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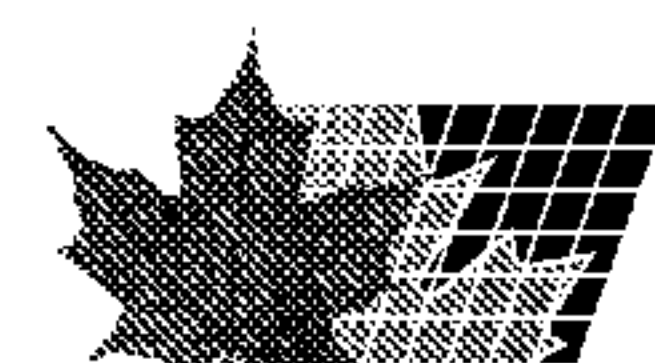
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(54) Titre : PRAMIPEXOL DESTINE AU TRAITEMENT DE LE THADA
(54) Title: PRAMIPEXOLE FOR THE TREATMENT OF ADHD

(57) **Abrégé/Abstract:**

The invention relates to the use of 2-amino-4,5,6,7-tetrahydro-6-n-propylamino-benzothiazole, the (+) or (-) enantiomers thereof, the pharmacologically acceptable acid addition salts of the same, and hydrates and solvates for producing a pharmaceutical for the prevention and/or treatment of ADHD.



Abstract

The invention relates to the use of 2-amino-4,5,6,7-tetrahydro-6-n-propylamino-
5 benzothiazole, the (+) or (-) enantiomer thereof, the pharmacologically acceptable
acid addition salts thereof as well as hydrates and solvates for preparing a
pharmaceutical composition for the prevention and/or treatment of ADHD.

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Pramipexole for the treatment of ADHD

The invention relates to the use of 2-amino-4,5,6,7-tetrahydro-6-n-propylamino-
5 benzothiazole, the (+) or (-) enantiomer thereof, the pharmacologically acceptable
acid addition salts thereof as well as hydrates and solvates for preparing a
pharmaceutical composition for the prevention and/or treatment of ADHD.

Background to the invention

10 2-Amino-6-n-propylamino-4,5,6,7-tetrahydrobenzo-thiazole is a dopamine agonist
which is also known in the art by the name pramipexole. Pramipexole and processes
for preparing it are known for example from EP-A-186 087 and US 4,886,812. It is
known in particular for the treatment of schizophrenia and particularly for the
treatment of Parkinson's disease. The prior art further discloses for example that
15 pramipexole lowers the prolactin serum level (DE 38 43 227).

Description of the invention

Surprisingly it has been found that pramipexole can be used in therapeutically
effective doses for the prevention and/or treatment of ADHD.

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Accordingly, the present invention relates to the use of 2-amino-4,5,6,7-tetrahydro-6-
n-propylamino-benzothiazole, optionally in the form of its (+) or (-) enantiomer,
optionally in the form of the pharmacologically acceptable acid addition salts as well
as hydrates and solvates for preparing a pharmaceutical composition for the
25 prevention and/or treatment of ADHD.

The abbreviation ADHD stands for "attention deficit hyperactivity disorder". It denotes
a disorder which affects both children and adults in the form of an attention deficit.
ADHD also refers to a hyperactivity disorder which is also observed both in children
30 and adults. Depending on which of the above disorders predominates, ADHD may
be observed in different degrees. There is the combined type in which both an
attention deficit and a hyperactivity disorder can be observed, the predominantly
inattentive type and the predominantly hyperactive-impulsive type.

35 The combined type is present when at least six out of nine symptoms of the attention
disorder and hyperactivity/impulsivity persist for at least six months. If at least six
symptoms of attention deficit but fewer than six of hyperactivity/impulsivity have
persisted for at least six months it is the predominantly inattentive type. The
predominantly hyperactive-impulsive type is present when at least six symptoms of

hyperactivity/impulsivity but fewer than six of attention deficit have persisted for a period of at least six months.

