable excipient is a first filler, a second filler, a disintegrant, a flow agent, a binder and a lubricant.

5 In yet another embodiment, the lubricant is talc.

In yet another embodiment, talc is present in an amount of up to 4% by weight of the composition.

10 In yet another embodiment, the lubricant further comprises stearic acid.

In yet another embodiment, the stearic acid is present in an amount of up to 2% by weight of the composition.

15

In yet another embodiment, the lubricant is stearic acid.

In yet another embodiment, the pharmaceutical composition is free of talc.

20

In yet another embodiment, the pharmaceutical composition is free of stearic acid.

In a further embodiment, the first filler is mannitol  
25 present in an amount of 6 to 16% by weight, the second  
filler is mannitol granulate present in an amount of 0 to  
56% by weight, the disintegrant is starch present in an  
amount of 15 to 38% by weight, the flow agent is colloidal  
silicon dioxide present in an amount of 1 to 2% by weight,  
30 and the binder is polyvinylpyrrolidone present in an amount  
of 3 to 8% by weight.

In yet a further embodiment, the first filler is mannitol present in an amount of 6.6% by weight, the second filler is mannitol granulate present in an amount of 56.1% by weight, the disintegrant is starch present in an amount of 15.2% by weight, the flow agent is colloidal silicon dioxide present in an amount of 0.9% by weight, the binder is polyvinylpyrrolidone present in an amount of 3.4% by weight, and the lubricant is talc in an amount of 3.8% by weight and stearic acid in an amount of 1.9% by weight.

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In yet a further embodiment, the first filler is mannitol present in an amount of 16.4% by weight, the disintegrant is starch present in an amount of 37.5% by weight, the flow agent is colloidal silicon dioxide present in an amount of 2.1% by weight, the binder is polyvinylpyrrolidone present in an amount of 8.4% by weight, and the lubricant is talc in an amount of 3.7% by weight and stearic acid in an amount of 1.9% by weight.

20 In yet a further embodiment, the pharmaceutical is in the form of tablets, capsules, pills, powders, or granules.

In yet a further embodiment, the pharmaceutical composition is in tablet form.

25

In yet a further embodiment, the pharmaceutical composition is in capsule form.

30 In yet a further embodiment, the pharmaceutical composition upon administration to a human subject provides a maximum blood plasma concentration of R(+)-6-(N-methyl, N-ethyl-carbamoyloxy)-N'-propargyl-1-aminoindan of at least 0.7 nmol/mL.

The subject invention also provides a pharmaceutical composition comprising R(+)-6-(N-methyl, N-ethyl-carbamoyloxy)-N'-propargyl-1-aminoindan  $\frac{1}{2}$  tartrate and a pharmaceutically acceptable carrier, formulated so as to provide upon administration to a human subject a maximum blood plasma concentration of R(+)-6-(N-methyl, N-ethyl-carbamoyloxy)-N'-propargyl-1-aminoindan of at least 0.7 nmol/mL.

10 In an embodiment, the pharmaceutical composition is formulated so as to provide in the human subject a blood plasma concentration of R(+)-6-(N-methyl, N-ethyl-carbamoyloxy)-N'-propargyl-1-aminoindan of at least 0.01 nmol/mL twelve hours after dosing.

15 In another embodiment, the pharmaceutical composition is formulated so as to provide in the human subject a blood plasma concentration of R(+)-6-(N-methyl, N-ethyl-carbamoyloxy)-N'-propargyl-1-aminoindan of at least 1.88 nmol/mL.

20 In another embodiment, the pharmaceutical composition is formulated so as to provide a monoamine oxidase B inhibition of 59%-91% upon administration to a human subject as determined by liquid scintillation counting.

25 In yet another embodiment, the pharmaceutical composition is formulated so as to provide a monoamine oxidase B inhibition of 75% upon administration to a human subject as determined by liquid scintillation counting.

30 In a further embodiment, the pharmaceutical composition is formulated so as to provide a 28%-86% decrease of 3,4-

dihydroxyphenylglycol plasma concentration upon administration to a human subject as determined by liquid scintillation counting.

- 5 In a further embodiment, the pharmaceutical composition is formulated so as to provide a 57% decrease of 3,4-dihydroxyphenylglycol plasma concentration upon administration to a human subject as determined by liquid scintillation counting.

10

In yet a further embodiment, the pharmaceutical composition administered comprises 25-105 mg R(+)-6-(N-methyl, N-ethyl-carbamoyloxy)-N'-propargyl-1-aminoindan ½ tartrate.

