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Ambroxol for treating painful conditions in the mouth and pharyngeal cavity

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Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

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(54) Title: AMBROXOL FOR TREATING PAINFUL CONDITIONS IN THE MOUTH AND PHARYNGEAL CAVITY

(54) Bezeichnung: AMBROXOL FÜR DIE BEHANDLUNG VON SCHMERZHAFTEN ZUSTÄNDEN IM MUND UND RACHENRAUM

(57) Abstract: The invention relates to the use of ambroxol and the pharmacologically compatible salts thereof for producing a medicament used for treating painful conditions in the mouth and pharyngeal cavity.

(57) Zusammenfassung: Die Erfindung betrifft die Verwendung von Ambroxol und dessen pharmakologisch verträglichen Salze zur Herstellung eines Arzneimittels zur Behandlung von schmerzhaften Zuständen im Mund-und Rachenraum.

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IN THE MATTER of a
Patent Application
by Boehringer Ingelheim Pharma GmbH & Co. KG

VERIFICATION OF TRANSLATION

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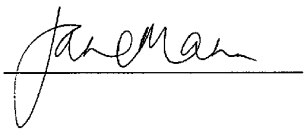
I, JANE ROBERTA MANN, B.A., of Frank B. Dehn & Co.,
59 St Aldates, Oxford OX1 1ST, am the translator of the documents attached and I state that the following is a true translation to the best of my knowledge and belief of the specification as published of International Patent Application No. PCT/EP03/01886 (WO 03/072094) of Boehringer Ingelheim Pharma GmbH & Co. KG.

Signature of translator 

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Ambroxol for the treatment of painful conditions in the mouth and pharyngeal cavity.

The invention relates to the use of ambroxol and the pharmacologically acceptable salts thereof for preparing a pharmaceutical composition for the treatment of painful conditions in the oral and pharyngeal cavity.

Background to the invention

Painkillers for relieving pain in the oral and pharyngeal cavity often have the drawback of side effects, e.g. in the form of local irritations.

The active substance ambroxol (trans-4-(2-amino-3,5-dibromobenzylamino)-cyclohexanol) is a known expectorant and mucolytic. It is used in oral preparations such as syrups, capsules, tablets, inhalable solutions, drops or suckable pastilles.

The aim of the present invention is to prepare a well-tolerated active substance for the treatment of pain in the oral and pharyngeal cavities.

Description of the invention

Surprisingly, it has been found that, when administered locally in suitable doses or concentrations, ambroxol has a very good pain-relieving effect in the oral and pharyngeal cavity in addition to being very well tolerated.

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 pain in the oral and/or pharyngeal cavity, selected from aphthae, gingivitis, parodontopathies, pressure points caused by prostheses, pain after oro-pharyngeal interventions, lesions on the mucous membrane in the oral and pharyngeal cavity and herpes simplex in the oral and pharyngeal cavity, particularly aphthae, gingivitis, parodontopathies, pressure points caused by

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prostheses, pain after oro-pharyngeal interventions, lesions on the mucous membrane in the oral and pharyngeal cavity and herpes simplex in the oral and pharyngeal cavity.

Accordingly, in one aspect, the invention provides use of ambroxol or a pharmacologically acceptable salts thereof for preparing a pharmaceutical composition with a pain-relieving effect lasting for a period of at least 3 hours after administration for the treatment of pain in the oral and/or pharyngeal cavity deriving from aphthae, gingivitis, parodontopathies, pressure points caused by prostheses, pain after oro-pharyngeal interventions, lesions on the mucous membrane in the oral and pharyngeal cavity and herpes simplex.

In another aspect, the invention provides a method for treating pain in the oral and/or pharyngeal cavity, selected from among aphthae, gingivitis, parodontopathies, pressure points caused by prostheses, pain after oro-pharyngeal interventions, lesions on the mucous membrane in the oral and pharyngeal cavity and herpes simplex in the oral and pharyngeal cavity, which comprises administering to a subject an effective amount of ambroxol or a pharmaceutically acceptable salt thereof to afford a pain-relieving effect lasting for a period of at least 3 hours after administration.

