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(71) Applicant *(for all designated States except DE, US)*: **BOEHRINGER INGELHEIM INTERNATIONAL GMBH** [DE/DE]; Binger Strasse 173, 55118 Ingelheim (DE).

(71) Applicant *(for DE only)*: **BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG** [DE/DE]; Binger Strasse 173, 55216 Ingelheim (DE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **HORIE, Toshiaki** [JP/JP]; 353-3 Nado, Taiei, Katori, Chiba JP-287-0205 (JP). **OKADA, Minoru** [JP/JP]; 4-7-20 Kioroshihigashi, Inzai, Chiba JP-270-1323 (JP). **OTAKI, Hiroshi** [JP/JP]; 3-17-1-703-Nishinohara, Inzai-ski, Chiba 270-1334 (JP). **UMEHARA, Norimitsu** [JP/JP]; 1000-4 Kamiyasumatu, Tokorozawa-Shi, Saitama 359-0025 (JP).

(74) Common Representative: **BOEHRINGER INGELHEIM INTERNATIONAL GMBH**; Binger Strasse 173, 55118 Ingelheim (DE).

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(54) Title: COMPOSITIONS COMPRISING MELOXICAM

(57) Abstract: The invention relates to a pharmaceutical composition comprising meloxicam or a pharmaceutically acceptable salt thereof and a second pharmaceutically active compound selected from the group consisting of antitussive agents, expectorants and anti-Hl-histamines.

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Compositions comprising meloxicam

This invention relates to a pharmaceutical composition comprising meloxicam or a pharmaceutically acceptable salt thereof and at least a second pharmaceutically active compound selected from the group consisting of antitussive agents, expectorants and anti-H1-histamines. Furthermore this invention relates to an oral pharmaceutical dosage form comprising such a composition. A further objective of this invention is related to the use of the composition and the oral pharmaceutical dosage form. In addition this invention relates to the use of meloxicam and at least a second pharmaceutically active compound selected from the group consisting of antitussive agents, expectorants and anti-H1-histamines for the manufacture of such an oral pharmaceutical dosage form. Furthermore, this invention relates to a method of treating or alleviating of an cold, including various symptoms thereof such as fever, sore throat, chills, headache, joint pain, muscular pain, runny nose, stuffy nose, sputum and/or sneezing.

Background of the invention

Common cold is an ordinary disease: average morbidity rate of common cold per person is 5 to 6 times in a year. Rhinovirus, parainfluenza virus, or adenovirus induces upper respiratory infections after a temporary loss of autonomic adjustments due to causes such as exposure to cold. Medicines suppressing infection or proliferation of viruses, which causes cold, have not been found until today except those for some diseases such as influenza A. Symptomatic therapy has, therefore, been mainly used for the treatment of common cold, and the principal purpose of the therapy is to prevent loss of bodily strength. Medicines for symptomatic therapy, alleviating various symptoms of common cold, contain non-steroidal anti-inflammatory drugs (NSAIDs) and antitussive agents or expectorants or anti-H1-histamines as active ingredients: NSAIDs have analgesic, anti-inflammatory and antipyretic actions. Antitussive agents alleviate symptoms such as cough and sneezing. Expectorants alleviate symptoms such as sputum. Anti-H1-histamines alleviate symptoms such as runny nose, stuffy nose and sneezing. However, these medicines do not have sufficient effects in treating or

alleviating symptoms of common cold in terms of balance between efficacy and safety.

Many NSAIDs are COX inhibitors, which nonspecifically inhibit cyclooxygenase (COX), a rate-limiting enzyme for biosynthesis of prostaglandin (PG) from arachidonic acid. Inhibition of COX contributes to anti-inflammatory, analgesic and antipyretic effects by inhibiting production of PGE_2, on the other hand, it also causes adverse drug reactions such as digestive disorders and renal disorders. Incidentally, COX includes two types of isoforms, i.e. COX-1 and COX-2. COX-1 is constitutively (a certain amount of protein is developed regardless of proliferation or environmental changes) developed in most of the organs such as stomach and kidneys. And it has become evident that COX-2 is induced by various inflammatory mediators or endotoxin in local inflammatory areas. Meloxicam is a known selective COX-2 inhibitor.

Oral pharmaceutical compositions for the treatment of common cold with strengthened expression of efficacy and superior safety by potentiating anti-inflammatory, analgesic, antipyretic, antitussive and/or expectorant effects, while alleviating side effects such as gastrointestinal disorders are desired.

A pharmaceutical composition comprising selective COX-2 inhibiting NSAIDs and antiallergics or anti-H1-histamines, which are mequitazine, ketotifen, epinastine, chlorpheniramine and carbinoxamine, as effective for treatment of rhinitis is disclosed in the Publication of the Japanese Patent Application JP2001-247481A. In example 2 of said application a composition comprising meloxicam, epinastine hydrochloride, phenylpropanolamine hydrochloride, and lysozyme chloride in tablet form is disclosed.

Objective of the present invention

The primary objective of this invention is to provide more effective pharmaceutical compositions for the treatment of a cold with improved efficacy and safety.

A further objective of this invention is to provide more effective pharmaceutical compositions for alleviation of symptoms of a cold, including various symptoms thereof such as fever, sore throat, chills, headache, joint pain, muscular pain, runny nose, stuffy nose, sputum and/or sneezing.

The invention also aims to provide pharmaceutical compositions and oral pharmaceutical dosage forms comprising an antitussive agent with improved efficacy and safety.

The invention also aims to provide pharmaceutical compositions and oral pharmaceutical dosage forms comprising an expectorant with improved efficacy and safety.

The invention also aims to provide pharmaceutical compositions and oral pharmaceutical dosage forms comprising a specific anti-H1-histamine with improved efficacy and safety.

A further aim of this invention is to provide a method of treating or alleviating of a cold, including various symptoms thereof such as fever, sore throat, chills, headache, joint pain, muscular pain, runny nose, stuffy nose, sputum and/or sneezing.

Description of the invention

This invention relates to new pharmaceutical compositions comprising meloxicam or a pharmaceutically acceptable salt thereof and a second pharmaceutically active compound selected from the group consisting of antitussive agents, expectorants and anti-H1-histamines. Preferably meloxicam or the salt thereof is present in an effective amount allowing itself to exert anti-inflammatory, analgesic and antipyretic effects.