The following criteria of assessment are symptoms of inattentiveness and
5 hyperactivity, which form the basis for classifying the abovementioned types of
ADHD (according to DSM IV = diagnostic and statistical manual of psychic disorders,
Version IV):

Inattentiveness

- 10 (a) frequently takes no notice of details or makes errors of haste in schoolwork, at
work or in other activities;
- (b) often has difficulty maintaining concentration for lengthy periods during tasks or
when playing;
- (c) frequently appears not to be listening when spoken to by other people;
- (d) often does not fully carry out instructions from other people and cannot complete
15 schoolwork, other work or duties in the workplace;
- (e) frequently has problems organising tasks and activities;
- (f) frequently avoids, is disinclined to do or often only undertakes under protest tasks
which require sustained mental effort;
- (g) frequently loses objects that he/she needs for tasks or activities;
- 20 (h) is often easily distracted by external stimuli;
- (i) is often forgetful during everyday activities;

Hyperactivity

- (a) frequently fidgets with hands or feet or shifts around on the chair;
- (b) often stands up in class or in other situations where people are expected to stay
25 seated ;
- (c) frequently runs around or climbs up excessively in situations where this is
inappropriate (in young people or adults this may be restricted to a subjective
feeling of restlessness);
- (d) often has trouble playing quietly or occupying him/herself quietly with leisure
30 activities;
- (e) is often "on the go" or frequently acts as if he/she were "driven";
- (f) often talks excessively; impulsiveness;
- (g) often bursts out with the answers before the question is finished;
- (h) has trouble waiting his/her turn;
- 35 (i) often interrupts and disturbs other people (e.g. interrupts conversations or breaks
into other people's games).

Accordingly the present invention relates to the use of 2-amino-4,5,6,7-tetrahydro-6-n-propylamino-benzothiazole, optionally in the form of the (+) or (-) enantiomer thereof, optionally in the form of the pharmacologically acceptable acid addition salts thereof as well as hydrates and solvates for preparing a pharmaceutical composition
5 for the prevention and/or treatment of attention deficits.

Moreover, the present invention relates to the use of 2-amino-4,5,6,7-tetrahydro-6-n-propylamino-benzothiazole, optionally in the form of the (+) or (-) enantiomer thereof, optionally in the form of the pharmacologically acceptable acid addition salts thereof
10 as well as hydrates and solvates for preparing a pharmaceutical composition for the prevention and/or treatment of hyperactivity disorders.

In another aspect the present invention relates to the use of 2-amino-4,5,6,7-tetrahydro-6-n-propylamino-benzothiazole, optionally in the form of the (+) or (-)
15 enantiomer thereof, optionally in the form of the pharmacologically acceptable acid addition salts thereof as well as hydrates and solvates for preparing a pharmaceutical composition for the prevention and/or treatment of hyperactivity disorders accompanied by attention deficit.

20 For treatment and/or prevention of the medical indications described above, in addition to monotherapy using pramipexole it is also possible, as an alternative, to carry out a combined therapy using pramipexole with one or more, preferably one other pharmaceutically active compound. It may prove effective, for example, to use a combination with active substances selected from among the α -sympathomimetics
25 and antidepressants, preferably tricyclic antidepressants, antidepressants of the SSRI or antidepressants of the MAO type.

In the case of a combined therapy pramipexole may preferably be used to treat the abovementioned conditions with one or more, preferably one of the following
30 substances: methylphenidate, amphetamine, amphetaminil, methamphetamine, pemoline, tomoxetin, desipramine, imipramine, bupropion and modafinil, of which methylphenidate, amphetamine, pemoline, tomoxetin and modafinil are particularly preferred.

35 Pramipexole may be used within the scope of the present invention as a racemate, in the form of its (+) or (-) enantiomer. Moreover, pramipexole may be used in the form of the pharmaceutically acceptable acid addition salts thereof as well as optionally in the form of its hydrates and/or solvates. By pharmaceutically acceptable acid addition salts are meant according to the invention the salts selected from the salts

of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid and maleic acid, of which the salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid and acetic acid are particularly preferred. The salts of hydrochloric acid are particularly important. Most preferably, within the scope of the present invention, therefore, the hydrochlorides of pramipexole are used, pramipexole dihydrochloride being of particular significance. Of the hydrates of pramipexole, pramipexole dihydrochloride monohydrate is particularly preferred.

The dosage of pramipexole naturally depends to a great extent on the clinical picture. For example, without restricting the present invention thereto, pramipexole may be used in doses of about 0.05 to 7.5 mg, preferably 0.1 to 5 mg per day. These doses are based on pramipexole in the form of its free base. Based on the salt form pramipexole dihydrochloride monohydrate which is preferably used, the doses mentioned above correspond to about 0.07 to 10.65 mg, preferably 0.14 to 7.1 mg of pramipexole dihydrochloride monohydrate per day.