The invention further relates to a pharmaceutical composition containing ambroxol or one of the pharmacologically acceptable salts thereof and one or more active substances selected from among the antiseptics, vitamins, corticoids, antiinflammatories, virostatics, antibiotics, antimycotics and proteolytic enzymes.
Suitable antiseptics are for example cetylpyridinium-Cl, dequalinium-Cl, chlorhexidine-digluconate, benzalkonium-Cl or ethacridine-lactate.
Suitable vitamins are for example dexpanthenol (pantothenic acid) or ascorbic acid.
Suitable corticoids are for example triamcinolone or prednisolone-acetate.
Suitable antiinflammatories are for example benzydamine-Cl or choline salicylate.
Suitable virostatics are for example acyclovir or idoxuridine.
Suitable antibiotics are for example thyrotricin or bacitracin.
Suitable antimycotics are for example amphotericin B or nystatin.
An example of a suitable proteolytic enzyme is lysozyme.

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Suitable ethereal oils are for example peppermint oil, thyme or sage oils.

The invention further relates to a pharmaceutical composition containing ambroxol or one of the pharmacologically acceptable salts thereof and one or more active substances, selected from the group consisting of lysozyme hydrochloride, dipotassium glycyrrhizinate, ammonium glycyrrhizinate, cetylpyridinium chloride, chlorpheniramine maleate, noscapine, dequalinium chloride, dextromethorphan, phenolphthalinate, potassium guaiacolsulphonate, dl-methylephedrine hydrochloride, chlorhexidine hydrochloride, and potassium cresolsulphonate.

Ambroxol is a metabolite of the secretolytic bromhexine. The two active substances represent a very well tolerated combination of active substances which positively influences the dual effect of ambroxol.

The invention therefore also relates to a pharmaceutical composition consisting of ambroxol, bromhexine or the pharmacologically acceptable salts thereof and pharmaceutical excipients, preferably with a ratio of ambroxol to bromhexine in the range from 4:1 to 6:1, more preferably 5:1.

A particularly preferred pharmaceutical composition is one wherein the single dose contains 15 to 50 mg of ambroxol, preferably 20 mg of ambroxol.

The invention further relates to a solid, suckable or slowly dissolving form of a pharmaceutical composition containing ambroxol and one or more active substances selected from among the antiseptics, vitamins, corticoids, antiinflammatories, antibiotics, antimycotics and proteolytic enzymes.

The invention further relates to the use of a pharmaceutical composition as described above for preparing a medicament for the treatment of pain in the oral and/or pharyngeal cavity, selected from aphthae, gingivitis, parodontopathies, pressure points caused by prostheses, pain after oro-pharyngeal interventions, lesions on the mucous membrane in the oral and pharyngeal cavity and herpes simplex in the oral and pharyngeal cavity.

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The invention further relates to the use of a pharmaceutical composition consisting of ambroxol hydrochloride, a flavouring, a lubricant, a matrix material, a sweetening agent and a polyethyleneglycol for preparing a pharmaceutical composition for the treatment of pain in the oral and/or pharyngeal cavity, selected from aphthae, gingivitis, parodontopathies, pressure points caused by prostheses, pain after oro-pharyngeal interventions, lesions on the mucous membrane in the oral and pharyngeal cavity and herpes simplex in the oral and pharyngeal cavity.

Suitable flavourings may be, for example, peppermint, eucalyptus or lemon, preferably peppermint flavouring.
Suitable matrix materials may be, for example, calcium carbonate, calcium phosphate or sorbitol, preferably sorbitol.
Suitable sweetening agents may be, for example, saccharin, saccharin sodium, cyclamate, glycerol or sugar, preferably saccharin sodium.
Suitable tablet lubricants may be, for example, polyethyleneglycols, preferably Macrogol 6000.
Suitable lubricants may be for example talcum or magnesium stearate, preferably talc.

The invention further relates to the use of a suckable tablet containing ambroxol based on sugar alcohols as the matrix material, characterised in that it contains a pharmaceutically acceptable layered silicate and a polyethyleneglycol, optionally together with other pharmaceutical excipients, taste or flavouring agents to prepare a pharmaceutical composition for treating pain in the oral and/or pharyngeal cavity, selected from aphthae, gingivitis, parodontopathies, pressure points caused by prostheses, pain after oro-pharyngeal interventions, lesions on the mucous membrane in the oral and pharyngeal cavity and herpes simplex in the oral and pharyngeal cavity.

The invention further relates to the use of ambroxol for preparing a pharmaceutical composition with a pain-relieving effect lasting for a period of at least 3 hours, preferably more than 3 hours, after administration.

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The invention also relates to the use of a pharmaceutical composition containing ambroxol for preparing a pharmaceutical composition with a pain-relieving effect lasting for a period of at least 3 hours, preferably more than 3 hours, after administration.

