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CA 2532308 A1 2005/01/27

(21) **2 532 308**

(12) **DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION**

(13) **A1**

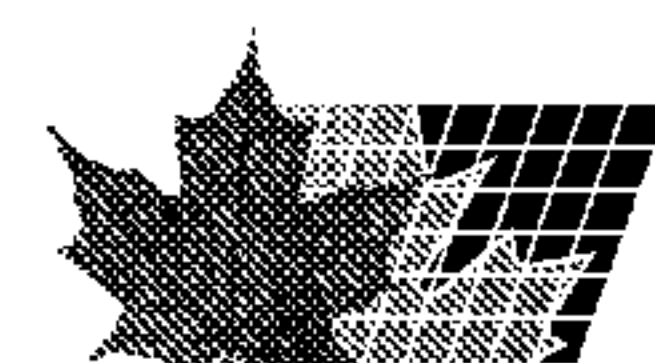
(86) Date de dépôt PCT/PCT Filing Date: 2004/07/15
(87) Date publication PCT/PCT Publication Date: 2005/01/27
(85) Entrée phase nationale/National Entry: 2006/01/13
(86) N° demande PCT/PCT Application No.: EP 2004/007851
(87) N° publication PCT/PCT Publication No.: 2005/007148
(30) Priorité/Priority: 2003/07/16 (103 32 473.9) DE

(51) Cl.Int./Int.Cl. **A61K 31/137** (2006.01),
A61P 25/08 (2006.01)
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(54) Titre : **AMBROXOL POUR LE TRAITEMENT DE L'EPILEPSIE**
(54) Title: **AMBROXOL FOR TREATING EPILEPSY**

(57) **Abrégé/Abstract:**

The invention concerns the use of ambroxol and its pharmaceutically acceptable salts for producing a medicine for treating epilepsy.



Abstract

The invention relates to the use of ambroxol and the pharmacologically acceptable salts thereof for preparing a pharmaceutical composition for the treatment of
5 epilepsy.

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Ambroxol for the treatment of epilepsy

The invention relates to the use of ambroxol and the pharmacologically acceptable
5 salts thereof for preparing a pharmaceutical composition for the treatment of
epilepsy.

Background to the invention

The active substance ambroxol (trans-4-(2-amino-3,5-dibromobenzylamino)-
10 cyclohexanol) is a known local anaesthetic, antitussive and expectorant. In addition,
ambroxol's effect as a sodium channel blocker is described in the literature (Society
for Neuroscience Abstracts, 2000, Vol. 26, No. 1-2). The potential activity of sodium
channel blockers as agents for treating epilepsy is also known from the prior art (Choi
H, Morrell MJ 2003, Expert Opin Pharmacother 4(2), 243-51).

15 Known sodium channel blockers which are used to treat epilepsy are, however,
limited in their efficacy. In addition, they frequently have undesirable side effects
(Perucca et al. 2000, Epilepsy Res 41, 107-139).

It is also known from the prior art that calcium channel blockers, such as for example
gabapentin, which inhibits the calcium channels directly or indirectly - by modulating
20 the expression of the alpha2delta subunit - (Alden KJ, Garcia J 2001, J Pharmacol
Exp Ther 297(2), 727-35; Vega-Hernandez A, Felix R 2002, Cell Mol Neurobiol 22(2),
185-90), may be suitable for treating epilepsy.

AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionate) receptor antagonism has also
25 been proposed as a possible therapeutic approach to the treatment of epilepsy (e.g.
Meldrum 1994, Neurology 44 (11 Suppl. 8), p.14-23).

The aim of the present invention is to provide an active substance for the treatment
of idiopathic and symptomatic epilepsy which has no or only negligible central
30 nervous and cardiovascular side effects. In addition, the active substance thus
prepared should be suitable for oral administration and thus have good
bioavailability.

Description of the invention

Surprisingly, ambroxol exhibits very good activity in the treatment of idiopathic and symptomatic epilepsy, for example in the treatment of focal or generalised epileptic attacks. At a pharmacologically effective dose there are no central nervous and cardiovascular side effects. Surprisingly, in addition to blocking the sodium channels, ambroxol also exhibits very good effects as a calcium channel blocker and as an AMPA receptor antagonist, which as additional mechanisms provide an enhanced antiepileptic activity.

