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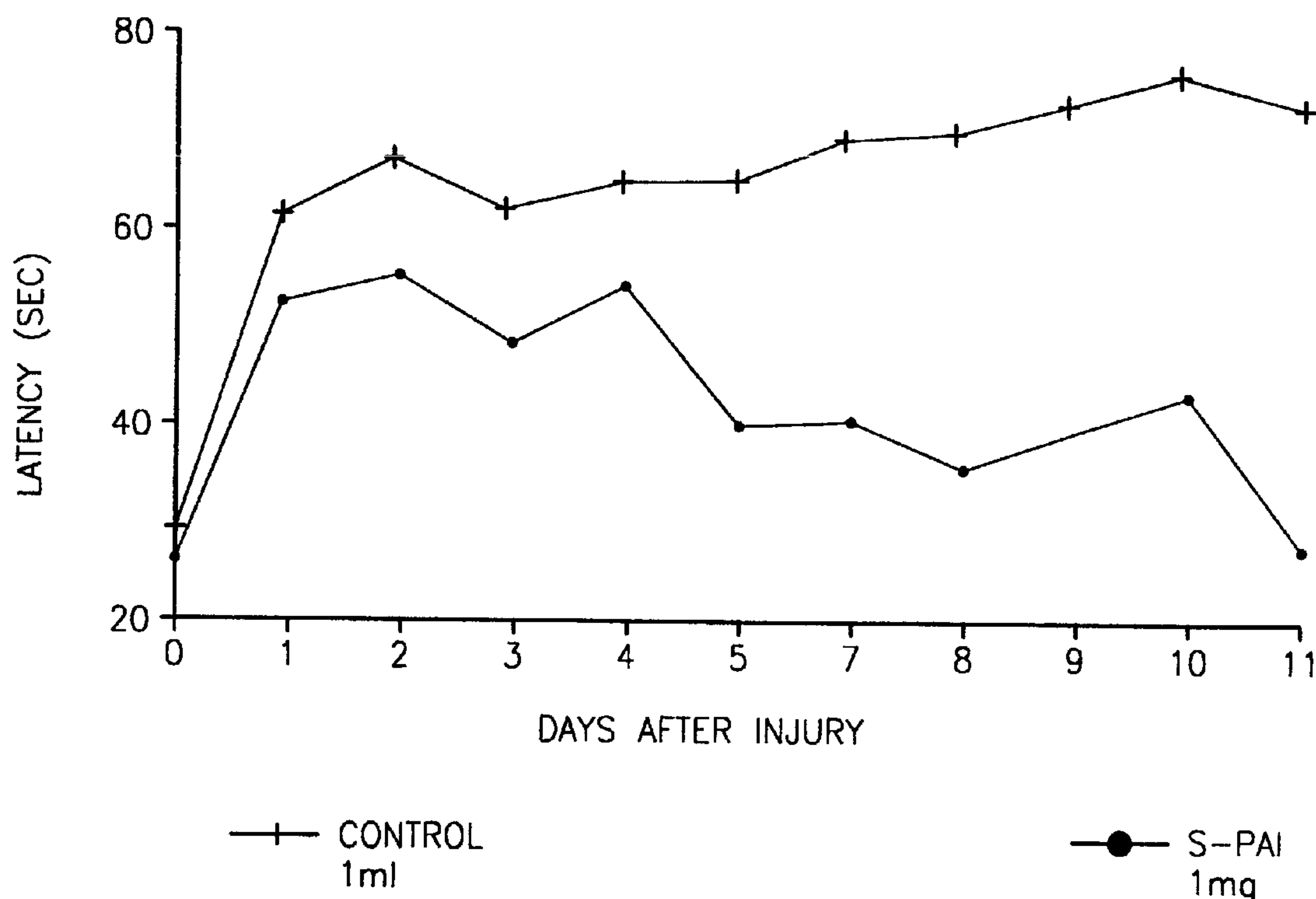
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(54) Titre : COMPOSITIONS PHARMACEUTIQUES COMPORTANT DES ELEMENTS S-(-)-N-PROPARGYL-1-AMINOINDANE

(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING S-(-)-N-PROPARGYL-1-AMINOINDAN



(57) **Abrégé/Abstract:**

Pharmaceutical compositions for the treatment of a neurological disorder or neurotrauma or for improving memory in a patient, comprising a therapeutically effective amount of S-(-)-N-propargyl-1-aminoindan or a pharmaceutically acceptable salt thereof as active ingredient, and a pharmaceutically active carrier. The pharmaceutical compositions are adapted, in particular for treating a neurological disorder or neurotrauma involving damage caused to the central or peripheral nervous system as a result of ischemic damage, stroke, hypoxia or anoxia, neurodegenerative diseases, Parkinson's Disease, Alzheimer's Disease, neurotoxic injury, head trauma injury, spinal trauma injury or any other form of nerve damage.