The pharmaceutical composition according to the invention is preferably administered 1 to 6 times, preferably 2 to 4 times a day.

Acids suitable for forming salts of ambroxol include 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 activity of ambroxol according to the invention is intended to be illustrated by the following examples of clinical trials which investigate the effectiveness of different strengths of suckable tablets containing ambroxol. These are intended solely to illustrate the invention and are not to be regarded as limiting.

Example 1

Investigation of the activity and tolerance of suckable tablets containing 20 mg of ambroxol hydrochloride (trans-4-[(2-amino-3,5-dibromo-benzyl)amino]cyclohexano hydrochloride, CAS Reg. No. 18683-91-5) compared with a placebo in treating acute sore throats

A multi-centred, prospective, placebo-controlled, randomised double-blind trial was carried out over two days' treatment with up to 6 suckable tablets containing ambroxol hydrochloride per day.

Patients: 218 patients (97 men, 121 women) with an average age of 39.4 ± 15 years (range from 17-81 years) were recruited; of these 215 patients were treated: 107 with 20 mg of ambroxol and 108 with placebo. 26 patients stopped the treatment early (13 in each treatment group). The intent-to-treat (ITT) population consisted of 208 patients (105 treated with ambroxol and 103 given the placebo); 196 patients formed the per-protocol (PP) population (97 with test substance and 99 with placebo). For the drug safety analysis, all the patients treated were studied.

Treatments: Double-blind treatment with up to 6 suckable tablets per day, which either contained 20 mg of ambroxol or constituted a placebo (suckable tablet without the active substance, but with a marked flavour of peppermint similar to the test substance)

End points: the average pain reduction, weighted for time, during the first 3 hours after administration of the first suckable tablet, standardised to the degree of initial

pain ($SPID_{norm}$); moreover, the assessment of effectiveness and tolerance by the patient at the end of each day of treatment

Results: In both treatment groups there was a reduction in the intensity of pain; the average $SPID_{norm}$ (± SD) after the first suckable tablet was 0.39 ± 0.27 for 20 mg ambroxol hydrochloride and 0.28 ± 0.25 for placebo.

The superiority of the ambroxol over the placebo was apparent from a statistically significant treatment effect (p=0.0029; - 95% confidence interval for the average difference between the ambroxol treatment groups minus placebo: 0.04 to 0.18). At the end of each successive day of ambulant treatment with up to 6 suckable tablets a statistically significantly larger number of patients reported a higher degree of effectiveness for the active treatment with ambroxol hydrochloride than for the administration of the placebo. The test substance was found to be tolerated just as well as the placebo.

Conclusion: The administration of suckable tablets containing 20 mg of ambroxol hydrochloride to patients with acute sore throat has an effective pain-relieving effect which is superior to the inherently beneficial effect of sucking a placebo.

Figure 1 shows the course, over time, of the average change in pain intensity (PID) for the period before taking the tablet (base line) up to 3 hours after taking the first suckable tablet containing 20 mg of ambroxol hydrochloride and placebo.

Example 2

Investigation of the activity and tolerance of suckable tablets containing 20 or 30 mg of ambroxol hydrochloride (trans-4-[(2-amino-3,5-dibromo-benzyl)amino]cyclohexano hydrochloride, CAS Reg. No. 18683-91-5) compared with a placebo in treating acute sore throats

A multi-centred, prospective, placebo-controlled, randomised double-blind trial was carried out over three days' treatment with up to 6 suckable tablets containing ambroxol hydrochloride per day.

Patients: 331 ambulant patients with acute uncomplicated sore throats of at least moderate severity but with no bacterial pharyngitis were investigated.

Treatments: Double-blind treatment with up to 6 suckable tablets per day containing either 20 mg or 30 mg of ambroxol hydrochloride or constituting a placebo (suckable

tablet without the active substance, but again with a marked flavour of peppermint similar to the test substance)

End points: the average pain reduction, weighted for time, during the first 3 hours after administration of the first suckable tablet, standardised to the degree of initial pain ($SPID_{norm}$); moreover, the assessment of effectiveness and tolerance by the patient at the end of each day of treatment

Results: All the treatments led to a reduction in the intensity of pain; the average $SPID_{norm}$ (± SD) after the first suckable tablet was taken was 0.53 ± 0.28 or 0.50 ± 0.30 for 20 mg and 30 mg ambroxol hydrochloride, respectively, and 0.38 ± 0.28 for placebo. The effect of the treatment was statistically significant. The superiority of the active treatments over the placebo could be clearly demonstrated (95% confidence interval (CI) for the average differences between the groups treated with suckable tablets containing 20 or 30 mg of ambroxol minus placebo: 0.08 to 0.23 or 0.05 to 0.20). At the end of each successive day of ambulant treatment with up to 6 suckable tablets per day a statistically significantly larger number of patients reported a higher degree of effectiveness for the active treatments with ambroxol hydrochloride than for the administration of the placebo. The test substance was found to be tolerated just as well as the placebo in all dosages.