10 The invention therefore relates to the use of ambroxol or one of the pharmacologically acceptable salts thereof for preparing a pharmaceutical composition for the treatment of epilepsy, with the exception of the epileptic state.

Preferably ambroxol or one of the pharmacologically acceptable salts thereof is used to prepare a pharmaceutical composition for the treatment of forms of epilepsy with focally starting attacks, most preferably forms of epilepsy with focally starting idiopathic or symptomatic attacks.

It is particularly preferred to use ambroxol or one of the pharmacologically acceptable salts thereof for preparing a pharmaceutical composition for the treatment of forms of epilepsy with generalised attacks, for example idiopathic, cryptogenic or symptomatic, or symptomatic generalised forms of epilepsy, most preferably idiopathic generalised attacks.

25 The present invention further relates to the use of an orally administered pharmaceutical composition containing ambroxol or one of the pharmacologically acceptable salts thereof, preferably in the form of a tablet.

The use of ambroxol is particularly preferred, the ambroxol being used in a daily dose of 30 mg to 4000 mg, preferably 150 mg to 3000 mg, most preferably 350 mg to 2500 mg, most preferably 500 mg to 2000 mg.

The present invention also relates to a pharmaceutical composition containing ambroxol and one or more active substances selected from the group consisting of

sodium channel blockers, calcium channel antagonists, preferably N, P/Q sub-type blockers, gallopamil, verapamil, diltiazem, nifedipine and amlodipine, glutamate receptor antagonists, preferably ketamine and memantine, 2,3-benzodiazepines, preferably Gyki compounds, quinoxaline-diones, preferably NBQX, anticonvulsants, preferably gabapentin, pregabalin, carbamazepine, lamotrigin, topiramate, phenytoin and levitiracetam, potassium channel openers, preferably retigabin.

Preferably, ambroxol or one of the pharmacologically acceptable salts thereof is used in combination with one or more other active substances, selected from the group consisting of sodium channel blockers, calcium channel antagonists, preferably N, P/Q sub-type blockers, gallopamil, verapamil, diltiazem, nifedipine and amlodipine, glutamate receptor antagonists, preferably ketamine and memantine, 2,3-benzodiazepines, preferably Gyki compounds, quinoxaline-diones, preferably NBQX, anticonvulsants, preferably gabapentin, pregabalin, carbamazepine, lamotrigin, topiramate, phenytoin and levitiracetam, potassium channel openers, preferably retigabin.

The name ambroxol within the scope of the present invention denotes both the base ambroxol, and also the solvates or hydrates thereof, preferably the base ambroxol.

Acids suitable for forming salts of ambroxol are for example hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, nitric acid, oxalic acid, malonic acid, fumaric acid, maleic acid, tartaric acid, citric acid, ascorbic acid and methanesulphonic acid, preferably hydrochloric acid.

The effects of ambroxol according to the invention will be illustrated by the Examples that follow. These serve merely to illustrate the invention and are not to be regarded as limiting it.

Ambroxol inhibits various neuronal sodium channel subtypes, the half-maximal inhibition of centrally expressed channels being at 111 μM (Weiser and Wilson 2002, Mol Pharmacol 62, 433-438).

Voltage-dependent calcium channels play an important role in neurotransmission. The blocking of these channels has been described as being helpful for the treatment of epilepsy (Alden KJ, Garcia J 2001, J Pharmacol Exp Ther 297(2), 727-35; Vega-Hernandez A, Felix R 2002, Cell Mol Neurobiol 22(2), 185-90).

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It has been found, surprisingly, that ambroxol also blocks voltage-dependent calcium channels in neurone cultures from rats in concentrations of 10 to 1000 μ M. Neurones were dissected from posterior root ganglia of adult rats and placed in short-term culture. The cells were investigated electrophysiologically by the Patch-Clamp method (voltage
10 terminal), and the flow of current through voltage-dependent calcium channels was measured after electrical stimulation (voltage jumps from -80 mV to 0 mV holding potential for 50 ms) in the presence and absence of ambroxol.