- 15 The subject invention also provides a method for inducing in a human subject a maximum blood plasma concentration of R(+)-6-(N-methyl, N-ethyl-carbamoyloxy)-N'-propargyl-1-aminoindan of at least 0.7 nmol/mL after one administration, comprising administering orally to the human subject a solid  
20 pharmaceutical composition comprising R(+)-6-(N-methyl, N-ethyl-carbamoyloxy)-N'-propargyl-1-aminoindan ½ tartrate and a pharmaceutically acceptable carrier so as to induce in the subject the blood plasma concentration.

- 25 In an embodiment of the method, the blood plasma concentration of R(+)-6-(N-methyl, N-ethyl-carbamoyloxy)-N'-propargyl-1-aminoindan 12 hours after administration is at least 0.01 nmol/mL.

- 30 In another embodiment of the method, the maximum blood plasma concentration of R(+)-6-(N-methyl, N-ethyl-carbamoyloxy)-N'-propargyl-1-aminoindan is 1.88 nmol/mL.

In another embodiment of the method, the pharmaceutical composition administered comprises 25-105 mg R(+)-6-(N-methyl, N-ethyl-carbamoyloxy)-N'-propargyl-1-aminoindan  $\frac{1}{2}$  tartrate.

5

The subject invention also provides a method of treating a subject afflicted with Parkinson's disease, Alzheimer's disease or dementia, depression or a neurological disorder comprising administering to the subject the pharmaceutical composition as described herein.

10

In an embodiment, the subject is afflicted with a neurological disorder and the neurological disorder is epilepsy, narcolepsy, amyotrophic lateral sclerosis ("ALS"), memory disorders, panic, post-traumatic stress disorder ("PTSD"), sexual dysfunction, attention deficit and hyperactivity syndrome ("ADHD"), attention deficit disorder, or Tourette's syndrome.

15

In another embodiment, the subject is afflicted with dementia and the dementia is static dementia, Alzheimer's-type dementia, senile dementia, presenile dementia, progressive dementia, vascular dementia or Lewy body dementia.

20

In another embodiment, the subject is afflicted with Alzheimer's disease.

25

In another embodiment, the subject is afflicted with Parkinson's disease.

30

The subject invention also provides a process for making the pharmaceutical composition comprising the step of wet

granulation. In an embodiment, the process comprises the step of wet granulation in the absence of water addition.

In a further embodiment, the step of wet granulation is  
5 performed in the presence of isopropanol.

In yet a further embodiment, the process is performed in the absence of ethanol.

10 As used herein, a "pharmaceutically acceptable" excipient is one that is suitable for use with humans and/or animals without undue adverse side effects (such as toxicity, irritation, and allergic response) commensurate with a reasonable benefit/risk ratio.

15 A dosage unit may comprise a single compound or mixtures of compounds thereof. A dosage unit can be prepared for oral dosage forms, such as tablets, capsules, pills, powders, and granules.

20 The drug substance can be administered in admixture with suitable pharmaceutical diluents, extenders, excipients, or carriers (collectively referred to herein as a pharmaceutically acceptable excipient) suitably selected  
25 with respect to the intended form of administration and as consistent with conventional pharmaceutical practices. The unit will be in a form suitable for oral administration. The drug substance can be administered alone but are generally mixed with a pharmaceutically acceptable excipient, and co-  
30 administered in the form of a tablet or capsule, liposome, or as an agglomerated powder. Capsule or tablets can be easily formulated and can be made easy to swallow or chew; other solid forms include granules, and bulk powders.

Specific examples of pharmaceutically acceptable excipients that may be used to formulate oral dosage forms of the present invention are described, e.g., in U.S. Pat. No. 3,903,297 to Robert, issued Sept. 2, 1975. Techniques and compositions for making dosage forms useful in the present invention are described in the following references:

Modern Pharmaceutics, Chapters 9 and 10 (Banker & Rhodes, Editors, 1979); Pharmaceutical Dosage Forms: Tablets (Lieberman et al., 1981); Ansel, Introduction to Pharmaceutical Dosage Forms 2nd Edition (1976); Remington's Pharmaceutical Sciences, 17th ed. (Mack Publishing Company, Easton, Pa., 1985); Advances in Pharmaceutical Sciences (David Ganderton, Trevor Jones, Eds., 1992); Advances in Pharmaceutical Sciences Vol 7. (David Ganderton, Trevor Jones, James McGinity, Eds., 1995); Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms (Drugs and the Pharmaceutical Sciences, Series 36 (James McGinity, Ed., 1989); Pharmaceutical Particulate Carriers: Therapeutic Applications: Drugs and the Pharmaceutical Sciences, Vol 61 (Alain Rolland, Ed., 1993); Drug Delivery to the Gastrointestinal Tract (Ellis Horwood Books in the Biological Sciences. Series in Pharmaceutical Technology; J. G. Hardy, S. S. Davis, Clive G. Wilson, Eds.); Modern Pharmaceutics Drugs and the Pharmaceutical Sciences, Vol 40 (Gilbert S. Banker, Christopher T. Rhodes, Eds.).