An advantage of the present invention is that the composition of the invention allows a reinforcement of the therapeutic effects such as analgesic, anti-inflammatory, antipyretic, antitussive and/or expectorant effects without the

need to increase the dose of meloxicam. It is possible to provide pharmaceutical compositions as oral pharmaceutical dosage forms with improved efficacy and safety. Possible side effects of common NSAIDs, as e.g. gastrointestinal disorders, are avoided or alleviated by using meloxicam. Thus the composition of the present invention is especially suitable for the treatment or alleviation of a cold, including various symptoms thereof such as fever, sore throat, chills, headache, joint pain, muscular pain, runny nose, stuffy nose, sputum and/or sneezing. The improved safety profile enables the use of such compositions in non-prescription drugs.

Meloxicam is a known selective COX-2 inhibitor which belongs to the acid enolcarboxamide (oxicam) type of non-steroidal anti-inflammatory drugs (NSAIDs). The compound (4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H1,2-benzothiazine-3-carboxamide 1,1-dioxide) is described in EP 0 002 482 B1 and US 4,233,299.

The invention may employ either meloxicam itself or a pharmaceutically acceptable salt thereof. The pharmaceutically acceptable salt of meloxicam includes sodium salt, potassium salt, ammonium salt, meglumine salt, tris salt, and salts of meloxicam with a basic amino acid as examples. Various salts of meloxicam are described in EP 0 002 482 B1, US 4,233,299 and WO 99/49867.

According to a first embodiment of this invention the pharmaceutical composition comprises meloxicam or a pharmaceutically acceptable salt thereof and at least one antitussive agent.

In addition to meloxicam and one or more antitussive agents mentioned above, the compositions of the first embodiment may also include other pharmacologically active substances such as an antacid and/or a central nervous system stimulant.

By using an antacid as a further ingredient an improvement of the bioavailability and/or a decrease of the possibility of side effects in the digestive system may be obtained.

The addition of a central nervous system stimulant may reinforce therapeutic

effects such as analgesic, anti-inflammatory and antipyresis without the necessity of increasing the dose of meloxicam.

Therefore a pharmaceutical composition according to this first embodiment may comprise meloxicam or a pharmaceutically acceptable salt thereof and one or more, preferably one antitussive agent and one or more, preferably one antacid. This composition may additionally comprise one or more, preferably one central nervous system stimulant.

A further pharmaceutical composition according to this first embodiment may comprise meloxicam or a pharmaceutically acceptable salt thereof and one or more, preferably one antitussive agent and one or more, preferably one central nervous system stimulant. This composition may additionally comprise one or more, preferably one antacid.

According to a second embodiment of this invention the pharmaceutical composition comprises meloxicam or a pharmaceutically acceptable salt thereof and at least one expectorant.

In addition to meloxicam and one or more expectorants mentioned above, the compositions of the second embodiment may also include other pharmacologically active substances such as an antacid, a central nervous system stimulant and/or an antitussive agent.

By using an antacid as a further ingredient an improvement of the bioavailability and/or a decrease of the possibility of side effects in the digestive system may be obtained.

The addition of a central nervous system stimulant may reinforce therapeutic effects such as analgesic, anti-inflammatory and antipyresis without the necessity of increasing the dose of meloxicam.

By using an antitussive agent as a further ingredient an additional alleviation of

symptoms, like e.g. cough and sneezing, can be obtained.

Therefore a pharmaceutical composition according to this second embodiment may comprise meloxicam or a pharmaceutically acceptable salt thereof and one or more, preferably one expectorant and one or more, preferably one antacid. This composition may additionally comprise one or more, preferably one central nervous system stimulant and/or one or more, preferably one antitussive agent.

A further pharmaceutical composition according to this second embodiment may comprise meloxicam or a pharmaceutically acceptable salt thereof and one or more, preferably one expectorant and one or more, preferably one central nervous system stimulant. This composition may additionally comprise one or more, preferably one antacid and/or one or more, preferably one antitussive agent.

Again a further pharmaceutical composition according to this second embodiment may comprise meloxicam or a pharmaceutically acceptable salt thereof and one or more, preferably one expectorant and one or more, preferably one antitussive agent. This composition may additionally comprise one or more, preferably one central nervous system stimulant and/or one or more, preferably one antacid.

According to a third embodiment of this invention the pharmaceutical composition comprises meloxicam or a pharmaceutically acceptable salt thereof and at least one anti-H1-histamine.

In addition to meloxicam and one or more anti-H1-histamines mentioned above, the compositions of the third embodiment may also include other pharmacologically active substances such as an antacid, a central nervous system stimulant, an antitussive agent, an expectorant and/or a vitamin.

By using an antacid as a further ingredient an improvement of the bioavailability and/or a decrease of the possibility of side effects in the digestive system may be obtained.

The addition of a central nervous system stimulant may reinforce therapeutic effects such as analgesic, anti-inflammatory and antipyresis without the necessity of increasing the dose of meloxicam.

By using an antitussive agent as a further ingredient an additional alleviation of symptoms, like e.g. cough and sneezing, can be obtained.

By using an expectorant an additional alleviation of symptoms of common cold, like e.g. fever, sore throat, chill, headache, joint pain, muscular pain, and/or sputum, can be obtained.

By using a vitamin as a further ingredient a reinforcement of analgesic, anti-inflammatory and antipyresis therapeutic effects is obtainable.

Therefore a pharmaceutical composition according to this third embodiment may comprise meloxicam or a pharmaceutically acceptable salt thereof and one or more, preferably one anti-H1-histamine according to this invention and one or more, preferably one antacid. This composition may additionally comprise one or more, preferably one central nervous system stimulant, one or more, preferably one or two antitussive agents, one or more, preferably one expectorant and/or one or more, preferably one vitamin.

A further pharmaceutical composition according to this third embodiment may comprise meloxicam or a pharmaceutically acceptable salt thereof and one or more, preferably one anti-H1-histamine according to this invention and one or more, preferably one central nervous system stimulant. This composition may additionally comprise one or more, preferably one antacid, one or more, preferably one or two antitussive agents, one or more, preferably one expectorant and/or one or more, preferably one vitamin.

Again a further pharmaceutical composition according to this third embodiment may comprise meloxicam or a pharmaceutically acceptable salt thereof and one or more, preferably one anti-H1-histamine according to this invention and one or more,

preferably one or two antitussive agents. This composition may additionally comprise one or more, preferably one central nervous system stimulant, one or more, preferably one antacid, one or more, preferably one expectorant and/or one or more, preferably one vitamin.