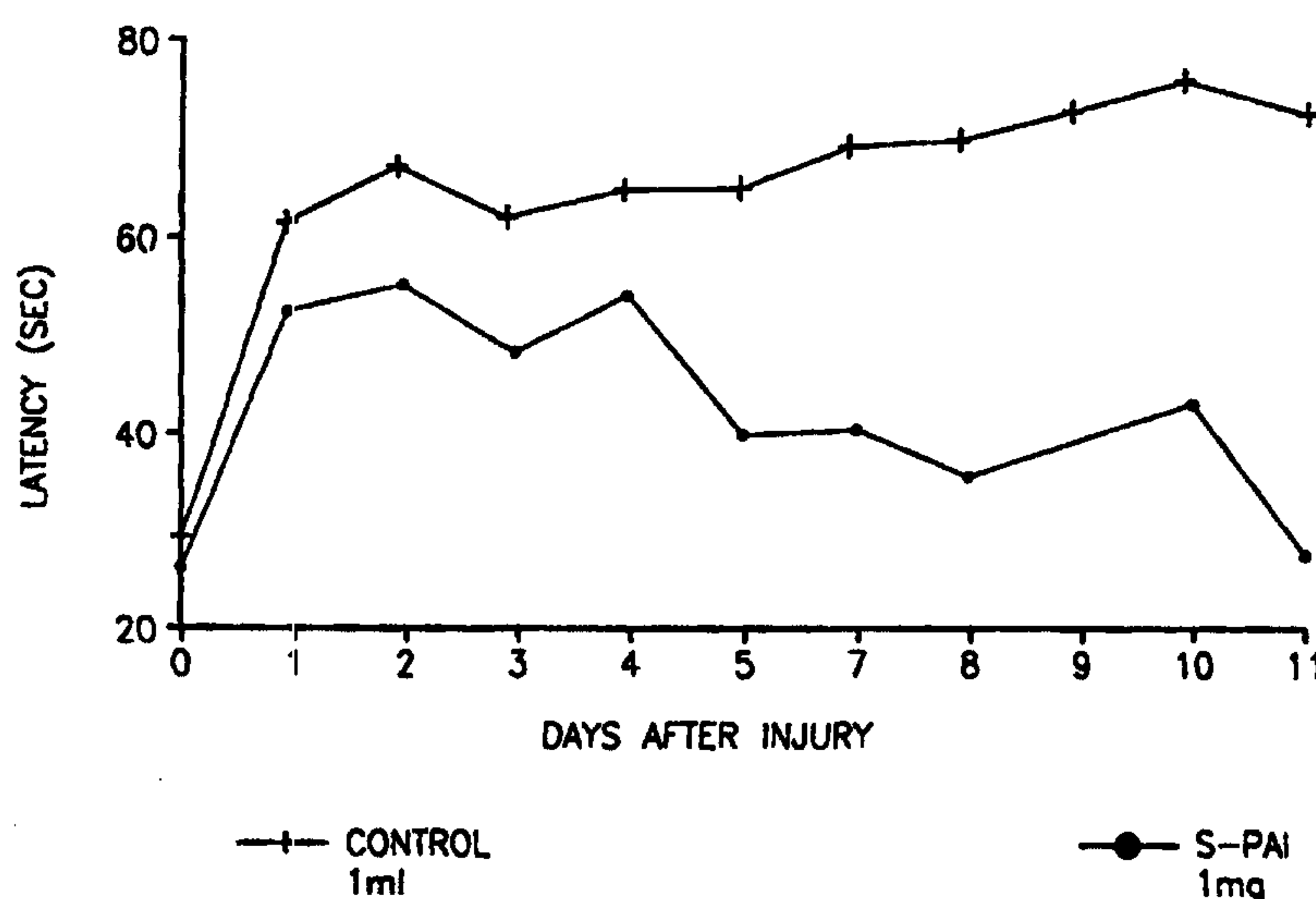


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(57) Abstract

Pharmaceutical compositions for the treatment of a neurological disorder or neurotrauma or for improving memory in a patient, comprising a therapeutically effective amount of S-(-)-N-propargyl-1-aminoindan or a pharmaceutically acceptable salt thereof as active ingredient, and a pharmaceutically active carrier. The pharmaceutical compositions are adapted, in particular for treating a neurological disorder or neurotrauma involving damage caused to the central or peripheral nervous system as a result of ischemic damage, stroke, hypoxia or anoxia, neurodegenerative diseases, Parkinson's Disease, Alzheimer's Disease, neurotoxic injury, head trauma injury, spinal trauma injury or any other form of nerve damage.

PHARMACEUTICAL COMPOSITIONS COMPRISING S-(-)-N-PROPARGYL-1-AMINOINDAN

FIELD OF THE INVENTION

The present invention concerns the novel therapeutical use of S-(-)-N-propargyl-1-aminoindan and pharmaceutically acceptable salts thereof for the treatment of neurological disorders or neurotrauma and for
5 improving memory in a patient.

As used herein, the term "*neurotrauma*" is meant to refer to damage caused to the central and/or peripheral nervous system as a result of ischemic damage such as a stroke, hypoxia or anoxia, neurodegenerative diseases, Parkinson's Disease, Alzheimer's Disease, neurotoxic injury, head
10 trauma injury, spinal trauma injury or any other form of nerve damage.

BACKGROUND OF THE INVENTION

R(-) deprenyl (also known as L-deprenyl), N, α -dimethyl-N-2-propenylphenethylamine) is a well-known inhibitor of the B-form of
15 monoamine oxidase enzyme (hereinafter "*MAO-B*").

PCT International Application No. WO92/17169 describes the activity of R(-) deprenyl in maintaining, preventing the loss of, or recovering nerve growth function. This publication includes a list of deprenyl-like derivatives that are suggested to possess similar activities,
20 although no data is given in support of this contention. Included in the list is AGN-1135 which is racemic N-propargyl-1-aminoindan.

In a subsequent article, Tatton, W.G., *et al.*, *J. Neuroscience*, 13(9), pp. 4042-4053, (1993) report that the neuroprotective activity of deprenyl is limited to the R(-) enantiomer. The S(-) enantiomer was 2000

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times less active in increasing the survival of axotomized immature rat facial mononeurons. Furthermore, it was demonstrated that neuroprotective activity is associated only with the R-enantiomers of propargyl derivatives that possess MAO-B inhibitory activity. Davis *et al.*, *J. Neurochem.* Supplement 1, 64:S60, (1995) (recording the data presented by the same author at the Twenty-sixth Meeting of the American Society for Neurochemistry, held in Santa Monica, California, USA on March 5-9, 1995) disclosed that in various models of neuroprotective activity, the R-enantiomers of certain aliphatic N-methylpropargylamines that are selective inhibitors of MAO-B, were more effective in rescuing damaged neurons than their corresponding S-enantiomers.

The development of the work on deprenyl has led to the belief that the neuroprotective activity does not involve inhibition of MAO-B, because sub-inhibitory levels of R(-) deprenyl have been observed to prevent nerve cell death (Tatton, *Movement Disorders*, 8(1):S20-S30, (1993)). It has been proposed that R(-) deprenyl is perhaps dependent on interaction with a subtype of MAO-B that possesses extreme sensitivity to R(-) deprenyl.

Yu *et al.*, *J. Neurosci.*, 63, pp. 1820-1827, (1994) have assessed the activity of R(-)- and S(+)-deprenyl and several aliphatic propargylamine derivatives in reversing the noradrenaline depletion in rodents induced by the administration of N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine (DSP-4). The end-point measured and described as an indication of "neuroprotective activity" was the percent restoration of noradrenaline as compared to untreated controls. In the results described, R(-) deprenyl and several of the higher N-aliphatically substituted propargylamines displayed "neuroprotective activity". S(+) deprenyl was described as acting like the known noradrenaline uptake inhibitor desipramine, having a far lower "neuroprotective activity" in comparison with R(-) deprenyl. In summary, S(+) deprenyl was shown to be a superior noradren-

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aline uptake inhibitor as compared to R(-) deprenyl, yet far inferior in the described measure of *"neuro-protective activity"*.

European Patent 436,492 discloses the R(+) enantiomer of N-propargyl-1-aminoindan (hereinafter referred to as *"R(+)PAI"*) as a selective irreversible inhibitor of MAO-B. Due to this specific activity R(+)PAI has also been proposed for use in the treatment of Parkinson's Disease, memory disorders, dementia (particularly of the Alzheimer's type), depression and hyperactive syndrome in children. U.S. Patents 5,387,612, 5,453,446 and 5,457,133 relate to R(+)PAI and to methods of treating patients suffering from Parkinson's Disease comprising administering R(+)PAI to the patient. In these U.S. patents emphasis is placed on the superior MAO-B inhibitory activity of R(+)PAI as compared to its antipode, the S(-) enantiomer of N-propargyl-1-aminoindan (hereinafter referred to as *"S(-)PAI"*). In *in vitro* assays R(+)PAI was found to be nearly 7,000 times more active as an inhibitor of MAO-B than S(-)PAI. It was also found in these assays that, whereas R(+)PAI is more than 29 times more selective for MAO-B than MAO-A (the A-form of monoamine oxidase enzyme), S(-)PAI showed no preference to either substrate. This effect was also observed in both acute and chronic *in vivo* administration.