Tablets may contain suitable binders, lubricants, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. For instance, for oral administration in the dosage unit form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert

excipient such as lactose, gelatin, agar, starch, sucrose, glucose, methyl cellulose, dicalcium phosphate, calcium sulfate, mannitol, sorbitol, microcrystalline cellulose and the like. Suitable binders include starch, gelatin, natural  
5 sugars such as glucose or beta-lactose, corn starch, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, povidone, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, sodium  
10 benzoate, sodium acetate, sodium chloride, stearic acid, sodium stearyl fumarate, talc and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, croscarmellose sodium, sodium starch glycolate and the like.



**Experimental Details**

Ladostigil tartrate can be prepared following the disclosure of PCT International Application Publication No. WO98/27055.

5

Alternatively, ladostigil tartrate can be prepared as indicated in the following example: In a 250 liter reactor, a solution of R(+)-6-(N-methyl, N-ethyl-carbamoyloxy)-N'-propargyl-1-aminoindan (8.3 kg) in isopropanol (52.4 liters) was heated to 60-65°C. The solution was seeded with 50 g of ladostigil tartrate and a solution of L-tartaric acid (2.4 kg) in isopropanol (38.5 liters) was added dropwise over 2.5-3.5 hours. The mixture was maintained at 60-65°C for 4-15 hr and was then gradually cooled to 0-5°C. The product was collected in a filter drier and was washed with cold isopropanol (77 liters). The wet material was dried in a filter drier in three stages until moisture content was less than 0.5%. In the first drying stage, the product was dried by static drying for 4 hours at 50-60°C and under vacuum of less than 50 mbar. In the second drying stage, the product was dried while being stirred for 2 hours at 50-60°C and under vacuum of less than 50 mbar. In the third drying stage the product was dried while being stirred for 2 hours at 78-82°C and under vacuum of less than 50 mbar.

25

This alternative process, which can be performed without the seeding step, is better suited for use in a pilot scale and a production scale than a method that follows PCT Application Publication No. WO98/27055. Ladostigil tartrate prepared using this alternative process results in crystals having bulk density of 0.22-0.29 and tapped density of 0.38-0.54 g/ml.

30

Regardless of how the crystalline ladostigil tartrate was prepared, initial attempts at formulating ladostigil tartrate encountered problems in terms of flowability and compressibility. As a result, improved formulations of  
 5 ladostigil tartrate are disclosed.

The first formulations of ladostigil tartrate, prepared by dry granulation, are shown in Table 1:

10 Table 1: First Formulations

Component (mg)	Pseudo-Proportional (mg/tablet)			Proportional (mg/tablet)	Function
	5mg	20mg	25mg	50mg	
Ladostigil Tartrate	6.4	25.68	32.0	64.0	Drug Substance
Mannitol	45.6	26.4	20.0	40.0	Filler
Pregelatinized Starch (STA-RX 1500)	40.0	40.0	40.0	80.0	Disintegrant
Syloid 244 FP	4.5	4.5	4.5	9.0	Flowing Agent
Stearic Acid	1.5	1.5	1.5	3.0	Lubricant
Sodium Stearyl Fumarate (Pruv)	2.0	2.0	2.0	4.0	Lubricant
<b>Total Weight</b>	<b>100.0</b>	<b>100.0</b>	<b>100.0</b>	<b>200.0</b>	

In the pseudo-proportional formulations, the amount of ladostigil tartrate and mannitol remains constant, but the ratio between the two changes; the amount of the other  
 15 excipients remains constant. The proportional formulation is double the formulation of the 25mg pseudo-proportional formulation.

These formulations proved to be stable at conditions of 30  
 20 °C/60% RH and RT/60% RH, but change in tablet color occurred at accelerated conditions, specifically 40°C/75% RH after 1-2 months.

In an attempt to increase stability, tablets were prepared according to the formulations in Table 2:

5 Table 2: Second Formulations

Excipients (mg)	Formulation			
	O	P	Q	R
Ladostigil Tartrate	32	32	32	32
Mannitol USP	42	42	42	20
Starch 1500	20	20	20	40
Syloid 244 (Colloidal Silicon Dioxide)	2.5	2.5	2.5	4.5
Stearic Acid	1.5	1.5	1.5	1.5
Pruv (Sodium stearyl fumarate)	0	2.0	0	2.0
Talc	0	0	2.0	0

Tablets using formulation O were manufactured using direct compression. On a small scale, the tablets using formulation O were manufactured without sticking problems. However, on a larger scale, and when other batches of ladostigil tartrate with different particle size distributions were used, there were sticking problems in the tableting process.