Again a further pharmaceutical composition according to this third embodiment may comprise meloxicam or a pharmaceutically acceptable salt thereof and one or more, preferably one anti-H1-histamine according to this invention and one or more, preferably one expectorant. This composition may additionally comprise one or more, preferably one central nervous system stimulant, one or more, preferably one antacid, one or more, preferably one or two antitussive agents and/or one or more, preferably one vitamin.

Again a further pharmaceutical composition according to this third embodiment may comprise meloxicam or a pharmaceutically acceptable salt thereof and one or more, preferably one anti-H1-histamine according to this invention and one or more, preferably one vitamin. This composition may additionally comprise one or more, preferably one central nervous system stimulant, one or more, preferably one antacid, one or more, preferably one expectorant and/or one or more, preferably one or two antitussive agents.

Of the beforementioned pharmaceutical compositions of the third embodiment with three or more active ingredients the following pharmaceutical compositions are preferred:

- a pharmaceutical composition comprising meloxicam or a pharmaceutically acceptable salt thereof and one or more, preferably one anti-H1-histamine according to this invention and one or more, preferably one or two antitussive agents;

- a pharmaceutical composition comprising meloxicam or a pharmaceutically acceptable salt thereof and one or more, preferably one anti-H1-histamine according to this invention and one or more, preferably one or two antitussive

agents and one or more, preferably one central nervous system stimulant;

- a pharmaceutical composition comprising meloxicam or a pharmaceutically acceptable salt thereof and one or more, preferably one anti-H1-histamine according to this invention and one or more, preferably one or two antitussive agents and one or more, preferably one central nervous system stimulant and one or more, preferably one vitamin;

- a pharmaceutical composition comprising meloxicam or a pharmaceutically acceptable salt thereof and one or more, preferably one anti-H1-histamine according to this invention and one or more, preferably one or two antitussive agents and one or more, preferably one central nervous system stimulant and one or more, preferably one expectorant.

In the following the preferred active ingredients in the compositions according to this invention are described in more detail.

The compositions according to this invention may comprise one or more antitussive agents as a second active ingredient in addition to meloxicam. Antitussive agents used in this invention are not limited if the agents exhibit antitussive action.

Examples of such antitussive agents are alloclamide hydrochloride, cloperastine hydrochloride, cloperastine fendizoate, pentoxyverine citrate, tipepidine citrate, tipepidine hibenzate, dibunate sodium, dextromethorphan hydrobromide, dextromethorphan phenolphthalein, codeine phosphate, dihydrocodeine phosphate, noscapine hydrochloride, noscapine, dl-methylephedrine hydrochloride, *dl*-methylephedrine saccharinate, ephedrine hydrochloride, ephedrine sulfate, dimemorfan phosphate, eprazinone hydrobromide, clofedanol hydrochloride, benproperine phosphate, pholcodine, fominoben hydrochloride, ephedra herb (*Ephedrae herba*), nandina fruit (*Nandinae fructus*) and etc. These antitussive agents can be used solely or mixed with more than two kinds.

Ephedra herb and nandina fruit can be used as a dried powder, a dried extract, a

soft extract, a fluid extract, a tincture, oil, and the like, preferably, a dried extract, a soft extract and a fluid extract.

Preferably the one or more antitussive agents are selected from the group consisting of tipepidine citrate, tipepidine hibenzate, dextromethorphan hydrobromide, codeine phosphate, dihydrocodeine phosphate, noscapine hydrochloride, noscapine, dl-methylephedrine hydrochloride, dimemorfan phosphate, ephedra herb, and nandina fruit. More preferably the one or more antitussive agents are selected from the group consisting of tipepidine citrate, dextromethorphan hydrobromide, dihydrocodeine phosphate, noscapine hydrochloride, noscapine, and dl-methylephedrine hydrochloride.

The compositions according to this invention may comprise one or more expectorants as a second or further active ingredient in addition to meloxicam. Expectorants used in this invention are not limited if the agents exhibit expectorant action. However, in terms of safety of the agents with minimum or no adverse event, expectorants used in the field of non-prescription drugs are preferred.

Examples of such expectorants are potassium guaiacolsulfonate, guaifenesin, potassium cresolsulfonate, bromhexine hydrochloride, ambroxol hydrochloride, L-carbocisteine, L-methylcysteine hydrochloride, ethyl L-cysteine hydrochloride, fudosteine, ipecac (*Ipecacuanhae radix*), lycoris bulb (*Lycoridis bulbus*), fritillaria bulb (*Fritillariae bulbus*), cherry bark (*Pruni cortex*), platycodon root (*Platycodi radix*), senega (*Senegae radix*), apricot kernel (*Armeniacae semen*), polygala root (*Polygalae radix*), glycyrrhiza (*Glycyrrhizae radix*), plantago seed (*Plantaginis semen*), plantago herb (*Plantaginis herba*), etc. These expectorants can be used solely or mixed with more than two kinds.

Lycoris bulb, fritillaria bulb, cherry bark, platycodon root, senega, polygala root, glycyrrhiza, plantago seed and plantago herb can be used such as a dried powder, a dried extract, a soft extract, a fluid extract, a tincture, oil, and the like.

Preferably the one or more expectorants are selected from the group consisting of

potassium guaiacolsulfonate, guaifenesin, bromhexine hydrochloride, ambroxol hydrochloride, L-carbocisteine, ethyl L-cysteine hydrochloride, fudosteine, platycodon root and glycyrrhiza. More preferably the one or more expectorants are selected from the group consisting of guaifenesin, bromhexine hydrochloride, ambroxol hydrochloride, L-carbocisteine and fudosteine.

As a second or further active ingredient in addition to meloxicam, the compositions according to this invention may comprise one or more anti-H1-histamines selected from the group as listed hereinbefore and hereinafter. These antihistamines can be used in one or mixed with more than two kinds.

The anti-H1-histamine is preferably selected from the group consisting of diphenhydramine, diphenylpyraline, clemastine, triprolidine, promethazine, alimemazine, isothipendyl, iproheptine, difeterol, tripelennamine, thonzylamine, fenethazine, methdilazine, mebhydroline, cyproheptadine, homochlorcyclizine, hydroxyzine, ebastine, cetirizine, emedastine, bepotastine, azelastine, oxatomide, fexofenadine, olopatadine, loratadine, acrivastine, brompheniramine and doxylamin, including pharmaceutically acceptable salts thereof.