PCT International Application Publication No. WO95/11016 further disclosed that R(+)PAI is active as a *"neuroprotective agent"*. The data therein describes its use in the prevention of NMDA induced cell death in rat cerebellum cells as well as in slowing neuronal degeneration when administered after crushing the rat optic nerve. No indication is given in this publication as regards the mechanism by which R(+)PAI may exert its *"neuroprotective"* effect.

The use of MAO inhibitors as neuronal rescue agents in clinical situations where neuronal survival is in jeopardy, might involve the important disadvantage resulting from their potential cardiovascular side-effects, alone or following drug-drug or drug-food interactions. These side-effects are attributed to partial or total inhibition of peripheral MAO-A, resulting in excessive concentrations of norepinephrine in the

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cardiovascular system (see for example, Physicians' Desk Reference 48th Edition, 1994, Medical Economics Data, Montvale, NJ, under Eldepryl). Selective MAO-B inhibitors such as R(-) deprenyl are less prone to compromise the cardiovascular system than the less specific agents such as pargyline or clorgyline, hence the former are probably the safer agents. However, the MAO subtype selectivity of these agents as determined under *in vitro* conditions tends to decrease dramatically when determined *in vivo*. Thus, the ratio of the *in vitro* IC₅₀ values of MAO-A/MAO-B for R(-) deprenyl has been reported by various authors as 400, 247, 360 and 16 (from a compilation by W. Paul and I. Szelenyi, in "*Inhibitors of Monoamine Oxidase-B*", I. Szelenyi editor, Birkhauser, Basel, p. 353, 1993), suggesting a safety factor of about 100 or more. The recommended daily dose of R(-) deprenyl in human subjects is 10 mg, with 30-40 mg considered as the dose at which cardiovascular function could be compromised (Physicians' Desk Reference *supra*). Thus, the safety factor in clinical practice is about 3 to 4, as compared to about 400 in experimental systems *in vitro*.

There still exists, therefore, a need for a "*neuroprotective agent*" that, while being effective is free from the side-effects associated with hitherto known neuroprotectants of the MAO-B inhibitor type.

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OBJECT OF THE INVENTION

It is thus an object of the present invention to provide a method and pharmaceutical compositions for treating CNS or PNS disorders, particularly those associated with neurotrauma, with an agent that possesses neuroprotective activity but does not display the peripheral side-effects associated with the known MAO-B inhibitors.

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SUMMARY OF THE INVENTION

The present invention, in accordance with one aspect thereof provides a method of treating a patient suffering from a neurological disorder or neurotrauma comprising administering to said patient a

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therapeutically effective amount of (S)-N-propargyl-1-aminoindan or a pharmaceutically acceptable salt thereof.

The invention specifically provides a method of treating a subject afflicted with a neurodegenerative disease, a neurotoxic injury, brain
5 ischemia or a stroke, which method comprises administering to the subject an amount of S(-)-N-propargyl-1-aminoindan or a pharmaceutically acceptable salt thereof.

The invention also specifically provides a method of treating a subject afflicted with neural injury following an episode of hypoxia or
10 anoxia, head trauma injury or spinal trauma injury which method comprises administering to the subject an amount of S(-)-N-propargyl-1-aminoindan or a pharmaceutically acceptable salt thereof.

The present invention further provides a method of preventing nerve death in a subject which comprises administering to the subject an
15 amount of S(-)-N-propargyl-1-aminoindan or the pharmaceutically acceptable salt thereof.

The present invention further provides a method of treating a subject afflicted with a memory disorder which comprises administering to the subject an amount of S(-)-N-propargyl-1-aminoindan or a pharmaceu-
20 tically acceptable salt thereof effective to improve the memory in the subject.

In accordance with another aspect, the invention provides a pharmaceutical composition for the treatment of a neurological disorder or neurotrauma or for improving memory in a patient which comprises a
25 therapeutically effective amount of S(-)-N-propargyl-1-aminoindan or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

In accordance with yet another aspect of the present invention, there is provided S(-)-N-propargyl-1-aminoindan or a pharmaceutically
30 acceptable salt thereof for use as a medicament for the treatment of a neurological disorder or neurotrauma or for improving memory in a patient.

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In accordance with yet another aspect of the present invention, there is provided the use of S(-)-N-propargyl-1-aminoindan or a pharmaceutically acceptable salt thereof as active ingredient in the manufacture of medicaments for improving memory in a patient.

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DETAILED DESCRIPTION OF THE INVENTION

S(-)-propargyl-1-aminoindan may be prepared as described in U.S. Patent 5,457,133 and compositions may be prepared in a similar manner to those described in that patent.

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in the practice of this invention, it is preferable that a pharmaceutically acceptable salt of S(-)-N-propargyl-1-aminoindan is used. Suitable pharmaceutically acceptable salts include, but are not limited to, the mesylate, maleate, fumarate, tartrate, hydrochloride, hydrobromide, esylate, p-toluene sulfonate, benzoate, acetate, phosphate and sulfate salts. Preferred are the hydrochloride, mesylate, esylate and sulfate salts of S(-)-N-propargyl-1-aminoindan. Most preferably, the pharmaceutically acceptable salt is the mesylate salt.

15

For the preparation of pharmaceutically acceptable acid addition salts of S(-)PAI, the free base can be reacted with the desired acids in the presence of a suitable solvent by conventional methods. Similarly, an acid addition salt may be converted to the free base form in a known manner.

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As stated above, the invention provides, in accordance with one aspect thereof, a pharmaceutical composition which comprises a therapeutically effective amount of S(-)-N-propargyl-1-aminoindan or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier. The "therapeutically effective amount" of the S(-)-N-propargyl-1-aminoindan or pharmaceutically acceptable salt thereof may be determined according to methods well known to those skilled in the art. These compositions may be prepared as medicaments to be administered orally, parenterally, rectally, or transdermally.

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The preferred dosages of the active ingredient, i.e., S(-)PAI, in the above compositions are within the following ranges. For oral or

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suppository formulations, 0.1–100 mg per dosage unit may be taken daily, and preferably 1–10 mg per dosage unit is taken daily. For injectable formulations, 0.1–100 mg/ml per dosage unit may be taken daily, and preferably 1–10 mg/ml per dosage unit is taken daily.

5 These compositions may be used alone to treat the above-listed disorders, or alternatively, as an adjunct to the conventional treatments.

Suitable forms for oral administration include tablets, compressed or coated pills, dragees, sachets, hard or soft gelatin capsules, sublingual tablets, syrups and suspensions.

10 In one embodiment, the pharmaceutically acceptable carrier is a solid and the pharmaceutical composition is a tablet. The therapeutically effective amount of the active ingredient may be from about 0.1 mg to about 100 mg, preferably from about 1 mg to about 10 mg.

15 In an alternative embodiment, the pharmaceutically acceptable carrier is a liquid and the pharmaceutical composition is an injectable solution. The therapeutically effective amount of the active ingredient may be from about 0.1 mg/ml to about 100 mg/ml, preferably from about 1 mg/ml to about 10 mg/ml. In one embodiment, the dosage form is an infusion.

