960171-8 IPOS

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WO 94/13287 PCT/EP93/03389

Use of 2-amino-6-A-propyl-amino-4,5,6,7-tetrahydrobenzothiazole (pramipexol) as a pharmaceutical composition having an antidepressant activity

The present invention relates to the use of 2-amino-6-n-propyl-amino-4,5,6,7-tetrahydrobenzothiazole, particularly the (-)-enantiomer thereof, and the pharmacologically acceptable acid addition salts thereof as pharmaceutical compositions having an antidepressant activity.

The compounds referred to above are known as pharmaceutical compositions primarily for treating schizophrenia and Parkinson's disease. Details of the preparation of these compounds, the (-)-enantiomers of which are also referred to in the literature as SND 919 or pramipexol, can be found in European Patent Application EP-A 85 116 016. Surprisingly, it has now been found that pramipexol has antidepressant properties. Particularly significant in this context is that the compound has an unexpectedly low α-receptor affinity and thus has a highly selective activity whilst being extremely well tolerated. The previously unknown long duration of activity of pramipexol (half life 12.5 hours) and its unexpectedly high bioavailability of more than 80% have proved particularly advantageous in the use of this substance as an antidepressant.

The antidepressant activity of pramipexol was demonstrated in preclinical trials in the "forced swimming test". Details of this behavioural test are described for example by Willner, Psychopharmacology 83, 1 - 16 (1984) and by Borsini and Meli, Psychopharmacology 94, 147 - 160 (1988).

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Pramipexol (SND 919) was investigated on eight rats, by comparison with amineptine, a known antidepressant. Both substances were dissolved in physiological saline solution and administered by parenteral route. The results are shown in Table 1.

Table 1: Investigation of SND 919 and amineptine in the "forced swimming test"

Compound	Dose mg/kg	Immobility time (sec.)
Saline solution	-	208 ± 10
SND 919	0.03	210 ± 14
SND 919	0.10	165 ± 6
SND 919	0.30	102 ± 17
Amineptine	20.00	134 ± 19

The results obtained demonstrate that SND 919 is clearly superior to amineptine.

Pramipexol can be given for the treatment of depression, in the form of conventional galenic preparations consisting essentially of an inert pharmaceutical carrier and an effective dose of the active substance, e.g. plain or coated tablets, capsules, lozenges, powders, solutions, suspensions, emulsions, syrups, suppositories, etc. A therapeutically active single dose for the indication discovered according to the invention is within the range from 0.1 to 30 mg, preferably from 1 to 5 mg. In addition to being administered by oral or intravenous route pramipexol may also be taken transdermally. Suitable release systems for this purpose are known from the prior art, e.g. European Patent Application 428 038.

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Example 1

Tablet core containing 5 mg of 2-amino-6-n-propyl-amino-4,5,6,7-tetrahydro-benzothiazole-dihydrochloride

Composition:
1 tablet core contains:

SND 919	5.0 mg
Lactose	33.5 mg
Corn starch	10.0 mg
Gelatine	1.0 mg
Magnesium stearate	0.5 mg
	50.0 mg

Method of preparation

The mixture of the active substance with lactose and corn starch is granulated with a 10% aqueous gelatine solution through a 1 mm mesh screen, then dried at 40°C and rubbed through the same screen once more. The granules thus obtained are mixed with magnesium stearate and compressed to form tablet cores. The procedure must be carried out in a darkened room.

Weight of core:	50 mg
Punch:	5 mm, convex

The tablet cores thus obtained are coated by known methods with a coating consisting essentially of sugar and talc. The finished coated tablets are polished with beeswax.

Weight of coated tablet: 100 mg

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Example 2

Drops containing 5 mg of 2-amino-6-n-propyl-amino-4,5,6,7-tetrahydro-benzothiazole-dihydrochloride

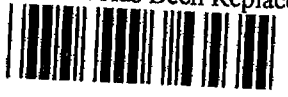
Composition:
100 ml of drops contain:

Methyl-p-hydroxybenzoate		0.035	g
n-Propyl-p-hydroxybenzoate		0.015	g
Aniseed oil		0.05	g
Menthol		0.06	g
Pure ethanol		10.0	g
SND 919		0.5	g
Citric acid		0.7	g
Sodium phosphate sec. x $2H_2O$		0.3	g
Sodium cyclamate		1.0	g
Glycerol		15.0	g
Distilled water	ad	100.0	ml

Method of preparation:

The p-hydroxybenzoates, aniseed oil and menthol are dissolved in ethanol (solution I). The buffer substances, the active substance and sodium cyclamate are dissolved in distilled water and glycerol is added (solution II). Solution I is stirred into solution II and the mixture is made up to the specified volume with distilled water. The finished drops solution is filtered through a suitable filter. The drops solution must be prepared and bottled away from the light and under protective gas.