As a result, formulations P, Q and R were manufactured using dry granulation, and using two different lubricants. This eliminated some of the sticking problems.

The stability of formulations O, P, Q and R was tested at 40°C/75% RH for 3 months, and determined by the color of the tablets at 0, 1, 2 and 3 months, which was verified by an HPLC assay of total impurities. The results are shown in Table 3:

Table 3: Stability Profile of Second Formulations

Formulation		0 months	1 month	2 months	3 months
R	Total impurities (percent)	0.16	0.5		
	Appearance	Off-white	Off-white/ creamy-yellow	Creamy-brown	
Q	Total impurities (percent)	0.07			0.23
	Appearance	White			Off-white
P	Total impurities (percent)	0.07	0.3	0.4	
	Appearance	White	Off-white/ yellow	Yellow	
O	Total impurities (percent)	0.07	0.15	0.23	0.29
	Appearance	White	Off-white	Off-white	Off-white

Formulation Q was the most stable, apparently due to the lack of sodium stearyl fumarate as a lubricant. Accordingly, optimization of double weight formulation Q was performed to increase compressibility and stability, and the results are shown in Table 4:

Table 4: Compressibility Profile of Third Formulations<sup>2</sup>

Formulation	Compressibility <sup>1</sup>	Ladostigil Tartrate (mg)	Starch 1500 (mg)	Syloid (mg)	Stearic acid (mg)	Talc (mg)
R1	2	64	40	5	3	4
S	1	64	40	5	3	8
T	5	64	40	5	6	4
U	5	64	40	5	6	8
V	1	64	40	5	3	
W	5	64	40	5	3	
X	5	64	40	9	4	8
Y	0.5	64	40	5	4	8
Z	Can't press	64	40	5	2	
AA	0-0.4	64	80	9	4	8
CC	0.2	64	80	5	4	8

<sup>1</sup> Compressibility was measured on a scale from 0 to 5, zero being most compressible and 5 being least compressible. The formulations graded 5 encountered severe sticking problems in the tableting process.

<sup>2</sup> In all formulations in Table 4, Mannitol USP was added as a filler in order to complete the tablet weight to 200 mg for each formulation.

Increasing the stearic acid levels to 8 mg/tablet (3% per tablet) increased the sticking problem. Thus, it was determined that 4 mg/tablet (2% per tablet) of stearic acid was the optimal amount.

In addition, increasing the disintegrant amount, i.e., Starch 1500, helped compressibility.

#### 15 Accelerated Stability Screening

Different formulations were kept at 55°C. Stability was assessed by color changes (relative to unheated tablets) after 6 or 14 days, the results of which are shown in Table 5:

20

Table 5: Stability of Third Formulations<sup>1</sup>

Formulation	Ladostigil Tartrate (mg)	Starch (mg)	Syloid (mg)	Stearic acid (mg)	Talc (mg)	6D	14D
R1	64	40	5	3	4	White	White
BB	64	40	9	4	4	White	White
Y	64	40	5	4	8	White	White
CC	64	80	5	4	8	White	White to off white
X	64	40	9	4	8	White	White to off white
AA	64	80	9	4	8	White to off white	White

<sup>1</sup>In the formulations of Table 5, Mannitol USP was added as a filler in order to complete the tablet weight to 200 mg for each formulation.

Formulations R1, Y, BB and CC were stable under accelerated conditions. A flow problem resulted, however, due to large variability in particle size distribution, resulting in a change in the crystallization method of ladostigil tartrate.

5

The manufacturing process was changed from the dry granulation process to a wet-granulation process as a result of the flow problem with the active ingredient. Water and ethanol are the two most common agents used in wet granulation. Granulation experiments were first performed with water. The appearance of the formulations containing those granulates became creamy to brownish after 1 day at 55°C, which indicated that ladostigil tartrate was unstable in the presence of water. Moreover, ladostigil tartrate was found to be incompatible with ethanol. Therefore, granulation experiments based on the CC formulation were performed with isopropanol.

Uniform, flowing granulates were obtained and tablets were compressed according to the two formulations in Table 6:

Table 6: Fourth Formulations

	A (mg)	B (mg)
<b>Ladostigil Tartrate</b>	64.0	64.0
<b>Mannitol USP/BP</b>	35	35
<b>Starch 1500</b>	80	80
<b>Pregelatinized starch</b>		
<b>Syloid 244 (Silicon Dioxide)</b>	4.5	-
<b>Polividone 30 (PVP)</b>	12.5	12.5
<b>Stearic acid</b>	3	4
<b>Talc</b>	8	8

Stability tests were performed on the two formulations in 40°C/75% RH stability conditions, the results of which are shown in Tables 7 and 8:

Table 7: Stability of Fourth Formulations

Batch	Time	R-CAI	CIONE	Relative Retention Time			Total	Appearance
				1.17	2.25-2.43	3.39-3.41		
A	Zero	0.1	*	*	*	*	0.1	white
	1 month	0.2	*	*	*	*	0.2	off white
	3 months	0.3	0.07	*	0.06	*	0.4	off white
B	Zero	0.08	*	*	*	*	0.08	white
	1 month	0.1	*	0.08	*	*	0.2	white
	2 months	0.2	*	*	*	*	0.2	white
	3 months	0.2	*	*	*	*	0.2	white/ off white
	4 months	0.2	*	*	0.09	*	0.3	white/ off white
	5 months	0.2	*	*	*	0.06	0.3	Beige/ yellow

\*The number is listed only when the impurity peak is greater than or equal to 0.05. All units are in percent.

- 5 R-CAI and CIONE are acronyms for the following impurities: Ethyl-methyl-carbamic acid 3-amino-indan-5-yl ester and Ethyl-methyl-carbamic acid 3-oxo-indan-5-yl ester, respectively.

Table 8: Dissolution Profile of Fourth Formulations

Batch No.	Time (min)	15	30	45
A	Zero	95	103	104
	1 month	88	97	98
	6 months	94		100
B	Zero		96	96
	1 month		97	99
	2 months		94	96
	3 months		94	96
	4 months		94	96
	5 months		95	96
	6 months		93	93

All units are in percent.

10

These two formulations were found to be uniform and stable. All alternative formulations were within specifications under stress conditions (40°C/75% RH) and the color showed no change after 4 months.

15

More binder (PVP) was later added in order to improve structure and flowing properties after granulation.

Final formulations comprising different amounts of ladostigil tartrate are shown in Table 9:

Table 9: Final Formulations

Excipient (mg)	Tablet equivalent to 20 mg Ladostigil Tartrate base	Tablet equivalent to 50 mg Ladostigil Tartrate base	Tablet equivalent to 80 mg Ladostigil Tartrate base	Function
Ladostigil Tartrate	25.6	64.0	102.4	Drug Substance
Mannitol USP/BP	13.4	33.5	53.6	Filler
Pregelatinized starch (starch 1500 NF)	32.0	80.0	128.0	Disintegrant
Syloid 244 (Colloidal Silicon Dioxide)	1.8	4.5	7.2	Disintegrant and flowing agent
Polividone 30 (PVP)	7.2	18.0	28.8	Binder
Mannitol granulate	120.0	-	-	Filler
Stearic acid	4.0	4.0	6.4	Lubricant
Talc	8.0	8.0	12.8	Lubricant
Isopropyl alcohol	q.s.	q.s.	q.s.	
Total tablet weight	212.0	212.0	339.2	

5

Stability tests were performed on the final formulations at 30°C/65% RH. The tablets were packaged in aluminum silver/aluminum soft blister packs.

10

15



Table 10: Stability of Final Formulations

Dose (mg)	Time (months)	R-CAI	CIONE	Total Impurities
20	0	0.06	<0.05	0.06
20	12	0.3	0.07	0.5
50	0	0.07	<0.02	0.07
50	12	0.3	0.08	0.5
80	0	0.07	<0.05	0.07
80	12	0.3	0.08	0.5

The impurities are listed in percent by weight.

Capsules were made from the excipients in Table 9. The capsules were determined to be stable at RT for 21 months, and at 30°C for 12 months.

#### **Administration of ladostigil tartrate to Alzheimer's disease patients**

10

8 patients, 7 female and 1 male, ages 62-81 with a median age of 68 and above with diagnosis of probable Alzheimer's disease according to DSM-IV (290.00 or 290.10) and NINCDS-ADRDA criteria were administered ladostigil tartrate as formulated in Table 9 according to the following schedule:

Week 1: 70 mg (50+20) once daily.

Week 2: 70 mg (50+20) twice daily.

Week 3 - Week 9: 100 mg (50\*2) twice daily.

20

4 patients (3 male and 1 female) aged 70 to 84 years old were in the placebo group.

Pharmacokinetic analysis was performed on Week 4 (maintenance analysis) and on Week 9 (termination analysis). At maintenance analysis (M), samples were collected pre-dose and at 0.25, 0.5, 1, 2, and 3 hours post-dose. At

termination analysis (T), samples were collected pre-dose and at 0.25, 0.5, 1, 2, 3, 4, 6, and hours post-dose.