The invention may employ the anti-H1-histamines in either a non-salt form or a pharmaceutically acceptable acid addition salt thereof. The pharmaceutically acceptable acid addition salts of those anti-H1-histamines according to this invention include diphenhydramine hydrochloride, diphenhydramine salicylate, diphenhydramine tannate, diphenhydramine citrate, diphenylpyraline hydrochloride, diphenylpyraline teoclate, clemastine fumarate, triprolidine hydrochloride, promethazine hydrochloride, promethazine methylenedisalicylate, alimemazine tartrate, isothipendyl hydrochloride, iproheptine hydrochloride, difeterol hydrochloride, difeterol phosphate, tripelennamine hydrochloride, thonzylamine hydrochloride, fenethazine hydrochloride, fenethazine tannate, methdilazine hydrochloride, mebhydroline napadisylate, cyproheptadine hydrochloride, homochlorcyclizine hydrochloride, hydroxyzine hydrochloride, hydroxyzine pamoate, cetirizine hydrochloride, emedastine difumarate, bepotastine besilate, azelastine hydrochloride, fexofenadine hydrochloride, olopatadine hydrochloride,

brompheniramine maleate and doxylamin succinate. In the foregoing and in the following the term "anti-H1-histamine" encompasses both the non-salt form and pharmaceutically acceptable acid addition salts of the anti-H1-histamines according to this invention.

Preferably the one or more anti-H1-histamines are selected from the group consisting of diphenhydramine hydrochloride, diphenhydramine salicylate, diphenhydramine tannate, diphenylpyraline hydrochloride, diphenylpyraline teoclate, clemastine fumarate, triprolidine hydrochloride, promethazine hydrochloride, promethazine methylenedisalicylate, alimemazine tartrate, isothipendyl hydrochloride, iproheptine hydrochloride, difeterol hydrochloride, difeterol phosphate, tripelennamine hydrochloride, thonzylamine hydrochloride, fenethazine hydrochloride, methdilazine hydrochloride and mebhydroline napadisylate.

Examples of suitable antacids are aminoacetic acid, synthetic aluminum silicate, hydrotalcite, magnesium oxide, dihydroxy aluminum aminoacetate, aluminum hydroxide gel, dried aluminum hydroxide gel, aluminum hydroxide-sodium bicarbonate co-precipitate, magnesium carbonate, magnesium aluminometasilicate, magnesium hydroxide, sodium hydrogencarbonate and calcium hydrogenphosphate.

Examples of suitable central nervous system stimulants are caffeine (3,7-dihydro-1,3,7-trimethyl-1H-purine-2,6-dione monohydrate), anhydrous caffeine (3,7-dihydro-1,3,7-trimethyl-1H-purine-2,6-dione) and a salt complex of caffeine and sodium benzoate (caffeine and sodium benzoate). Also combinations of two or more central nervous system stimulants may be used.

Examples of suitable vitamins are vitamin B_1, vitamin B_2, vitamin C and hesperidin.

According to a preferred embodiment, the pharmaceutical composition according to this invention further comprises at least one pharmaceutically acceptable carrier and/or excipient. Suitable carriers and excipients are known to the one skilled in the

art and are described for example in Japanese Pharmaceutical Excipients Directory 2000 (edited by Japan Pharmaceutical Excipients Council, issued by Yakuji Nippo, Ltd.). Examples of suitable carriers and/or excipients are lactose, sucrose, glucose, mannitol, xylitol, corn starch, potato starch, wheat starch, rice starch, tapioca starch, sodium carboxymethyl starch, microcrystalline cellulose, ethylcellulose, hydroxypropylmethylcellulose, low substituted hydroxypropylcellulose, hydroxypropylcellulose, croscarmellose sodium, carmellose, carmellose potassium, carmellose calcium, carmellose sodium, polyvinylpyrrolidone, propyleneglycol, polyethyleneglycol, glycerol, vegetable oils, waxes, crospovidone, agar, light anhydrous silicic acid, magnesium stearate, talc, titanium oxide, acacia, sodium alginate, ethanol and purified water.

In addition this invention relates to a pharmaceutical dosage form which comprises a pharmaceutical composition according to this invention.

The amount of meloxicam used for the oral pharmaceutical dosage form described in the invention is preferably in the range from 1 to 30 mg, more preferably in the range from 2.5 to 15 mg, and most preferably in the range from 5 to 10 mg. These amounts correspond to the preferred dosage ranges with respect to an adult and once daily given dose.

According to the first embodiment of this invention the at least one second pharmaceutically active compound is selected from the group consisting of antitussive agents. Although the amount of the one or more antitussive agents in the oral pharmaceutical dosage form according to the present invention may be varied depending on the type of the antitussive agent. It preferably lies in the range from 1 to 12000 mg, and more preferably in the range from 2 to 10000 mg. These amounts correspond to the preferred dose given daily to an adult. In the following preferred amounts to be given daily to an adult (in the following called "daily combination dosage") of suitable antitussive agents comprised in a composition according to this invention are specified.

The daily combination dosage of alloclamide hydrochloride for an adult is usually

between 2 and 150 mg, preferably between 5 and 100 mg, more preferably between 7.5 and 75 mg.

Daily combination dosage of chloperastine hydrochloride for an adult is usually between 1 and 60 mg, preferably between 2 and 50 mg, more preferably between 4.8 and 48 mg.

Daily combination dosage of cloperastine fendizoate for an adult is usually between 2 and 105 mg, preferably between 5 and 90 mg, more preferably between 8.4 and 84 mg.

Daily combination dosage of pentoxyverine citrate for an adult is usually between 1 and 120 mg, preferably between 2 and 60 mg, more preferably between 4.8 and 48 mg.

Daily combination dosage of tipepidine citrate for an adult is usually between 1 and 120 mg, preferably between 4 and 90 mg, more preferably between 6 and 60 mg.

Daily combination dosage of tipepidine hibenzate for an adult is usually between 1 and 120 mg, preferably between 4 and 90 mg, more preferably between 7.5 and 75 mg.

Daily combination dosage of dibunate sodium for an adult is usually between 1 and 180 mg, preferably between 4 and 120 mg, more preferably between 9 and 90 mg.

Daily combination dosage of dextromethorphan hydrobromide for an adult is usually between 1 and 120 mg, preferably between 2 and 96 mg, more preferably between 4.8 and 48 mg.

Daily combination dosage of dextromethorphan phenolphthalein for an adult is usually between 1 and 120 mg, preferably between 2 and 96 mg, more preferably between 7.2 and 72 mg.