20 In a further alternative embodiment, the carrier is a gel and the pharmaceutical composition is a suppository.

For parenteral administration the invention provides ampoules or vials that include an aqueous or non-aqueous solution or emulsion of the active ingredient. For rectal administration there are provided suppositories
25 with hydrophilic or hydrophobic vehicles. For topical application as ointments and transdermal delivery there are provided suitable delivery systems as known in the art.

The invention will be described in more detail in the following non-limiting Examples.

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EXAMPLES**CHEMICAL EXAMPLES****EXAMPLE 1****5 Di-(S-(-)-N-Propargyl-1-aminoindan) D-tartrate****a) Racemic N-propargyl-1-aminoindan**

To a mixture of racemic 1-aminoindan (64 g), 15% aqueous sodium hydroxide solution (141 g), water (107 mL) and toluene (192 mL) there was added propargyl benzenesulfonate (94.3 g) during 20 minutes at ambient
10 temperature. The resulting mixture was heated to 45°C for 4 hours, at which time the pH was confirmed to be >12 (45% sodium hydroxide added if necessary) and the phases were separated. To the organic phase water (64 mL) was added and the pH was adjusted to 2 with 33% aqueous sulfuric acid. The aqueous phase was separated, diluted with water and mixed with
15 toluene. The pH was adjusted to 6 with 25% aqueous sodium hydroxide and the phases separated. The aqueous phase was extracted again with toluene, ensuring a pH=6. The combined organic layers were concentrated *in vacuo* to yield 51 g of crude racemic N-propargyl-1-aminoindan as a yellow oil.

20 b) Di-(S-(-)-N-propargyl-1-aminoindan) D-tartrate

To a solution of crude racemic N-propargyl-1-aminoindan (46.5 g) in isopropanol (157 mL) at reflux, was added a solution of D-tartaric acid (15.3 g) in water (28 mL). After 1 hour of reflux the mixture was slowly cooled to ambient temperature and the resulting precipitate was isolated by
25 filtration with suction and washed with isopropanol. The crude di-(S-(-)-N propargyl-1-aminoindan) D-tartrate was recrystallized from 1 L of isopropanol containing 15% of water to yield 26.5 grams of the title compound: m.p. 175-177°C, $[\alpha]_D -34.3^\circ$ (1.5, H₂O); Anal. calcd. for C₂₈H₃₂O₆N₂: C, 68.26; H, 6.56; N, 5.69; Found: C, 68.76; H, 6.57; N, 5.61;

30

EXAMPLE 2**S-(-)-N-Propargyl-1-aminoindan mesylate**

A solution of di-(S-(-)-N-propargyl-1-aminoindan) D-tartrate (15 g) from Example 1, and methanesulfonic acid (6 g) in isopropanol (150 mL) was heated to reflux for 30 minutes.

- 5 The reaction mixture was allowed to cool to room temperature and the resulting precipitate isolated by suction filtration to yield the title compound (11.1 g) with m.p. 157°C. $[\alpha]_D -22^\circ$. Anal. calcd. for $C_{13}H_{17}NSO_3$: C, 58.43; H, 6.37; N, 5.24; S, 11.98; Found: C, 58.70; H, 6.39; N, 5.20; S, 11.82.

10 **EXAMPLE 3**

S-(-)-N-Propargyl-1-aminoindan mesylate

To a solution of sodium hydroxide (4.8 g) in water (80 mL) was added di-(S-(-)-N-propargyl-1-aminoindan) D-tartrate from Example 1 and toluene (80 mL). After stirring for 30 minutes, the mixture was filtered through Celite™ with suction and the organic layer was
15 separated and washed water. The organic phase was concentrated *in vacuo*, diluted with isopropanol and reconcentrated. The residue was dissolved in isopropanol (125 mL) and treated with methanesulfonic acid (11.5 g). The resulting mixture was heated to reflux for 30 minutes, filtered (Celite™) and allowed to cool to ambient temperature. The resulting precipitate was collected by filtration and washed with isopropanol to yield the title
20 compound with identical physical and chemical properties as the product of Example 2.

EXAMPLE 4**S-(-)-N-Propargyl-1-aminoindan mesylate**

- 25 The method of Example 1a was repeated except that S-(-)-1-aminoindan, prepared according to International Publication No. WO 96/21640, was used instead of racemic 1-aminoindan. The resulting yellow oil (30 grams) was dissolved in 180 mL of isopropanol, 17.7 grams of methane-sulphonic acid were added and the resulting mixture heated to

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reflux and allowed to cool. The precipitate was isolated by filtration and recrystallized from isopropanol with activated charcoal to give the title compound with identical physical and chemical properties as the compound of Example 2.

5

EXAMPLE 5

S-(-)-N-Propargyl-1-aminoindan hydrochloride

12.4g of S-(-)-1-aminoindan and 12.9g of potassium carbonate were added to 95 ml of acetonitrile. The resulting suspension was heated to 60°
10 and 5.6g of propargyl chloride were added dropwise. The mixture was stirred at 60°C for 16 hours, whereafter most of the volatiles were removed by distillation *in vacuo*. The residue was partitioned between 10% aqueous sodium hydroxide and methylene chloride. The organic phase was dried and the solvent removed *in vacuo*. The residue was flash chromatographed on
15 silica gel, eluting with 40% ethyl acetate/60% hexane. Fractions containing the free base of the title compound were combined and the solvent replaced by ether. The ethereal solution was treated with gaseous HCl and the resulting precipitate was isolated by suction filtration and recrystallized from isopropanol to yield 6.8g of the title compound. The product exhibited $[\alpha]_D$
20 -30.3° (2% ethanol), m.p. 183–5°C.

Biological Examples

Example 1

Lack of inhibition of MAO activity *in vivo* by S(-) PAI mesylate

25 Rats (male Sprague-Dawley-derived) weighing 250 ± 20 g were treated with one of the enantiomers or the racemic form of PAI by intraperitoneal injection (ip) or oral gavage (po), and decapitated 1h or 2h later respectively. Groups of three rats were used for each dose level of substance, and MAO activity determined in brain and liver using
30 the general technique described in Example 19 of US Patent 5,387,612. The amount of protein in each incubation was determined using the Follin-Lowry method, and enzyme activity calculated as

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nmol of substrate metabolized per hour of incubation for each mg of protein. Activity of MAO in tissues from animals treated with the enantiomers or the racemic form of PAI was expressed as a percentage of the enzyme activity in a group of control animals administered vehicle (water for oral administration, 0.9% saline for ip injection).

Results

None of the dose levels used produced any obvious behavioral alterations. The doses producing 50% inhibition of MAO-A and MAO-B (IC₅₀) were calculated from the inhibition curves, and are shown in Table 1. These data reflect the extremely low activity of S(-)PAI mesylate for inhibition of MAO-A and MAO-B, compared to the selectivity of R(+)-PAI mesylate for MAO-B inhibition.

Table 1

IC-50 values (mg/kg) for Inhibition of MAO-A and MAO-B by S(-)PAI mesylate, or R(+)-PAI mesylate in rat brain and liver following intraperitoneal injection (ip) or oral administration (po).