Conclusion: The administration of suckable tablets containing 20 or 30 mg of ambroxol hydrochloride to patients with acute sore throat has a markedly effective pain-relieving effect which is superior to the inherently beneficial effect of sucking a placebo. Both doses were tolerated equally well.

Figure 2 shows the course, over time, of the average change in pain intensity (PID) for the period before taking the tablet (base line) up to 3 hours after taking the first suckable tablet containing 20 mg or 30 mg of ambroxol hydrochloride and placebo.

Ambroxol may be used on its own or combined with other pharmacologically active substances. It may be applied in any of the preparation forms which are suitable for local use. Preparations suitable for sucking or dissolving slowly in the mouth include, for example, tablets or sweets based on sugar or sugar substitutes or pastille-like products with a gum arabic or gelatine base.

Examples of semisolid preparations for application to the oral mucosa include gels, for example, especially gels based on cellulose or acrylate.
Suitable solutions for spraying, gargling and rinsing include aqueous preparations, advantageously with the addition of viscosity-increasing substances such as modified celluloses, acrylic acid derivatives or polyvinyl compounds.
In addition, the semisolid and liquid forms in particular may contain sweetening agents and moisture retainers such as glycols and sugar alcohols, for example.
All the forms are flavoured in the conventional way, e.g. by the addition of ethereal oils.

The preparations may be produced by methods known in pharmacy.

The following examples of pharmaceutical formulations illustrate the present invention without restricting its scope:

Example 1)

Suckable pastille	per pastille	
ambroxol hydrochloride	20.0	mg
peppermint flavouring	16.0	mg
sorbitol	1373.5	mg
saccharin sodium	0.5	mg
Macrogol 6000	30	mg
talc	60	mg

Example 2)

Suckable pastille	per tablet
Ambroxol hydrochloride	20.0 mg
Lysozyme hydrochloride	5.0 mg
Dipotassium glycyrrhizinate	2.5 mg
Cetylpyridinium Chloride	1.0 mg
Chlorpheniramine Maleate	1.0 mg
Xylitol	920.5 mg
D-Mannitol	9.5 mg
Polyvinylpyrrolidone	21.0 mg
Stearic acid	10.0 mg
Peppermint oil	6.0 mg
light anhydrous silicic acid	1.0 mg
talc	1.0 mg
magnesium stearate	1.5 mg

Example 3)

Suckable pastille	per tablet
Ambroxol hydrochloride	20.0 mg
Noscapine	5.0 mg
Dequalinium Chloride	0.125 mg
Sucrose (purified)	908.675 mg
l-Menthol	1.0 mg
Peppermint oil	0.6 mg
Lemon flavour	3.6 mg
Corn starch	30.0 mg
Polyvinylpyrrolidone	21.0 mg
Magnesium Stearate	10.0 mg

Example 4)

Suckable pastille	per tablet	
Ambroxol hydrochloride	20.0	mg
Dextromethorphan phenolphthalinate	10.0	mg
Potassium guaiacolsulphonate	23.3	mg
Cetylpyridinium Chloride	1.0	mg
Sucrose (purified)	869.7	mg
Peppermint flavour	16.0	mg
Corn starch	30.0	mg
Polyvinylpyrrolidone	20.0	mg
Magnesium Stearate	10.0	mg

Example 5)

Suckable pastille	per tablet	
Ambroxol hydrochloride	20.0	mg
dl-Methylephedrine Hydrochloride	6.25	mg
Chlorhexidine Hydrochloride	5.0	mg
Lactose	905.25	mg
Low-substituted Hydroxypropylcellulose	25.0	mg
Hydroxypropylcellulose	20.0	mg
Peppermint flavour	16.0	mg
Magnesium Stearate	2.5	mg

Example 6)

Suckable pastille	per tablet	
Ambroxol hydrochloride	20.0	mg
Ammonium glycyrrhizate	1.67	mg
Potassium Cresolsulphonate	30.0	mg
Lactose	884.83	mg
Low-substituted Hydroxypropylcellulose	25.0	mg
Hydroxypropylcellulose	20.0	mg
Peppermint flavour	16.0	mg
Magnesium Stearate	2.5	mg

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. Use of ambroxol or a pharmacologically acceptable salts thereof for preparing a pharmaceutical composition with a pain-relieving effect lasting for a period of at least 3 hours after administration for the treatment of pain in the oral and/or pharyngeal cavity deriving from aphthae, gingivitis, parodontopathies, pressure points caused by prostheses, pain after oro-pharyngeal interventions, lesions on the mucous membrane in the oral and pharyngeal cavity and herpes simplex.