Daily combination dosage of codeine phosphate for an adult is usually between 1 and 60 mg, preferably between 2 and 50 mg, more preferably between 4.8 and 48 mg.

Daily combination dosage of dihydrocodeine phosphate for an adult is usually between 1 and 30 mg, preferably between 2 and 25 mg, more preferably between 2.4 and 24 mg.

Daily combination dosage of noscapine hydrochloride and noscapine for an adult is usually between 1 and 120 mg, preferably between 2 and 96 mg, more preferably between 4.8 and 48 mg.

Daily combination dosage of *dl*-methylephedrine hydrochloride and dl-methylephedrine saccharinate for an adult is usually between 1 and 150 mg, preferably between 3 and 75 mg, more preferably between 6 and 60 mg.

Daily combination dosage of ephedrine hydrochloride and ephedrine sulfate for an adult is usually between 1 and 75 mg, preferably between 2 and 50 mg, more preferably between 3 and 37.5 mg.

Daily combination dosage of dimemorfan phosphate for an adult is usually between 1 and 60 mg, preferably between 2 and 45 mg, more preferably between 3 and 30 mg.

Daily combination dosage of eprazinone hydrochloride for an adult is usually between 1 and 90 mg, preferably between 3 and 75 mg, more preferably between 6 and 60 mg.

Daily combination dosage of clofedanol hydrochloride for an adult is usually between 1 and 150 mg, preferably between 5 and 100 mg, more preferably between 7.5 and 75 mg.

Daily combination dosage of benproperine phosphate for an adult is usually between 2 and 160 mg, preferably between 4 and 120 mg, more preferably between 8 and 80 mg.

Daily combination dosage of pholcodine for an adult is usually between 3 and 180 mg, preferably between 6 and 135 mg, more preferably between 9 and 90 mg.

Daily combination dosage of fominoben hydrochloride for an adult is usually between 6 and 480 mg, preferably between 12 and 360 mg, more preferably between 24 and 240 mg.

Daily combination dosage of ephedra herb for an adult is usually between 10 and 5000 mg, preferably between 20 and 4500 mg, more preferably between 40 and 4000 mg as ephedra herb substance.

Daily combination dosage of nandina fruit for an adult is usually between 10 and 12000 mg, preferably between 20 and 11000 mg, more preferably between 50 and 10000 mg as ephedra herb substance.

According to the second embodiment of this invention the at least one second pharmaceutically active compound is selected from the group consisting of expectorants. Although the amount of the one or more expectorants in the oral

pharmaceutical dosage form according to the present invention may be varied depending on the type of the expectorant. It preferably lies in the range from 0.1 to 12000 mg, and more preferably in the range from 1 to 10000 mg. These amounts correspond to the preferred dose given daily to an adult. In the following preferred amounts to be given daily to an adult (in the following called "daily combination dosage") of suitable expectorants comprised in a composition according to this invention are specified.

A daily combination dosage of potassium guaiacolsulfonate for an adult is usually between 5 and 500 mg, preferably between 10 and 350 mg, more preferably between 25 and 250 mg.

A daily combination dosage of guaifenesin, for an adult is usually between 5 and 900 mg, preferably between 10 and 500 mg, more preferably between 25 and 250 mg.

A daily combination dosage of potassium cresolsulfonate, for an adult is usually between 5 and 540 mg, preferably between 10 and 360 mg, more preferably between 27 and 270 mg.

A daily combination dosage of bromhexine hydrochloride for an adult is usually between 0.1 and 24 mg, preferably between 0.5 and 18 mg, more preferably between 1 and 12 mg.

A daily combination dosage of ambroxol hydrochloride for an adult is usually between 1 and 90 mg, preferably between 2 and 60 mg, more preferably between 4 and 45 mg.

A daily combination dosage of L-carbocisteine for an adult is usually between 25 and 1500 mg, preferably between 50 and 1050 mg, more preferably between 75 and 750 mg.

A daily combination dosage of L-methylcysteine hydrochloride and ethyl L-cysteine hydrochloride for an adult is usually between 10 and 600 mg, preferably between 20 and 450 mg, more preferably between 30 and 300 mg.

A daily combination dosage of fudosteine for an adult is usually between 30 and 2400 mg, preferably between 60 and 1800 mg, more preferably between 120 and 1200 mg.

A daily combination dosage of ipecac as ipecac substance for an adult is usually

between 1 and 60 mg, preferably between 2 and 55 mg, more preferably between 5 and 50 mg.

A daily combination dosage of lycoris bulb as lycoris bulb substance for an adult is usually between 4 and 1000 mg, preferably between 6 and 900 mg, more preferably between 8 and 800 mg.

A daily combination dosage of fritillaria bulb as fritillaria bulb substance for an adult is usually between 5 and 4000 mg, preferably between 10 and 3000 mg, more preferably between 25 and 2500 mg.

A daily combination dosage of cherry bark, platycodon root, senega or apricot kernel each in the form of a crude drug substance for an adult is usually between 10 and 5000 mg, preferably between 20 and 4500 mg, more preferably between 40 and 4000 mg.

A daily combination dosage of polygala root, glycyrrhiza or plantago seed each in the form of a crude drug substance for an adult is usually between 10 and 6000 mg, preferably between 25 and 5500 mg, more preferably between 50 and 5000 mg.

A daily combination dosage of plantago herb as plantago herb substance for an adult is usually between 10 and 12000 mg, preferably between 50 and 11000 mg, more preferably between 100 and 10000 mg.

According to the third embodiment of this invention the at least one second pharmaceutically active compound is selected from the group consisting of anti-H1-histamines. Although the amount of the one or more anti-H1-histamines in the oral pharmaceutical dosage form according to the present invention may be varied depending on the type of the anti-H1-histamine, it preferably lies in the range from 0.1 to 450 mg, and more preferably in the range from 0.1 to 150 mg. These amounts correspond to the preferred dose given daily to an adult. In the following preferred amounts to be given daily to an adult (in the following called "daily combination dosage") of suitable anti-H1-histamines comprised in an oral pharmaceutical dosage form according to this invention are specified.

A daily combination dosage of diphenhydramine hydrochloride, diphenhydramine citrate, diphenhydramine salicylate and diphenhydramine tannate for an adult is usually between 5 and 450 mg, preferably between 10 and 150 mg, more

preferably between 15 and 75 mg.