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Example 3

Suppositories containing 10 mg of 2-amino-6-n-propyl-amino-4,5,6,7-tetrahydro-benzothiazole-dihydrochloride

1 suppository contains:

SND 919	10.0 mg
Suppository mass (e.g. Witepsol W 45)	1690.0 mg
	1700.0 mg

Method of preparation:

The finely powdered substance is stirred into the molten suppository mass cooled to 40°C, using an immersion homogeniser. At 35°C the mass is poured into slightly chilled moulds.

Weight of suppository: 1.7 g

Example 4

Ampoules containing 5 mg of 2-amino-6-n-propyl-amino-4,5,6,7-tetrahydro-benzothiazole-dihydrochloride

1 ampoule contains:

SND 919		5.0 mg
Citric acid		7.0 mg
Sodium phosphate sec. x $2H_2O$		3.0 mg
Sodium pyrosulphite		1.0 mg
Distilled water	ad	1.0 ml

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Method of preparation:

The buffer substances, active substance and sodium pyrosulphite are dissolved successively in water which has been decocted and cooled under CO_2 gas. The solution is made up to the specified volume with decocted water and filtered free from pyrogens.

Packaging:	in brown ampoules under protective gas
Sterilisation:	20 minutes at 120°C

The ampoule solution must be prepared and packaged in a darkened room.

Example 5

Coated tablets containing 10 mg of 2-amino-6-n-propyl-amino-4,5,6,7-tetrahydrobenzothiazole-dihydrochloride

1 tablet core contains:

SND 919	10.0 mg
Lactose	35.5 mg
Corn starch	12.0 mg
Gelatine	1.0 mg
Magnesium stearate	0.5 mg
	59 mg

Method of preparation:

As in Example 1.

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Claims

1. Use of 2-amino-6-n-propyl-amino-4,5,6,7-tetrahydrobenzothiazole and the pharmacologically acceptable acid addition salts thereof for treating depression.

2. Use of (-)-2-amino-6-n-propyl-amino-4,5,6,7-tetrahydrobenzothiazole and the pharmacologically acceptable acid addition salts thereof as pharmaceutical compositions having an antidepressant activity.

3. Use of 2-amino-6-n-propyl-amino-4,5,6,7-tetrahydrobenzothiazole and the pharmacologically acceptable acid addition salts thereof for preparing a pharmaceutical composition for treating depression.

4. Use of (-)-2-amino-6-n-propyl-amino-4,5,6,7-tetrahydrobenzothiazole and the pharmacologically acceptable acid addition salts thereof for preparing a pharmaceutical composition for treating depression.

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Abstract

The invention relates to the use of pramipexol as a pharmaceutical composition having an antidepressant activity.

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Menthol		0.06	g
Pure ethanol		10.0	g
SND 919		0.5	g
Citric acid		0.7	g
Sodium phosphate sec. x $2H_2O$		0.3	g
Sodium cyclamate		1.0	g
Glycerol		15.0	g
Distilled water	ad	100.0	ml

Method of preparation:

The p-hydroxybenzoates, aniseed oil and menthol are dissolved in ethanol (solution I). The buffer substances, the active substance and sodium cyclamate are dissolved in distilled water and glycerol is added (solution II). Solution I is stirred into solution II and the mixture is made up to the specified volume with distilled water. The finished drops solution is filtered through a suitable filter. The drops solution must be prepared and bottled away from the light and under protective gas.

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Method of preparation:

The buffer substances, active substance and sodium pyrosulphite are dissolved successively in water which has been decocted and cooled under CO_2 gas. The solution is made up to the specified volume with decocted water and filtered free from pyrogens.

Packaging:	in brown ampoules under protective gas
Sterilisation:	20 minutes at 120°C

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As in Example 1.

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3. Use of 2-amino-6-n-propyl-amino-4,5,6,7-tetrahydrobenzothiazole and the pharmacologically acceptable acid addition salts thereof for preparing a pharmaceutical composition for treating depression.

4. Use of (-)-2-amino-6-n-propyl-amino-4,5,6,7-tetrahydrobenzothiazole and the pharmacologically acceptable acid addition salts thereof for preparing a pharmaceutical composition for treating depression.

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Date: 18/2/97

ABSTRACT

USE OF 2-AMINO-6-A-PROPYL-AMINO-4,5,6,7-TETRAHYDROBENZOTHIAZOLE (PRAMIPEXOL) AS A PHARMACEUTICAL COMPOSITION HAVING AN ANTIDEPRESSANT ACTIVITY

The invention relates to the use of pramipexol as a pharmaceutical composition having an antidepressant activity.

Claims

1. Use of 2-amino-6-n-propyl-amino-4,5,6,7-tetrahydrobenzothiazole and the pharmacologically acceptable acid addition salts thereof for preparing a pharmaceutical composition for treating depression.

2. Use of (-)-2-amino-6-n-propyl-amino-4,5,6,7-tetrahydrobenzothiazole and the pharmacologically acceptable acid addition salts thereof for preparing a pharmaceutical composition for treating depression.

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