	MAO-A		MAO-B	
	S(-)PAI mesylate	R(+)-PAI mesylate	S(-)PAI mesylate	R(+)-PAI mesylate
ip brain	>10	1.2	>10	0.07
ip liver	>10	5	>10	0.06
po brain	>10	>5	>10	0.17
po liver	>10	>5	>10	0.05

Example 2

Neuroprotective effect of S(-)PAI in the hypobaric hypoxia model

The model used is analogous to the one described by M.Nakanishi et al., Life Sci. 13: 467-476 (1973); and by Y. Oshiro et al., J. Med. Chem. 34: 2014-2023 (1991). A group of 4 ICR male mice each weighing 20-25 g were placed in a 2.5 L glass chamber (A) at atmospheric pressure. Chamber A is connected to a 12 L chamber (B) through a valve which is initially

pressure. Chamber A is connected to a 12 L chamber (B) through a valve which is initially closed. The air in chamber B was evacuated to a pressure of 100 mmHg. The valve between the two chambers was opened rapidly, whereupon the pressure in chamber A fell within 14 seconds to 200 mmHg. The survival time of the mice in chamber A was determined to a maximum hypobaric exposure of 15 minutes. Effect of drug pretreatment on survival is calculated as the percent of the survival time of the drug-treated group as compared to saline-injected or vehicle-injected group. Control groups were tested twice, before and after each experiment and consisted of 12 to 16 mice, 4 per group. Each tested group always consisted of 4 mice in order to ensure a constant residual volume of oxygen in all tests. Survival time range of control mice was 108-180 seconds. The effect of each dose of the test drug was determined in duplicate, using a total of 8 mice, 4 per group. All drugs were administered i.p. one hour prior to hypoxia. Positive reference drugs were sodium pentobarbital at a dose of 40 mg/kg, or diazepam at a dose of 10 mg/kg, given 0.5 hour prior to hypoxia. Results are shown in Table 2.

Table 2. Effect of drug-treatment on relative survival time of mice at 200 mmHg, as percent of corresponding control

Agent	i.p dose mg/kg	%protection \pm SD relative to control
saline/vehicle	0.5ml	100
Diazepam	10	430 \pm 59, p<0.001
	5	249 \pm 166, p<0.05
Pentobarbital	40	446 \pm 10.5, p<0.001
	20	325 \pm 166, p<0.002
R(-)Deprenyl	100	102 \pm 75, (ns)
	50	79 \pm 23, (ns)
	10	97 \pm 70, (ns)
(R)(+) PAI mesylate	100	358 \pm 179, p<0.001
	50	410 \pm 151, p<0.001
	10	116 \pm 47, (ns)

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Agent	i.p dose mg/kg	%protection \pm SD relative to control
(S)(-)-PAI mesylate	100	390 \pm 197, p<0.002
	50	406 \pm 247, p<0.01
	10	34 \pm 47 (ns)

Example 3.

Locomotor activity and brain infarct size in male Wistar rats after middle cerebral artery occlusion (MCA-O) in the absence and presence of PAI enantiomers.

A modification of the procedure described by Tamura et al was used (Tamura A, Graham D, McCulloch J, Teasdale GH (1981) J. Cereb. Blood Flow and Metab. 1 : 53-60). Male Wistar rats (Olac England-Jerusalem) weighing 300-400g each, were anesthetized with a solution of Equitesine administered i.p. at a dose of 3 ml/kg. Equitesine consists of 13.5 ml sodium pentothal solution (60 mg/ml), 3.5 g chloral hydrate, 1.75 g MgSO₄, 33 ml propylene glycol, 8.3 ml absolute alcohol, made up to 83 ml with distilled water.

Surgery was performed with the use of a high magnification operating microscope, model SMZ-2B, type 102 (Nikon, Japan). In order to expose the left middle cerebral artery, a cut was made in the temporal muscle. The tip of the coronoid process of mandible was excised as well and removed with a fine rongeur. Craniectomy was made with a dental drill at the junction between the median wall and the roof of the inferotemporal fossa.

The dura matter was opened carefully using a 27 gauge needle. The MCA was permanently occluded by microbipolar coagulation at low power setting, beginning 2-3 mm medial to the olfactory tract between its cortical branch to the rhinal cortex and the laterate striate arteries. After coagulation, the MCA was severed with microscissors and divided to ensure complete occlusion. Following this, the temporalis muscle was sutured and laid over the craniectomy

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site. The skin was closed with a running 3-0 silk suture. A sham craniectomy operation was performed on a parallel group of rats, but without cauterization of the MCA.

During the entire surgical operation (20-25 min) in either group, body temperature was maintained at 37 to 38°C by means of a body-temperature regulator (Kyoritsu, Japan)

5 consisting of a self-regulating heating pad connected to a rectal thermistor. At 24 and 48 hours post surgery a neurological score was taken in order to assess the severity of the injury in the drug-treated rats with respect to their untreated controls. At 48 hours, the animals were anesthetized with Equitesine and the severity of the injury was visualized by 2,3,5-triphenyl tetrazolium chloride (TTC) staining. The volume of brain tissue incurring
10 damage following ischemia was determined.

Drugs were administered as an i.p. injection in 0.3-0.4 ml distilled water, according to the following schedule:

15 3 mg/kg within 30min before surgery; 2 mg/kg 60 min after occlusion; 3 mg/kg within 20-24 hours after surgery.

After 48 hours of ischemia induced by permanent occlusion, morphometric measurement of
20 infarct volume was performed as follows by TTC staining. TTC 1% in saline was prepared immediately before use and protected from exposure to light by aluminum foil wrap. MCA-O rats were deeply anesthetized and a 23-gauge butterfly needle with an extended tubing and a 20 ml syringe was inserted into the ventricle via thoracotomy. The right atrium was incised to allow outflow of saline. Heparine 50 i.u. in saline was delivered until the perfusate was
25 bloodless. A 30-ml TTC- filled syringe was exchanged for the saline syringe and TTC was injected into the left ventricle at a rate of 5 ml/min. Both perfusate solutions were administered at 37.5°C The brains were removed and immersed into 20 ml of 1% TTC contained in tightly closed glass vials. These were further placed for 2 hours in a water bath maintained at 37°C . The TTC solution was decanted, the brains removed, wiped dry and
30 placed into 10% buffered formalin solution for 3 days. Six coronal slices each 2 mm thick, 3,5,7,9,11 and 13mm distal from the frontal pole were obtained with a brain matrix (Harvard Apparatus, South Natick, MA). Infarction areas were measured with a video imaging and analyzer from both sides of the coronal slices and expressed in mm². The volume of the

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infarcted region in mm^3 was calculated by taking the sum of the ischemic areas in all six slices. Infarct volumes are shown in Table 4 below.

5 Neurological score.

The neurological score consists of the sum total of a series of ratings assigned to the performance of specific locomotor activities in a given rat. The scale runs from 0 (fully normal rats) to 13 (fully incapacitated rats). Most parameters are
10 rated as either 0 (normal), or 1 (incapacitated); others are graded. The following tests were used in the present study:

General observational tests: hypoactivity; sedation; piloerection.