A daily combination dosage of diphenylpyraline hydrochloride and diphenylpyraline teoclate for an adult is usually between 0.1 and 15 mg, preferably between 0.5 and 10 mg, more preferably between 1 and 5 mg.

A daily combination dosage of clemastine fumarate for an adult is usually between 0.1 and 4.5 mg, preferably between 0.2 and 3 mg, more preferably between 0.3 and 1.5 mg.

A daily combination dosage of triprolidine hydrochloride for an adult is usually between 0.1 and 9 mg, preferably between 0.3 and 6 mg, more preferably between 0.5 and 4 mg.

A daily combination dosage of promethazine hydrochloride and promethazine methylenedisalicylate for an adult is usually between 1 and 75 mg, preferably between 3 and 60 mg, more preferably between 5 and 40 mg.

A daily combination dosage of alimemazine tartrate for an adult is usually between 0.1 and 10 mg, preferably between 0.5 and 7.5 mg, more preferably between 1 and 5 mg.

A daily combination dosage of isothipendyl hydrochloride for an adult is usually between 0.1 and 24 mg, preferably between 0.5 and 12 mg, more preferably between 1 and 7 mg.

A daily combination dosage of iproheptine hydrochloride for an adult is usually between 10 and 225 mg, preferably between 20 and 200 mg, more preferably between 30 and 150 mg.

A daily combination dosage of difeterol hydrochloride and difeterol phosphate for an adult is usually between 5 and 180 mg, preferably between 10 and 135 mg, more preferably between 18 and 90 mg.

A daily combination dosage of tripelennamine hydrochloride for an adult is usually between 5 and 200 mg, preferably between 10 and 150 mg, more preferably between 20 and 100 mg.

A daily combination dosage of thonzylamine hydrochloride for an adult is usually between 2 and 100 mg, preferably between 5 and 75 mg, more preferably between 10 and 50 mg.

A daily combination dosage of fenethazine hydrochloride for an adult is usually between 2 and 180 mg, preferably between 5 and 90 mg, more preferably between

10 and 50 mg.

A daily combination dosage of fenethazine tannate for an adult is usually between 5 and 270 mg, preferably between 15 and 200 mg, more preferably between 27 and 135 mg.

A daily combination dosage of methdilazine hydrochloride for an adult is usually between 0.1 and 16 mg, preferably between 0.5 and 12 mg, more preferably between 1 and 8 mg.

A daily combination dosage of mebhydroline napadisylate for an adult is usually between 10 and 300 mg, preferably between 20 and 225 mg, more preferably between 30 and 150 mg.

A daily combination dosage of cyproheptadine hydrochloride for an adult is usually between 0.1 and 12 mg, preferably between 0.5 and 8 mg, more preferably between 1 and 6 mg.

A daily combination dosage of homochlorcyclizine hydrochloride for an adult is usually between 1 and 60 mg, preferably between 3 and 45 mg, more preferably between 6 and 30 mg.

A daily combination dosage of hydroxyzine hydrochloride for an adult is usually between 1 and 60 mg, preferably between 3 and 45 mg, more preferably between 6 and 30 mg.

A daily combination dosage of hydroxyzine pamoate for an adult is usually between 5 and 140 mg, preferably between 10 and 105 mg, more preferably between 15 and 70 mg.

A daily combination dosage of ebastine for an adult is usually between 0.1 and 10 mg, preferably between 0.5 and 7.5 mg, more preferably between 1 and 5 mg.

A daily combination dosage of cetirizine hydrochloride for an adult is usually between 0.5 and 20 mg, preferably between 1 and 15 mg, more preferably between 2 and 10 mg.

A daily combination dosage of emedastine difumarate for an adult is usually between 0.1 and 4 mg, preferably between 0.2 and 3 mg, more preferably between 0.4 and 2 mg.

A daily combination dosage of bepotastine besilate for an adult is usually between 1 and 40 mg, preferably between 2 and 30 mg, more preferably between 3 and 20 mg.

A daily combination dosage of azelastine hydrochloride for an adult is usually between 0.1 and 4 mg, preferably between 0.2 and 3 mg, more preferably between 0.4 and 2 mg.

A daily combination dosage of oxatomide for an adult is usually between 1 and 60 mg, preferably between 3 and 45 mg, more preferably between 6 and 30 mg.

A daily combination dosage of fexofenadine hydrochloride for an adult is usually between 5 and 240 mg, preferably between 10 and 180 mg, more preferably between 20 and 120 mg.

A daily combination dosage of olopatadine hydrochloride for an adult is usually between 0.5 and 20 mg, preferably between 1 and 15 mg, more preferably between 2 and 10 mg.

A daily combination dosage of loratadine for an adult is usually between 0.5 and 20 mg, preferably between 1 and 15 mg, more preferably between 2 and 10 mg.

A daily combination dosage of acrivastine for an adult is usually between 0.5 and 24 mg, preferably between 1 and 18 mg, more preferably between 2 and 12 mg.

A daily combination dosage of brompheniramine maleate for an adult is usually between 1 and 32 mg, preferably between 2 and 28 mg, more preferably between 4 and 24 mg.

A daily combination dosage of doxylamin succinate for an adult is usually between 5 and 150 mg, preferably between 10 and 100 mg, more preferably between 15 and 75 mg.

The oral pharmaceutical dosage form of the invention may be orally given in divided doses, as e.g. 2, 3 or 4 doses per day. However, the oral pharmaceutical dosage form is preferably given orally once a day. Dose adjustment of meloxicam and the antitussive agent may reflect age, body weight, and manifesting symptoms.

The oral pharmaceutical dosage form described in the present invention comprises tablets, granules, fine granules, powders, capsules, caplets, soft capsules, pills, oral solutions, syrups, dry syrups, chewable tablets, troches, effervescent tablets, drops, suspension, fast dissolving tablets or oral fast-dispersing tablets. Any of these formulations may be prepared using regular methods, and, in addition to the aforementioned components, any additives in common use may be used upon

preparation of these formulations, if necessary. In addition, preparations formed into microparticles such as microcapsules, nanocapsules, microspheres, nanospheres, and liposomes may also be included in the aforementioned formulations.

In addition, further components of the oral pharmaceutical dosage form and the formulation of all ingredients are preferably chosen in view of the desired mechanical, chemical and biological stability, release rate, masking of the taste, visual appearance, etc..