Table 11

Patient Number	1	2	3	4	5	6	7	8
MAO (T) (%)	-55	-85	-98	-76	-89	-76	-54	-64
DHPG (T) (%)	-63	-86	ND	ND	>-79	-73	-30	-13

AUC (ng\*hr/mL)

ladostigil (M)	314	589	1005	927	436	551	52	500
ladostigil (T)	246	2305	1449	482	398	901	118	350

C<sub>max</sub> (nmol/mL)

ladostigil (M)	1.1	1.2	3.5	3.9	1.4	1.5	0.2	1.7
ladostigil (T)	0.7	3.8	3.9	1.6	1.0	2.5	0.4	1.3

5

Mean C<sub>max</sub> after dosing and mean C<sub>min</sub> (concentration at pre-dose) of ladostigil tartrate at maintenance analysis (M) and at termination analysis (T) were determined and are listed in Table 12, as well as half life (t<sub>1/2</sub>) at termination. The concentration measurements are expressed in nmol/ml and the t<sub>1/2</sub> is expressed in terms of hours.

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Table 12: Pharmacokinetic Analysis

Analyte	C <sub>min</sub> (M)	C <sub>min</sub> (T)	C <sub>max</sub> (M)	C <sub>max</sub> (T)	t <sub>1/2</sub>
Ladostigil Tartrate	0.0164	0.0109	2.02	1.88	1.08

15 Monoamine oxidase B ("MAO-B") inhibition in plasma samples from the aforementioned patients was determined at baseline and at termination analysis using liquid scintillation counting. The percent inhibition was calculated for each patient, and the mean percent inhibition was then determined to be 75% (standard deviation=16) at the termination analysis.

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Decrease of 3,4-dihydroxyphenylglycol ("DHPG") in plasma is indicative of monoamine oxidase inhibition, especially in the brain. DHPG plasma concentrations were measured in 6 of the aforementioned patients at baseline and at termination  
5 analysis, using HPLC equipped with an electrochemical detector.

The decrease in DHPG concentration in the six patients was determined. The average decrease in DHPG concentration was  
10 determined to be 57% with a standard deviation of 29.

The data show that the analytes were present at pre-dose (which corresponds to 12 hours after the previous dose) both at maintenance and at termination analyses.

15

There is evidence of significant MAO-B inhibition.

Cholinesterase inhibition at pre-dose administration both at maintenance and at termination analyses was also evident.

**What is claimed:**

1. A pharmaceutical composition comprising R(+)-6-(N-methyl, N-ethyl-carbamoyloxy)-N'-propargyl-1-aminoindan  $\frac{1}{2}$  tartrate, at least one pharmaceutically acceptable excipient and up to 5% by weight of the composition of water.
2. The pharmaceutical composition of claim 1, comprising 2-5% water.
3. The pharmaceutical composition of claim 2, comprising 2-3.5% water.
4. A pharmaceutical composition comprising R(+)-6-(N-methyl, N-ethyl-carbamoyloxy)-N'-propargyl-1-aminoindan  $\frac{1}{2}$  tartrate, at least one pharmaceutically acceptable excipient and no more than 0.5% by weight of the composition of magnesium stearate.
5. The pharmaceutical composition of claim 4, free of magnesium stearate.
6. A pharmaceutical composition comprising R(+)-6-(N-methyl, N-ethyl-carbamoyloxy)-N'-propargyl-1-aminoindan  $\frac{1}{2}$  tartrate, at least one pharmaceutically acceptable excipient and no more than 1.5% by weight of the composition of sodium stearyl fumarate.
7. The composition of claim 6, comprising no more than 0.5% by weight of the composition of sodium stearyl fumarate.

8. The pharmaceutical composition of claim 6, free of sodium stearyl fumarate.
9. The pharmaceutical composition of any one of claims 1 to 3 or 6 to 8, wherein no more than 0.5% by weight of the composition is magnesium stearate.
10. The pharmaceutical composition of claim 9, free of magnesium stearate.
11. The pharmaceutical composition of any of claims 1 to 3, 9 or 10, wherein no more than 0.5% by weight of the composition is sodium stearyl fumarate.
12. The pharmaceutical composition of claim 11, free of sodium stearyl fumarate.
13. The pharmaceutical composition of any of claims 1 to 12, wherein no more than 0.5% by weight of the composition is stearic acid.
14. The pharmaceutical composition of claim 13, free of stearic acid.
15. The pharmaceutical composition of any one of claims 1-12, wherein the at least one pharmaceutically acceptable excipient is a first filler, a second filler, a disintegrant, a flow agent, a binder or a lubricant.
16. The pharmaceutical composition of claim 15, wherein the lubricant is talc.