15 Motor reflex. Rats were lifted by the tail about 15 cm above the floor. Normal rats assume a posture in which they extend both forelimbs towards the floor and spread the hind limbs to the sides in a trapeze-like manner. MCAO, when severe, causes consistent flexion of the contralateral limb.

20 Motor ability. This is seen as the ability to grasp a rod 1 cm in diameter by the contralateral limb for 5-15 sec when the rat is left hanging on the rod through the arm pit.

25 Motor coordination. Normal rats are able to walk up and down a beam, 5 cm wide placed at a moderate slant. Failure to walk the beam in either direction reveals some motor incoordination, lack of balance and limb weakness .

30 Gait. Ability to restore normal position to either hind contralateral or fore contralateral limb when intentionally displaced while on a narrow beam .

Balance. Ability to grasp and balance on a narrow beam 2 cm wide.

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Locomotor activity. Total movements over a period of 15 min in an automated activity cage.

Ratings assigned to each of the above parameters are given in Table 3

Table 3. Neurological scores assigned to each of 10 parameters of posture and locomotion

Parameter	Score	
a. Activity in home cage	normal=0	hypoactive=1
b. Sedation	none=0	marked=1
c. Piloerection	none=0	marked=1
d. Extension of contralateral forelimb towards floor when lifted by tail	good=0	flexed limb=1
e. Spread of contralateral hind limb when lifted by tail (trapezoid posture)	good=0	flexed limb=1
f. Grasp rod with contralateral limb for 5-15 sec. when suspended by armpit	good=0	poor=1
g. Walk on beam 5cm wide	good=0	poor= 1
h. Restoration of contralateral hind and/or forelimb to original position when intentionally displaced	good=0	poor=1 (one limb) 2 (two limbs)
i. Grasping & balance on beam 2cm wide	good=0	poor= 1
j. Motor activity with respect to control (15min in activity cage)	0-25% of control=3 26-50% of control=2 51-75% of control=1 76-100% of control=0	
k. Tendency to lean on contralateral side	1	
l. Contralateral circling when pulled by tail	1	
m. Contralateral circling spontaneous.	1	

Results

The neurological severity score (NSS) and infarct volume were both significantly lower in the S(-) PAI treated rats than in saline-treated rats, as shown in Table 4.

Table 4. Neurological severity score \pm SEM and brain infarct size \pm SEM in rats after permanent middle cerebral artery occlusion in the rat.

Parameter	S(-)PAI treated	saline treated	p value
Number of rats	24	24	
5 Mean NSS \pm SEM after 24 hours	6.5 \pm 0.48	7.2 \pm 0.36	0.0543
Mean NSS \pm SEM after 48 hours	5.0 \pm 0.41	6.6 \pm 0.44	0.0114
Mean infarct size \pm SEM, (mm ³)	200 \pm 13	240 \pm 11.2	0.0259
10 Percent improvement in NSS over saline treated at 48 hours	24		

Under similar operating conditions, treatment with R(+)PAI resulted in about a 20% improvement in neurological score severity. Thus, neuroprotection in this particular model of neuronal insult was afforded almost equally by both the R- and S-enantiomers of the corresponding N-propargyl-1-aminoindan.

Example 4

Lack of effect of S(-) -PAI on reserpine induced ptosis in rats

20 Reserpine-induced ptosis and its reversal test. Reserpine causes depletion of catecholamine stores, especially norepinephrine. This effect in the live animal is manifested, among other things, in ptosis. Drugs that can prevent or inhibit reserpine-induced ptosis act either directly as noradrenergic agonists, or indirectly by decreasing
25 or preventing the metabolic elimination of endogenous norepinephrine. MAO inhibitors belong to the latter category.

Rats were premedicated with either saline, R(-)deprenyl or S(-)PAI i.p. and then, 2 hours later, were injected with reserpine 5mg/kg i.p. The degree of ptosis was scored
30 on a 0 to 4 scale, where 4 represents eyes completely open, and 0 represents eyes completely closed. The data shown in Table 5 are consistent with the premise that S(-) - PAI does not cause an increase in endogenous norepinephrine concentrations.

Table 5. Mean score of reserpine-induced ptosis (5mg/kg i.p.) with and without premedication with MAO inhibitors. Scores; taken 2 hours following reserpine administration

5

10

Agent	dose (mg/kg)	(n)	Mean score
saline		12	0.86
R(-)Deprenyl	5	3	1.3
	10	6	3.16
S(-)PAI	5	6	1.8
	10	6	2.5
	20	6	1.5

Example 5.

15

Lack of pressor response of intravenous S(-)PAI in the anesthetized cat.

20

Cats were anesthetized with i.v.nembutal 25 mg/kg. Anesthesia was maintained by additional injections of nembutal, 5mg./kg, as needed. The femoral artery was cannulated and connected to a Statham pressure transducer for blood pressure recordings on a Grass multichannel Polygraph. The femoral vein was cannulated for i.v. injection of drugs. The results are given in Table 6 and show that neither mean arterial blood pressure (MABP) nor heart rate (HR) were affected by intravenous S(-)PAI given in increasing doses up to a cumulative dose of 1 mg/kg and as long as 45-60 minutes after injection.

25

Table 6. Changes in mean arterial blood pressure and heart rate in the nembutal anesthetized cat 45-60 min after intravenous injection of S(-)PAI

30

Dose	Change in MABP (mmHg)	Change in HR (beats/min)
0.01	4	-8
0.03	7	-12

Dose	Change in MABP (mmHg)	Change in HR (beats/min)
0.01	-5	-10
0.03	5	8
0.1	-12	0
1.0	2	-5

Example 6.**Lack of effect of S(-)PAI on the pressor response to catecholamines in the cat.**

MAO inhibitors usually potentiate the pressor response to catecholamines because they block their metabolic elimination by the enzyme MAO, especially subtype A. Cats treated with S(-)PAI as described in Example 5 were further challenged with each of the following pressor agents: Phenylephrine, tyramine and norepinephrine. In each case, there was no significant potentiation of the pressor response after pretreatment with S(-)PAI at 1 mg/kg i.v. Results are given in Table 7.

Table 7. Pressor response to intravenous catecholamines in the anesthetized cat, before and after pretreatment with S(-)PAI, given as an i.v. injection of 1 mg/kg

Agent & dose (μ g/kg)	Δ mean arterial pressure (mmHg) before S(-)PAI	Δ mean arterial pressure (mmHg) after S(-)PAI
norepinephrine 0.02	8	12
0.05	23	32
0.10	31	23
0.20	46	46
phenylephrine 0.20	9	2
0.50	17	17
1.0	21	17
2.0	40	42
tyramine 2.0	11	3
5.0	19	9

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Agent & dose ($\mu\text{g/kg}$)	Δ mean arterial pressure (mmHg) before S(-)PAI	Δ mean arterial pressure (mmHg) after S(-)PAI
10.0	26	28
20.0	42	39

5

Example 7.**Lack of cardiovascular effects of S(-)PAI in the conscious rat after acute oral administration.**

10 A chronic-indwelling catheter was implanted in the caudal artery under light anesthesia with avertin. The animals were allowed to recover and were tested 24 hours after implantation. The catheter was connected to a Statham pressure transducer and blood pressure was recorded on a Grass multichannel Polygraph. During this period, the rat was
15 kept in its home cage in order to minimize handling and undue manipulations known to affect blood pressure.