2. Use as claimed in claim 1 wherein the composition contains ambroxol or a pharmacologically acceptable salt thereof and one or more active substances selected from among the antiseptics, vitamins, corticoids, antiphlogistics, antibiotics, antimycotics and proteolytic enzymes.

3. Use as claimed in claim 1 or claim 2 wherein the composition contains ambroxol or a pharmacologically acceptable salt thereof and one or more active substances selected from the group consisting of lysozyme hydrochloride, dipotassium glycyrrhizinate, ammonium glycyrrhizinate, cetylpyridinium chloride, chlorpheniramine maleate, noscapine, dequalinium chloride, dextromethorphane, phenolphthalinate, potassium guaiacolsulphonate, dl-methylephedrine hydrochloride, chlorhexidine hydrochloride, and potassium cresolsulphonate.

4. Use as claimed in any of claims 1 to 3 wherein the composition consists of ambroxol, bromhexine or a pharmacologically acceptable salt thereof and pharmaceutical excipients.

5. Use as claimed in any of claims 1 to 4 wherein the composition is in the form of a single dose containing 15 to 50 mg ambroxol.

6. Use as claimed in any of claims 2 to 4 wherein the composition is in the form of a solid, suckable or slowly dissolving formulation.

7. Use as claimed in any of claims 2 to 5 wherein the composition is in the form of a semisolid formulation in the form of a gel.

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8. Use of a pharmaceutical composition consisting of ambroxol hydrochloride, a flavouring, a lubricant, a matrix material, a sweetening agent and a polyethyleneglycol for preparing a medicament for the treatment of pain in the oral and/or pharyngeal cavity, selected from among aphthae, gingivitis, parodontopathies, pressure points caused by prostheses, pain after oro-pharyngeal interventions, lesions on the mucous membrane in the oral and pharyngeal cavity and herpes simplex in the oral and pharyngeal cavity.

9. Use according to claim 1 wherein the ambroxol is contained in a suckable tablet based on sugar alcohols as the matrix material, and contains a pharmaceutically acceptable layered silicate and a polyethyleneglycol, optionally together with other pharmaceutical excipients, taste or flavouring agents.

10. A method for treating pain in the oral and/or pharyngeal cavity, selected from among aphthae, gingivitis, parodontopathies, pressure points caused by prostheses, pain after oro-pharyngeal interventions, lesions on the mucous membrane in the oral and pharyngeal cavity and herpes simplex in the oral and pharyngeal cavity, which comprises administering to a subject an effective amount of ambroxol or a pharmaceutically acceptable salt thereof to afford a pain-relieving effect lasting for a period of at least 3 hours after administration.

11. The method as claimed in claim 10 wherein the ambroxol or a pharmacologically acceptable salt thereof is administered as a composition with one or more active substances selected from among the antiseptics, vitamins, corticoids, antiphlogistics, antibiotics, antimycotics and proteolytic enzymes.

12. The method as claimed in claim 10 or claim 11 wherein the ambroxol or a pharmacologically acceptable salt thereof is administered as a composition with one or more active substances selected from the group consisting of lysozyme hydrochloride, dipotassium glycyrrhizinate, ammonium glycyrrhizinate, cetylpyridinium chloride, chlorpheniramine maleate, noscapine, dequalinium chloride, dextromethorphane, phenolphthalinate, potassium guaiacolsulphonate,

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dl-methylephedrine hydrochloride, chlorhexidine hydrochloride, and potassium cresolsulphonate.

13. The method as claimed in any of claims 10 to 12 which comprises administering a composition consisting of ambroxol, bromhexine or a pharmacologically acceptable salt thereof and pharmaceutical excipients.

14. The method as claimed in any of claims 10 to 13 which comprises administering a composition in the form of a single dose containing 15 to 50 mg ambroxol.

15. The method as claimed in any of claims 11 to 14 wherein the composition is in the form of a solid, suckable or slowly dissolving formulation.