17. The pharmaceutical composition of claim 16, wherein talc is present in an amount of up to 4% by weight of the composition.
18. The pharmaceutical composition of claim 16, wherein the lubricant further comprises stearic acid.
19. The pharmaceutical composition of claim 18, wherein the stearic acid is present in an amount of up to 2% by weight of the composition.
20. The pharmaceutical composition of claim 15, wherein the lubricant is stearic acid.
21. The pharmaceutical composition of claim 20, free of talc.
22. The pharmaceutical composition of claim 15, 16 or 17, free of stearic acid.
23. The pharmaceutical composition of any one of claims 15-22, wherein the first filler is mannitol present in an amount of 6 to 16% by weight, the second filler is mannitol granulate present in an amount of 0 to 56% by weight, the disintegrant is starch present in an amount of 15 to 38% by weight, the flow agent is colloidal silicon dioxide present in an amount of 1 to 2% by weight, and the binder is polyvinylpyrrolidone present in an amount of 3 to 8% by weight.
24. The pharmaceutical composition of any one of claims 15-19, wherein the first filler is mannitol present in an amount of 6.6% by weight, the second filler is mannitol

granulate present in an amount of 56.1% by weight, the disintegrant is starch present in an amount of 15.2% by weight, the flow agent is colloidal silicon dioxide present in an amount of 0.9% by weight, the binder is polyvinylpyrrolidone present in an amount of 3.4% by weight, and the lubricant is talc in an amount of 3.8% by weight and stearic acid in an amount of 1.9% by weight.

25. The pharmaceutical composition of any one of claims 15-19, wherein the first filler is mannitol present in an amount of 16.4% by weight, the disintegrant is starch present in an amount of 37.4% by weight, the flow agent is colloidal silicon dioxide present in an amount of 2.1% by weight, the binder is polyvinylpyrrolidone present in an amount of 8.4% by weight, and the lubricant is talc in an amount of 3.7% by weight and stearic acid in an amount of 1.9% by weight.
26. The pharmaceutical composition of any of claims 1-25 in the form of tablets, capsules, pills, powders, or granules.
27. The pharmaceutical composition of claim 26 in tablet form.
28. The pharmaceutical composition of claim 26 in capsule form.
29. The pharmaceutical composition of any one of claims 1-27, which upon administration to a human subject provides a maximum blood plasma concentration of R(+)-

6-(N-methyl, N-ethyl-carbamoyloxy)-N'-propargyl-1-aminoindan of at least 0.7 nmol/mL.

30. A pharmaceutical composition comprising R(+)-6-(N-methyl, N-ethyl-carbamoyloxy)-N'-propargyl-1-aminoindan  $\frac{1}{2}$  tartrate and a pharmaceutically acceptable carrier, formulated so as to provide upon administration to a human subject a maximum blood plasma concentration of R(+)-6-(N-methyl, N-ethyl-carbamoyloxy)-N'-propargyl-1-aminoindan of at least 0.7 nmol/mL.
31. The pharmaceutical composition of claim 30, formulated so as to provide in the human subject a blood plasma concentration of R(+)-6-(N-methyl, N-ethyl-carbamoyloxy)-N'-propargyl-1-aminoindan of at least 0.01 nmol/mL twelve hours after dosing.
32. The pharmaceutical composition of claim 30, formulated so as to provide in the human subject a blood plasma concentration of R(+)-6-(N-methyl, N-ethyl-carbamoyloxy)-N'-propargyl-1-aminoindan of at least 1.88 nmol/mL.
33. The pharmaceutical composition of claim 30, formulated so as to provide a monoamine oxidase B inhibition of 59%-91% upon administration to a human subject as determined by liquid scintillation counting.
34. The pharmaceutical composition of claim 33, formulated so as to provide a monoamine oxidase B inhibition of 75% upon administration to a human subject as determined by liquid scintillation counting.



35. The pharmaceutical composition of claim 30, formulated so as to provide a 28%-86% decrease of 3,4-dihydroxyphenylglycol plasma concentration upon administration to a human subject as determined by liquid scintillation counting.
36. The pharmaceutical composition of claim 35, formulated so as to provide a 57% decrease of 3,4-dihydroxyphenylglycol plasma concentration upon administration to a human subject as determined by liquid scintillation counting.
37. The pharmaceutical composition of any one of claim 30-36, wherein the pharmaceutical composition administered comprises 25-105 mg R(+)-6-(N-methyl, N-ethyl-carbamoyloxy)-N'-propargyl-1-aminoindan  $\frac{1}{2}$  tartrate.
38. A method for inducing in a human subject a maximum blood plasma concentration of R(+)-6-(N-methyl, N-ethyl-carbamoyloxy)-N'-propargyl-1-aminoindan of at least 0.7 nmol/mL after one administration, comprising administering orally to the human subject a solid pharmaceutical composition comprising R(+)-6-(N-methyl, N-ethyl-carbamoyloxy)-N'-propargyl-1-aminoindan  $\frac{1}{2}$  tartrate and a pharmaceutically acceptable carrier so as to induce in the subject the blood plasma concentration.
39. The method of claim 38, wherein the blood plasma concentration of R(+)-6-(N-methyl, N-ethyl-carbamoyloxy)-N'-propargyl-1-aminoindan 12 hours after administration is at least 0.01 nmol/mL.