Two strains of rats were used: WKY rats and matching SHR (Spontaneously Hypertensive Rats) rats. WKY rats were from a local strain, weighing about 250g each. In
20 these, the maximum fluctuations of the mean arterial pressure (MAP) and heart rate (HR) were 8 mmHg and 49 beats per min, respectively, in the resting state.

SHR rats were purchased from Charles River breeders, England. The animals were allowed to acclimatize and recover from the journey and were used at the age of three months, in order
25 to match their WKY controls. SHR hypertension develops gradually from the age of one month to the age of three months. At this stage, blood pressure is already elevated above normotensive levels.

S(-)PAI was administered in a volume of 10ml/kg. Blood pressure and heart rate were then
30 monitored for the duration of 45-60 minutes. Results are given in Table 8 and show that acute oral administration of S(-)PAI had no effect on either parameter in either strain of rats.

Table 8. Cardiovascular effects of S(-)PAI in conscious rats 45-60 min after oral administration.

	Rat Strain	Dose	Change in MBAP (mmHg)	Change in HR (beats/min)
5	WKY	1	-9	70
			-24	-130
		2	-6	-20
			9	70
10		5	0	0
			0	0
		10	0	0
		20	0	0
			-12	0
15	SHR	1	-16	-30
		2	-12	0
		5	13	0
			-6	-40
20		10	4	0

Example 8.

Lack of effect of S(-)PAI on systolic blood pressure in SHR rats after chronic oral administration at 2 mg/kg/day.

25 Spontaneously hypertensive rats, three month-old, were used. Each rat was given a daily dose of 2 mg/kg S(-) PAI in tap water 10 ml/kg. Controls received an equivalent volume of tap water. Treatment lasted 14 days. During this period, systolic blood pressure was monitored on days 0, 4, 7 and 11, using a tail-cuff procedure. On day 14, systolic blood pressure was
 30 determined using the indwelling catheter procedure described in Example 7. The results are given in Tables 9 and 10. Chronic oral treatment with S(-)PAI at 2 mg/kg/day had no effect on the intraindividual and interindividual profile of systolic blood pressure and heart rate.

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Table 9. Effect of S(-)PAI (2mg/kg p.o.) on systolic blood pressure and heart rate measured by tail cuff in SHR rats over a 2 week period.

5		Day of Treatment	Change in Mean Systolic Blood Pressure (mmHg)	Change in Heart rate (beats/min)
	TAP WATER	0	169.55±7.73	374.09±37.17
		4	177.82±9.08	403±23.3
		7	177.67±10.21	392.67±24.66
10		11	178±8.65	371.25±27.22
	S(-)PAI	0	166.88±6.11	404.13±32.86
		4	168.5±12.8	394.5±37.43
		7	172.13±14.62	394.38±24.47
		11	167.43±14.23	408±40.04

Table 10. Cardiovascular effect of 2-week chronic oral treatment with S(-)PAI in SHR rats measured directly by an implanted catheter.

	Mean arterial blood pressure	Systolic blood pressure	Heart rate
TAP WATER	107.65±9.59	138.37±13.41	404.55±49.82
S(-)PAI	107.88±5.35	140.79±6.55	366.11±34.99

Example 9

Lack of effect of S(-)PAI on body weight in SHR rats after chronic oral dosing at 2 mg/kg/day.

25

The rats used in Example 8 above, were additionally monitored for weight gain/loss as an additional marker for the rate of food consumption. MAO inhibitors usually elevate central catecholamines which may depress appetite. Chronic treatment with S(-)PAI at 2 mg/kg/day had no effect on body weight throughout 14 days of treatment. Results are given in Table 11.

30

Table 11. Effect on SHR rat body weight after 2 week chronic oral treatment with S(-)PAI.

	Day	Weight (g)
TAP WATER	0	317±32.64
	7	302.22±35.17
	14	312.89
S(-)PAI	0	294.13±32.06
	7	292.25±28.47
	14	307.33±24.13

Summary

Examples 4-9 show that S(-)PAI has minimal or no effect on several MAO mediated effects.

Example 10

Effect of S(-)PAI following closed head injury (CHI) in mice

The procedure for closed head injury followed was as described for rats in Shohami et al. (J Neurotrauma (1993) 10(2) 109-119) with changes as described.

Animals: Male Sabra mice (Hebrew University strain) weighing 34-40g were used. They were housed in groups of 10 per cage, in a 12hr:12hr light:dark cycle. Food and water were provided ad libitum.

25

Trauma was induced under anaesthesia. A longitudinal incision was performed in the skin covering the skull and the skin retracted to expose the skull. The head was fixed manually at the lower plane of the impact apparatus. A weight of 333g was delivered by an electric device from a distance of 3cm to the left hemisphere, 1-2mm lateral to the midline in the midcoronal plane. S-PAI was injected sub-cutaneously (1mg/kg) once 15 min. after CHI.

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Assessment of Motor Function.

Motor function and reflexes were evaluated in the injured mice at different times after closed head injury (CHI) using a neurological severity score (NSS*) as shown in Table 12 below, which is modified from that described for rats. One point was awarded for the lack of a tested reflex or for the inability to perform the tasks outline in the Table. The maximal score that can be reached at 1 hour post-CHI is 25 points and at later times, 21 points. The difference in NSS at 1hr and at any other time reflects the spontaneous recovery, and is referred to as Δ NSS. A score of 15-19 at 1hr denotes severe injury, 11-14 denotes moderate injury and less than 10 denotes mild injury.

- 10 * The NSS assessed in this Example is different from that in Example 3, both in the parameters assessed and in the scoring system.

Table 12 Neurological Severity Score for mice after Closed Head Injury

15	Parameter	Points at 1 hour post-CHI	Points at any other time
	Inability to exit from a circle (30cm diameter) when left in its center		
	for 30min	1	
	for 60 min	1	
	for >60 min	1	1
20	Loss of righting reflex		
	for 10 second	1	
	for 20 seconds	1	
	for >30 seconds	1	1
	Hemiplegia - inability of mouse to resist forced changes in position	1	1
	Flexion of hind limb when lifted by tail	1	1
25	Inability to walk straight when placed on the floor	1	1
	Reflexes		
	Pinna reflex	1	1
	Corneal reflex	1	1
	Startle reflex	1	1
	Clinical grade		
	Loss of seeking behaviour	1	1
30	Prostration	1	1

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Parameter	Points at 1 hour post-CHI	Points at any other time
Loss of reflexes		
Left forelimb	1	1
Right forelimb	1	1
Left hindlimb	1	1
Right hindlimb	1	1
Functional test		
Failure in beam balancing task (0.5cm wide)		
for 20 seconds	1	1
for 40 seconds	1	1
for > 60 seconds	1	1
Failure in round stick balancing task (0.5cm in diameter)		
for 10 seconds	1	1
Failure in beam walking task		
3cm wide	1	1
2cm wide	1	1
1cm wide	1	1
Maximum Points	25	21

15

Assessment of Reference Memory

Morris Water Maze Test: the water maze consists of a circular aluminium pool, 1m in diameter and 60cm in depth, filled with water to a depth of 17.5cm. The hidden goal platform is a glass vessel (15cm diameter x 16.5cm height) placed upside down at a fixed location in the pool, 1cm below the surface of the water. The water temperature is maintained at 24°C and the pool is always placed in the same position in the room to provide the same extra-maze cues. Prior to CHI, mice were given 3 trials per day for 5 consecutive days to establish a baseline performance - measured as the latency to find the platform from the same start location. Commencing 24hr after CHI mice were retested daily for 2 weeks in 3 trials per day.