16. The method as claimed in any of claims 11 to 15 wherein the composition is in the form of a semisolid formulation in the form of a gel.

17. A method for the treatment of pain in the oral and/or pharyngeal cavity, selected from among aphthae, gingivitis, parodontopathies, pressure points caused by prostheses, pain after oro-pharyngeal interventions, lesions on the mucous membrane in the oral and pharyngeal cavity and herpes simplex in the oral and pharyngeal cavity which comprises administering to a subject in need thereof a pharmaceutical composition consisting of ambroxol hydrochloride, a flavouring, a lubricant, a matrix material, a sweetening agent and a polyethyleneglycol.

18. A method as claimed in claim 10 wherein the ambroxol is contained in a suckable tablet based on sugar alcohols as the matrix material, and contains a pharmaceutically acceptable layered silicate and a polyethyleneglycol, optionally together with other pharmaceutical excipients, taste or flavouring agents.

19. Use according to claim 1 or 8; or a method according to claim 10 or 17, substantially as hereinbefore described and/or exemplified.

Drawings (sheet 1 of 2)

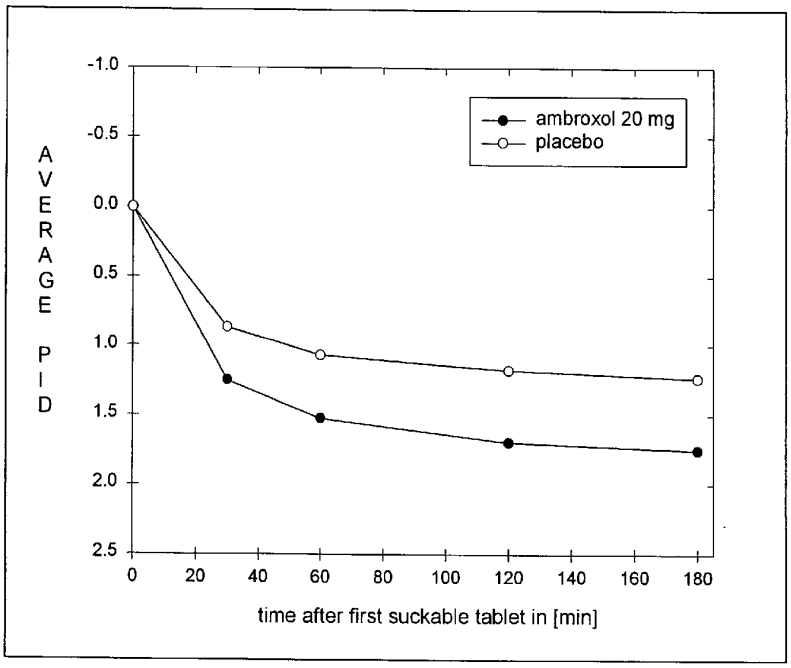

Figure 1

Drawings (sheet 2 of 2)

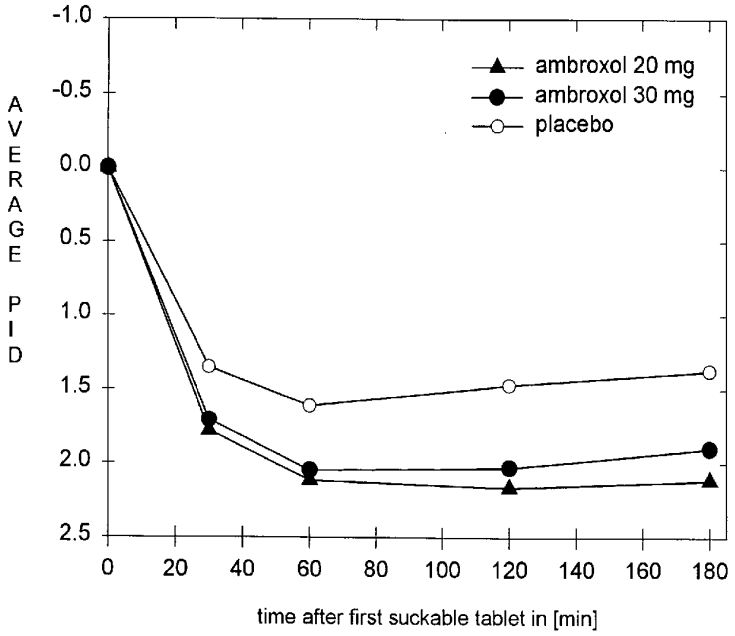

Figure 2