For example, the pharmaceutically active substances, i.e. meloxicam or a pharmaceutically salt thereof and the second pharmaceutically active agent, can be dispensed in separate granules, multi-layer granules, multi-layer tablets or dry coated tablets, tablets of separated granules, microcapsules, etc.. Coating preparations such as sugarcoated tablets, film coating tablets, coating granule, can be used as well as chewable tablets, oral fast dispersing tablets, matrix tablets, matrix granules, effervescent tablets, dusting powder, solid solutions, etc. These methods can also be combined. Moreover, the properties of the inventive oral pharmaceutical dosage form such as stability, release, continuance, disintegration, distinglation, dissolution, concealment of taste, improvement in usage etc. can be regulated by the addition of additives known in the art.

According to a preferred embodiment the oral dosage form is a combination of a first dosage form comprising meloxicam or a pharmaceutically acceptable salt thereof and a second dosage form comprising the at least second pharmaceutically active compound. Preferably the first dosage form releases the active ingredients faster than the second dosage form. The first dosage form may further comprise the second pharmaceutically active compound and optionally further active ingredients. The second dosage form may comprise further active ingredients. Preferably the second dosage form does not comprise meloxicam.

For example the dosage form is a two layer tablet wherein the first layer comprises meloxicam or a pharmaceutical acceptable salt thereof and optionally a second

pharmaceutically active compound, as for example an antitussive agent or an expectorant or an anti-H1-histamine, and optionally further active ingredients and pharmaceutically acceptable carriers and/or excipients. The second layer comprises the second pharmaceutically active compound, as for example an antitussive agent or an expectorant or an anti-H1-histamine, and optionally further active ingredients and pharmaceutically acceptable carriers and/or excipients, whereby the second layer has slow release properties compared with the first layer.

According to a further example the dosage form is a capsule comprising two kinds of granules. The first kind of granules comprise meloxicam or a pharmaceutical acceptable salt thereof and optionally a second pharmaceutically active compound, as for example an antitussive agent or an expectorant or an anti-H1-histamine, and optionally further active ingredients and pharmaceutically acceptable carriers and/or excipients. The second kind of granules comprise the second pharmaceutically active compound, as for example an antitussive agent or an expectorant or an anti-H1-histamine, and optionally further active ingredients and pharmaceutically acceptable carriers and/or excipients, whereby the second kind of granules have slow release properties compared with the first kind of granules.

These formulations may be prepared using regular methods by adding generally available pharmaceutical additives such as excipients, binders, disintegrators, lubricants, coating agents, sugar coating agents, plasticizers, antifoaming agents, polish, foaming agents, antistatic agents, desiccant, surfactant, solubilizer, buffer agents, resolvents, solubilizing agents, solvents, diluents, stabilizers, emulsifying agents, suspension, suspending agents, dispersing agents, isotonizing agents, adsorbents, reducing agents, antioxidant, wetting agents, wet modifier, filler, extender, adhesives, viscous agent, softeners, pH modifiers, antiseptics, preservatives, sweetening agents, corrigent, refrigerative agents, flavoring agents, perfume, fragrance, and coloring matters to the pharmacologically active compounds.

Examples of such additives are described in Japanese Pharmaceutical Excipients Directory 2000 (edited by Japan Pharmaceutical Excipients Council, issued by

Yakuji Nippo, Ltd.).

These preparations are preferably manufactured by adding pharmaceutical additives to the pharmacologically active compounds.

The pharmaceutical compositions and dosage forms according to this invention are advantageously usefull as analgesics, antipyretics, antitussives, expectorants and/or antihistaminics.

The invention relates to the use of the pharmaceutical composition and of the oral pharmaceutical dosage form, both as described hereinbefore, for the treatment and alleviation of a cold, including various symptoms thereof such as fever, sore throat, chills, headache, joint pain, muscular pain, cough, runny nose, stuffy nose, sputum and/or sneezing.

The pharmaceutical compositions and dosage forms of the invention are effective for the treatment and alleviation of a cold, including various symptoms thereof such as fever, sore throat, chills, headache, joint pain, muscular pain, cough, runny nose, stuffy nose, sputum and/or sneezing.

Furthermore, this invention relates to the use of a pharmaceutical composition as described hereinbefore for the manufacture of a medicament for the treatment or alleviation of a cold, including various symptoms thereof such as fever, sore throat, chills, headache, joint pain, muscular pain, cough, runny nose, stuffy nose, sputum and/or sneezing.

In addition, this invention relates to the use of meloxicam or a pharmaceutically acceptable salt thereof for the manufacture of an oral pharmaceutical dosage form according to this invention.

Thus, the invention also relates to the use of a pharmaceutically active compound selected from the group consisting of antitussive agents, expectorants and anti-H1-histamines for the manufacture of an oral pharmaceutical dosage form

according to this invention.

Consequently, this invention further relates to a method of treating or alleviating of a cold, including various symptoms thereof such as fever, sore throat, chills, headache, joint pain, muscular pain, cough, runny nose, stuffy nose, sputum and/or sneezing, in a patient in need of such treatment, which comprises orally administering to the patient a pharmaceutical composition according to this invention.

The patient to be treated according to this invention is a mammal, preferably a human.

The preferred daily dose orally administered to the patient according to this invention is in the range of 1 to 30 mg meloxicam, more preferably 2.5 to 15 mg meloxicam, and

a) in case the second pharmaceutically active compound is an antitussive agent, an amount of 1 to 12000 mg, more preferably 2 to 10000 mg, of the antitussive agent;

b) in case the second pharmaceutically active compound is an expectorant, an amount of 0.1 to 12000 mg, more preferably 1 to 10000 mg, of the expectorant;

c) in case the second pharmaceutically active compound is an anti-H1-histamine, an amount of of 0.1 to 450 mg, more preferably 0.1 to 150 mg, of the anti-H1-histamine.

The preferred doses regarding the various second pharmaceutically active compounds were specified above. Therefore, the amount of the dosage form to be taken by a patient per day, i.e. the number of tablets, capsules, caplets, troches, etc., or the amount of granules, syrup, solution, suspension, etc., e.g. measured in grams or milliliters, is such that the above specified preferred daily dose is achieved.

Meloxicam or a pharmaceutically acceptable salt thereof and the at least one pharmaceutically active compound are preferably combined in a single oral dosage form as described above. Both meloxicam or a salt thereof and the at least one

pharmaceutically active compound may also be simultaneously administered in two separate oral dosage forms, one containing meloxicam or a salt thereof and the other containing the second pharmaceutically active compound.