25

ResultsAssessment of Motor Function.

Table 13. Change in Neurological Severity Score after Closed Head Injury in Mice

30

Drug/dose	N	Δ NSS, 24 hr post-CHI	Δ NSS, 7 days post-CHI	Δ NSS, 14 days post-CHI
Saline, 1ml/kg	51	4.75 \pm 0.17	5.83 \pm 0.36	5.96 \pm 0.4
S(-)PAI, 1mg/kg	16	5.06 \pm 0.25	7.19 \pm 0.28	7.88 \pm 0.36

Assessment of Reference Memory

Figure 1 shows the reduction in latency for mice treated with S(-)PAI compared to saline treated controls after CHI. It appears that immediately post-CHI mice forget the location of
5 the goal. Memory is enhanced following treatment with S(-)PAI, as compared to saline treated mice.

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The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. Pharmaceutical compositions for the treatment of a neurological disorder for
5 neurotrauma or for improving memory in a post-closed head injury (CHI) patient, comprising
a therapeutically effective amount of S-(-)-N-propargyl-1-aminoindan or a pharmaceutically
acceptable salt thereof as active ingredient, and a pharmaceutically active carrier.
2. Pharmaceutical compositions according to claim 1 wherein no S-(-)-N-
10 propargyl-1-aminoindan hydrochloride is present.
3. A pharmaceutical composition according to claims 1 or 2, adapted for oral,
rectal, intra-venous, transdermal or parenteral administration.
- 15 4. A pharmaceutical composition according to claims 1 to 3 in unit dosage form
comprising from about 0.1 mg to about 100 mg of said active ingredient.
5. A pharmaceutical composition according to claim 4 comprising from about 10
mg to about 100 mg of said active ingredient.
20
6. A pharmaceutical composition according to any one of claims 1 or 3 to 5
comprising as active ingredient the hydrochloride, mesylate, esylate or sulfate salt of S-(-)-N-
propargyl-1-aminoindan.
- 25 7. A pharmaceutical composition according to any one of claims 1 to 6 for
treating a neurological disorder or neurotrauma comprising damage caused to the central
peripheral nervous system as a result of ischemic damage, stroke, hypoxia or anoxia,
neurodegenerative diseases. Parkinson's Disease, Alzheimer's Disease, neurotoxic injury,
head trauma injury, or spinal trauma injury.
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8. A pharmaceutical composition according to claim 1 for improving memory in a post-CHI patient.

9. Use of S-(-)-N-propargyl-1-aminoindan or a pharmaceutically acceptable salt thereof as a medicament for the treatment of a neurological disorder for neurotrauma or for improving memory in a post-closed head injury (CHI) patient.

10. Use of S-(-)-N-propargyl-1-aminoindan for the use according to claim 9, wherein the medicament is adapted for oral, rectal, intra-venous, transdermal or parenteral administration.

11. Use of S-(-)-N-propargyl-1-aminoindan according to claim 9 wherein a dosage of said medicament is from about 1 mg to about 100 mg.

12. The use according to claim 11 wherein the dosage is from about 10 mg to about 100 mg.

13. The use according to claim 9 wherein the hydrochloride, mesylate, esylate and sulfate salt of S-(-)-N-propargyl-1-aminoindan is used.

14. The use according to claim 9, wherein the medicament is for the treatment of a neurological disorder or neurotrauma comprising damage caused to the central nervous system as a result of ischemic damage, stroke, hypoxia or anoxia, neurodegenerative diseases, Parkinson's Disease, Alzheimer's Disease, neurotoxic injury, head trauma injury, or spinal trauma injury.

15. The use according to claim 9, wherein the medicament is for improving the memory in a post-CHI patient.

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16. Use of S-(-)-N-propargyl-1-aminoindan or a pharmaceutically acceptable salt thereof in the manufacture of medicaments for the treatment of a neurological disorder or neurotrauma.

5 17. Use according to claim 16, wherein the medicaments are adapted for oral, rectal, intra-venous, transdermal or parenteral administration.

18. Use according to claim 16, wherein the medicaments comprise S-(-)-N-propargyl-1-aminoindan or a salt thereof at a dosage from about 0.1 mg to about 100 mg.

10

19. Use according to claim 18, wherein the dosage is from about 10 mg to about 100 mg.

20. Use according to claim 16 of the hydrochloride, mesylate, esylate, or sulfate
15 salt of S-(-)-N-propargyl-1-aminoindan.

21. Use according to claim 16, wherein the neurological disorder or neurotrauma comprises damage caused to the central or peripheral nervous system as a result of ischemic damage, stroke, hypoxia or anoxia, neurodegenerative diseases, Parkinson's Disease,
20 Alzheimer's Disease, neurotoxic injury, head trauma injury, or spinal trauma injury.

22. Use of S-(-)-N-propargyl-1-aminoindan or a pharmaceutically acceptable salt thereof as active ingredient in the manufacture of medicaments for improving memory in a post-closed head injury (CHI) patient.

25

23. Use of (S)-N-propargyl-1-aminoindan or a pharmaceutically acceptable salt thereof to treat neurotrauma.

24. Use of (S)-N-propargyl-1-aminoindan or a pharmaceutically acceptable salt
30 thereof to treat a neurodegenerative disease.

25. Use of (S)-N-propargyl-1-aminoindan or a pharmaceutically acceptable salt thereof to treat neurotoxic injury.
26. Use of (S)-N-propargyl-1-aminoindan or a pharmaceutically acceptable salt thereof to treat brain ischemia.
27. Use of (S)-N-propargyl-1-aminoindan or a pharmaceutically acceptable salt thereof to treat stroke.
28. Use of (S)-N-propargyl-1-aminoindan or a pharmaceutically acceptable salt thereof to treat neural injury following an episode of hypoxia or anoxia.
29. Use of (S)-N-propargyl-1-aminoindan or a pharmaceutically acceptable salt thereof to treat head trauma injury.
30. Use of (S)-N-propargyl-1-aminoindan or a pharmaceutically acceptable salt thereof to treat spinal trauma injury.
31. Use of (S)-N-propargyl-1-aminoindan or a pharmaceutically acceptable salt thereof to prevent nerve death.
32. Use of (S)-N-propargyl-1-aminoindan or a pharmaceutically acceptable salt thereof to treat memory disorder in a post-closed head injury (CHI) patient.

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Fig. 1