One possible dosing method, which is to be understood as being merely an illustrative example, is described below, based on pramipexole in the form of its free base: individual dosage titration at weekly intervals depending on activity and acceptability.

1st week: 1 tablet containing 0.088 mg of pramipexole 3 times a day;

2nd week: 1 tablet containing 0.18 mg of pramipexole 3 times a day;

3rd week and thereafter: 1/2 tablet containing 0.7 mg of pramipexole 3 times a day.

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Within the scope of the use according to the invention pramipexole may be administered orally, transdermally, intrathecally, by inhalation or parenterally. Suitable preparations include for example tablets, capsules, suppositories, solutions, syrups, emulsions, dispersible powders or patches. Regarding possible embodiments of a transdermal preparation which may be used according to the invention we now refer to the embodiments described by way of example in US 5112842, to which reference is hereby expressly made. Suitable tablets may be produced for example by mixing the active substance or substances with known excipients, for example inert diluents, such as calcium carbonate, calcium phosphate or lactose, disintegrants such as corn starch or alginic acid, binders such as starch or gelatine, lubricants such as magnesium stearate or talc, and/or agents for achieving delayed release such as carboxymethylcellulose, cellulose acetate phthalate, or polyvinyl acetate. The tablets may also consist of several layers.

The following are some examples of pharmaceutical preparations which may be used according to the invention. These are intended solely as an illustration without restricting the subject matter of the invention thereto.

5 **Tablet 1:**

	Ingredients:	mg
	pramipexole dihydrochloride monohydrate	1.00
	mannitol	121.50
10	maize starch	79.85
	highly dispersed silicon dioxide, anhydrous	2.30
	Polyvidone K25	2.35
	magnesium stearate	3.00
	Total	210.00

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Tablet 2:

	Ingredients:	mg
	pramipexole	0.5
20	mannitol	122.0
	maize starch. dried	61.8
	maize starch	18.0
	highly dispersed silicon dioxide, anhydrous	2.4
	Polyvidone K25	2.3
25	magnesium stearate	3.0
	Total	210.0

Tablet 3:

30

	Ingredients:	mg
	pramipexole	0.25
	mannitol	61.00
	maize starch	39.90
35	highly dispersed silicon dioxide, anhydrous	1.20
	Polyvidone K25	1.15
	magnesium stearate	1.5
	Total	105.00

Tablet 4:

	Ingredients:	mg
	pramipexole	0.125
5	mannitol	49.455
	maize starch dried	25.010
	maize starch	7.300
	highly dispersed silicon dioxide, anhydrous	0.940
	Polyvidone K25	0.940
10	magnesium stearate	1.230
	Total	85.000

Solution for injection:

15	pramipexole dihydrochloride monohydrate	0.3 mg
	sodium chloride	0.8 mg
	benzalkonium chloride	0.01 mg
	water for injections ad 100 ml	

Patent Claims

- 1) Use of 2-amino-4,5,6,7-tetrahydro-6-n-propylamino-benzothiazole, optionally in the form of the pharmacologically acceptable acid addition salts thereof as well as hydrates and solvates for preparing a pharmaceutical composition for the prevention and/or treatment of ADHD.
- 2) Use according to claim 1, characterised in that 2-amino-4,5,6,7-tetrahydro-6-n-propylamino-benzothiazole is used in the form of the (+) or (-) enantiomer thereof.
- 3) Use according to claim 1 or 2, for the prevention and/or treatment of attention deficits.
- 4) Use according to claim 1 or 2, for the prevention and/or treatment of hyperactivity disorders.
- 5) Use according to claim 1 or 2, for the prevention and/or treatment of hyperactivity disorders accompanied by attention deficits.
- 6) Use according to one of claims 1 to 5, characterised in that pramipexole is used in combination with one or more other pharmaceutical substances.
- 7) Use according to claim 6, characterised in that the active substance is selected from among the α -sympathomimetics and antidepressants.
- 8) Use according to claim 6 or 7, characterised in that pramipexole is used with one or more active substances selected from among methylphenidate, amphetamine, amphetaminil, methamphetamine, pemoline, tomoxetin, desipramine, imipramine, bupropion and modafinil.
- 9) Use according to one of claims 1 to 8, characterised in that pramipexole is used in the form of a pharmaceutically acceptable acid addition salt which is selected from the salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid and maleic acid.
- 10) Use according to one of claims 1 to 9, characterised in that pramipexole is used in doses of about 0.05 to 7.5 mg, preferably about 0.1 to 5 mg per day.