40. The method of claim 38 or 39, wherein the maximum blood plasma concentration of R(+)-6-(N-methyl, N-ethyl-carbamoyloxy)-N'-propargyl-1-aminoindan is 1.88 nmol/mL.
41. The method of any one of claims 38-40, wherein the pharmaceutical composition administered comprises 25-105 mg R(+)-6-(N-methyl, N-ethyl-carbamoyloxy)-N'-propargyl-1-aminoindan  $\frac{1}{2}$  tartrate.
42. A method of treating a subject afflicted with Parkinson's disease, Alzheimer's disease or dementia, depression or a neurological disorder comprising administering to the subject the pharmaceutical composition of any of claims 1-37.
43. The method of claim 42, wherein the subject is afflicted with a neurological disorder and the neurological disorder is epilepsy, narcolepsy, amyotrophic lateral sclerosis ("ALS"), memory disorders, panic, post-traumatic stress disorder ("PTSD"), sexual dysfunction, attention deficit and hyperactivity syndrome ("ADHD"), attention deficit disorder, or Tourette's syndrome.
44. The method of claim 42, wherein the subject is afflicted with dementia and the dementia is static dementia, Alzheimer's-type dementia, senile dementia, presenile dementia, progressive dementia, vascular dementia or Lewy body dementia.
45. The method of claim 42, wherein the subject is afflicted with Alzheimer's disease.

46. The method of claim 42, wherein the subject is afflicted with Parkinson's disease.
47. A process for making the pharmaceutical composition of any of claims 1-37 comprising the step of wet granulation.
48. The process of claim 47, comprising the step of wet granulation in the absence of water addition.
49. The process of claim 47 or 48, wherein the step of wet granulation is performed in the presence of isopropanol.
50. The process of any one of claims 47 to 49, wherein the process is performed in the absence of ethanol.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/06636

## A. CLASSIFICATION OF SUBJECT MATTER

IPC: C03B 27/04( 2006.01)

USPC: 65/111

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. : Please See Continuation Sheet

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)  
East: cassette, glass sheet, rack, enclosure, thin wall

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 1,534,864 (OLIVER et al) 19 December 1919 (19.12.1919), page 1, lines 7-8, 25-45, page 2, lines 1-16.	1 ----- 5, 13, 17
X --- Y	US 6,588,232 (SUZUKI et al) 08 July 2003 (08.07.2003), column 6, lines 10, 35, 46-48, 59-60, column 14, lines 53-60, figures 16, 4, & 5.	1 ----- 5, 13, 17
Y	US 5,974,833 (VAHA-ANTILA et al) 02 November 1999 (02.11.1999), column 1, lines 40-50.	5, 12, 13, 17, 20
Y	US 6,176,023 B1 (DOCHE) 23 January 2001 (23.01.2001), column 1, line 28 to column 3, line 45, column 5, lines 42-48, column 12, lines 7-8, 31-34, figures 1A, 1A, 2A & 2B.	2, 8, 11-13, 17, 18, 20,
Y	US 4,086,263 (ROWLEY) 25 April 1978 (25.04.1978), column 2, lines 33-35, column 3, lines 56-57, column 4, lines 25-34, figure 1.	3-4, 9-10



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	"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
"E" earlier application or patent published on or after the international filing date	"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
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"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
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Mail Stop PCT, Attn: ISA/US  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, Virginia 22313-1450

Facsimile No. (571) 273-3201

Authorized officer

Steven Griffin

Telephone No. 571-272-1700

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/06636

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

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2,026,165 (GOODWILLIE) 01 August 1934 (01.08.1934), page 3, lines 18-22.	14
Y	US 6,053,011 (LISEC) 25 April 2000 (25.04.2000), column 3, lines 35-38.	14
Y	US 4,488,192 (TRESEDER) 11 December 1984 (11.12.1984), column 3, lines 1-31.	6, 15, 18
A	JP 411079389A (TAKASHIMA et al) 23 March 1999 (23.03.1999).	1, 5, 13, 17
A	JP 11079388A (TAKASHIMA et al) 23 March 1999 (23.03.1999).	1, 5, 13, 17

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US05/06636

Continuation of B. FIELDS SEARCHED Item 1:

65/111, 63, 69, 41, 95, 114, 117, 118, 157, 194, 254, 274, 289, 104, 24, 25.2, 102, 106, 182.1, 182.2, 348, 355: 134/48; 432/184, 204, 120, 121, 210; 34/202; 271/198, 264, 7