Ionotropic glutamate receptors of the AMPA sub-type are also essential for the
15 excitatory neurotransmission. The blocking of AMPA receptors has been described as being helpful for the treatment of epilepsy (e.g. Meldrum 1994, Neurology 44(11 Suppl. 8), p.14-23).

In HEK 293 cells which express heterologously human GluR1/2 receptors, ambroxol surprisingly inhibits glutamate-induced membrane currents in concentrations ranging from
20 30-1000 μ M.

HEK 293 cells which expressed functionally recombinant human GluR1/2 receptors were electrophysiologically investigated by the Patch-Clamp method (voltage terminal). The administration of 1 mM glutamate (for 1 s at a holding potential of -80 mV) induced membrane currents which were inhibited by the joint administration of ambroxol.

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Ambroxol may be used on its own or in combination with other pharmacologically active substances. Suitable preparations include for example tablets, capsules, suppositories, solutions, elixirs, emulsions or dispersible powders. Suitable tablets may be obtained, for example, by mixing the active substance(s) with known excipients, for example inert
30 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 delaying release, such as carboxymethyl cellulose, cellulose acetate phthalate or polyvinyl acetate. The tablets may also comprise several layers.

Coated tablets may be prepared accordingly by coating cores produced analogously to the tablets with substances normally used for tablet coatings, for example collidone or shellac, gum arabic, talc, titanium dioxide or sugar. To achieve delayed release or prevent incompatibilities the core may also consist of a number of layers. Similarly the tablet coating may consist of a number of layers to achieve delayed release, possibly using the excipients mentioned above for the tablets.

Syrups or elixirs containing the active substances or combinations thereof according to the invention may additionally contain a sweetener such as saccharine, cyclamate, glycerol or sugar and a flavour enhancer, e.g. a flavouring such as vanillin or orange extract. They may also contain suspension adjuvants or thickeners such as sodium carboxymethyl cellulose, wetting agents such as, for example, condensation products of fatty alcohols with ethylene oxide, or preservatives such as p-hydroxybenzoates.

Solutions for injection are prepared in the usual way, e.g. with the addition of preservatives such as p-hydroxybenzoates, or stabilisers such as alkali metal salts of ethylenediamine tetraacetic acid, and transferred into injection vials or ampoules.

Capsules containing one or more active substances or combinations of active substances may for example be prepared by mixing the active substances with inert carriers such as lactose or sorbitol and packing them into gelatine capsules.

Suitable suppositories may be made for example by mixing with carriers provided for this purpose, such as neutral fats or polyethyleneglycol or the derivatives thereof.

A therapeutically effective daily dose is in the range from 30 mg to 4000 mg, preferably 150 mg to 3000 mg, most preferably 350 mg to 2500 mg, most preferably 500 mg to 2000 mg, in adults.

The Examples which follow illustrate the present invention without restricting its scope:

Examples of pharmaceutical formulations

A)	<u>Tablets</u>	<u>per tablet</u>
5	ambroxol	800 mg
	lactose	140 mg
	maize starch	240 mg
	polyvinylpyrrolidone	20 mg
	magnesium stearate	10 mg

10

Ambroxol, lactose and some of the maize starch are mixed together. The mixture is screened, then moistened with a solution of polyvinylpyrrolidone in water, kneaded, wet-granulated and dried. The granules, the remaining maize starch and the magnesium stearate are screened and mixed together. The mixture is compressed to produce tablets of suitable shape and size.

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B)	<u>Tablets</u>	<u>per tablet</u>
	ambroxol	800 mg
	maize starch	190 mg
20	lactose	55 mg
	microcrystalline cellulose	35 mg
	polyvinylpyrrolidone	20 mg
	sodium-carboxymethyl starch	30 mg
	magnesium stearate	10 mg

25

Ambroxol, some of the corn starch, lactose, microcrystalline cellulose and polyvinylpyrrolidone are mixed together, the mixture is screened and worked with the remaining corn starch and water to form a granulate which is dried and screened. The sodium-carboxymethyl starch and the magnesium stearate are added and mixed in and the mixture is compressed to form tablets of a suitable size.

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	C) <u>Coated tablets</u>	<u>per coated tablet</u>
	ambroxol	500 mg
	maize starch	45 mg
	lactose	30 mg
5	polyvinylpyrrolidone	5 mg
	magnesium stearate	5 mg

Ambroxol, maize starch, lactose and polyvinylpyrrolidone are thoroughly mixed and moistened with water. The moist mass is pushed through a screen with a 1 mm mesh size, dried at about 45°C and the granules are then passed through the same screen. After the magnesium stearate has been mixed in, convex tablet cores with a diameter of 11 mm are compressed in a tablet-making machine. The tablet cores thus produced are coated in known manner with a covering consisting essentially of sugar and talc. The finished coated tablets are polished with wax.

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	D) <u>Capsules</u>	<u>per capsule</u>
	Ambroxol	250 mg
	maize starch	268.5 mg
	magnesium stearate	1.5 mg

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Ambroxol and maize starch are mixed and moistened with water. The moist mass is screened and dried. The dry granules are screened and mixed with magnesium stearate. The finished mixture is packed into size 1 hard gelatine capsules.

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	E) <u>Parenteral solution</u>	
	Ambroxol	500 mg
	Citric acid monohydrate	100 mg
30	sodium hydroxide	35 mg
	mannitol	1500 mg
	water for inj.	50 ml

The ambroxol is dissolved in water at its own pH or optionally at pH 4.5 to 5.5 and mannitol is added to make it isotonic. The solution obtained is filtered free from pyrogens and the filtrate is transferred under aseptic conditions into injection vials which are then sealed with rubber stoppers and autoclaved.

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F) Suppositories

Ambroxol	450	mg
solid fat	1650	mg

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The hard fat is melted. At 40°C ambroxol is homogeneously dispersed therein. The mixture is cooled to 38°C and poured into slightly chilled suppository moulds.

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G) Oral solution

ambroxol	150	mg
hydroxyethylcellulose	50	mg
sorbic acid	5	mg
sorbitol (70%)	600	mg
glycerol	200	mg
flavouring	15	mg
water ad	10	ml

20

25 Distilled water is heated to 70°C . Hydroxyethylcellulose is dissolved therein with stirring. After the addition of sorbitol solution and glycerol the mixture is cooled to ambient temperature. At ambient temperature sorbic acid, flavouring and ambroxol are added. To eliminate air from the suspension it is evacuated with stirring.

30

Patent Claims

- 5 1. Use of ambroxol or one of the pharmacologically acceptable salts thereof for preparing a pharmaceutical composition for the treatment of epilepsy, with the exception of epileptic states.
- 10 2. Use of ambroxol or one of the pharmacologically acceptable salts thereof according to claim 1 for preparing a pharmaceutical composition for the treatment of idiopathic epilepsy.
- 15 3. Use of ambroxol or one of the pharmacologically acceptable salts thereof according to claim 1 for preparing a pharmaceutical composition for the treatment of symptomatic epilepsy.
4. Use of an orally administered pharmaceutical composition containing ambroxol or one of the pharmacologically acceptable salts thereof according to claims 1 to 3.
- 20 5. Use according to one of claims 1 to 3, characterised in that ambroxol is used in a daily dose of 30 mg to 4000 mg.
- 25 6. Pharmaceutical composition containing ambroxol and one or more active substances selected from the group consisting of sodium channel blockers, calcium channel antagonists, glutamate receptor antagonists, quinoxaline-diones, anticonvulsants, and potassium channel openers.
- 30 7. Use of ambroxol or one of the pharmacologically acceptable salts thereof according to one of claims 1 to 4 in combination with one or more other active substances, selected from the group consisting of sodium channel blockers, calcium channel antagonists, glutamate receptor antagonists, quinoxaline-diones, anticonvulsants and potassium channel openers.

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