The compositions and dosage forms of the present invention are explained by the following examples which however do not limit the scope of the present invention. The examples 1.1 to 1.6 illustrate the first embodiment of the present invention, the examples 2.1 to 2.6 illustrate the second embodiment of the present invention and the examples 3.1 to 3.6 illustrate the third embodiment of the present invention.

Examples

Example 1.1

Tablet

The following ingredients were homogeneously mixed. The resulted mixed particles were compressed with a mold to prepare tablets at 250 mg each.

Meloxicam	45 g
Tipepidine hibenzate	150 g
dl-Methylephedrine hydrochloride	120 g
Lactose	579 g
Microcrystalline cellulose	576 g
Light anhydrous silicic acid	15 g
Talc	9 g
Magnesium stearate	6 g

Example 1.2

Powder

The following ingredients were homogeneously mixed. The resulted mixed particles were divided into portions of 500 mg to prepare powder compositions.

Meloxicam	15 g
Dimemorfan phosphate	20 g
Corn starch	475 g

Lactose	480 g
Magnesium stearate	10 g

Example 1.3

Two layer tablet

The following ingredients of the layer A and the layer B were processed through a regular method to provide mixed particles, respectively, and the particles were compressed to form two-layer tablets at 220 mg (layer A 100mg, layer B 120mg) each.

Layer A	
Meloxicam	45 g
Dihydrocodeine phosphate	48 g
dl-Methylephedrine hydrochloride	120 g
Noscapine	96 g
Lactose	429 g
Microcrystalline cellulose	426 g
Sodium lauryl sulfate	12 g
Light anhydrous silicic acid	12 g
Talc	6 g
Magnesium stearate	6 g
Layer B	
Dihydrocodeine phosphate	96 g
dl-Methylephedrine hydrochloride	240 g
Noscapine	192 g
Lactose	226 g
Fumaric acid	132 g
Hydroxypropylmethylcellulose 2208	180 g
Hydrogenated oil	120 g
Stearic acid	120 g
Glycerol esters of fatty acids	120 g
Magnesium stearate	14 g

Example 1.4

Granules

The following ingredients were prepared as granules through a regular method to prepare mixed particles, and packed to give an amount of 1500 mg per one pack for granules.

Meloxicam	15 g
Dextromethorphan hydrobromide	32 g
Ephedra herb extract	440 g
(corresponds to Ephedra herb	2 kg)
Nandina fruit extract	700 g
(corresponds to Nandina fruit	3.84 kg)
Calcium carboxymethylcellulose	240 g
Mannitol	1260 g
Corn starch	280 g
Aspartame	15 g
Acesulfame potassium	15 g
Fragrant materials	3 g

Example 1.5

Capsules

The following ingredients were prepared as fast release granules and slow release granules through regular methods, and capsule-filled to give an amount of 225 mg (fast release granules: 75 mg, slow release granules: 150 mg) per one capsules.

Fast release granules	
Meloxicam	60 g
Dihydrocodeine phosphate	64 g
dl-Methylephedrine hydrochloride	160 g
Noscapine	128 g
Microcrystalline cellulose	788 g
Slow release granules	
Dihydrocodeine phosphate	128 g

dl-Methylephedrine hydrochloride	320 g
Noscapine	256 g
Fumaric acid	176 g
Microcrystalline cellulose	1304 g
Ethylcellulose (coating layer)	128 g
Hydroxypropylmethylcellulose (coating layer)	32 g
Glycerol esters of fatty acids (coating layer)	44 g
Talc (coating layer)	12 g

Example 1.6

Capsules

The following ingredients were prepared as fast release granules and slow release granules through regular methods, and capsule-filled to give an amount of 225 mg (fast release granules: 75 mg, slow release granules: 150 mg) per one capsules.

Fast release granules	
Meloxicam	60 g
Cloperastine hydrochloride	128 g
dl-Methylephedrine hydrochloride	160 g
Anhydrous caffeine	200 g
Microcrystalline cellulose	652 g
Slow release granules	
Cloperastine hydrochloride	256 g
dl-Methylephedrine hydrochloride	320 g
Anhydrous caffeine	400 g
Fumaric acid	240 g
Microcrystalline cellulose	704 g
Methacrylic acid copolymer S (coating layer)	336 g
Glycerol esters of fatty acids (coating layer)	100 g
Talc (coating layer)	44 g

Example 2.1

Tablet

The following ingredients were homogeneously mixed. The resulted mixed particles were compressed with a mold to prepare tablets at 250 mg each.

Meloxicam	45 g
Cherry bark extract	240 g
(corresponds to Cherry bark	400g)
Lactose	591 g
Microcrystalline cellulose	594 g
Light anhydrous silicic acid	15 g
Talc	9 g
Magnesium stearate	6 g

Example 2.2

Powder

The following ingredients were homogeneously mixed. The resulted mixed particles were divided into portions of 750 mg to prepare powder compositions.

Meloxicam	15 g
L-carbocisteine	500 g
Corn starch	490 g
Lactose	480 g
Magnesium stearate	15 g

Example 2.3

Two layer tablet

The following ingredients of the layer A and the layer B were processed through a regular method to provide mixed particles, respectively, and the particles were compressed to form two-layer tablets at 220 mg (layer A 100mg, layer B 120mg) each.

Layer A

Meloxicam	45 g
Ambroxol hydrochloride	90 g
Dihydrocodeine phosphate	48 g

dl-Methylephedrine hydrochloride	120 g
Lactose	435 g
Microcrystalline cellulose	426 g
Sodium lauryl sulfate	12 g
Light anhydrous silicic acid	12 g
Talc	6 g
Magnesium stearate	6 g
Layer B	
Ambroxol hydrochloride	180 g
Dihydrocodeine phosphate	96 g
dl-Methylephedrine hydrochloride	240 g
Lactose	181 g
Fumaric acid	129 g
Hydroxypropylmethylcellulose 2208	180 g
Hydrogenated oil	120 g
Stearic acid	120 g
Glycerol esters of fatty acids	120 g
Magnesium stearate	14 g

Example 2.4

Granules

The following ingredients were prepared as granules through a regular method to prepare mixed particles, and packed to give an amount of 1200 mg per one pack for granules.

Meloxicam	15 g
Glycyrrhiza extract	180 g
(corresponds to Glycyrrhiza	1.5 kg)
Platycodon root extract	200 g
(corresponds to Platycodon root	2 kg)
Senega extract	72 g
(corresponds to Senega	1.2 kg)
Calcium carboxymethylcellulose	240 g

Mannitol	1360 g
Corn starch	307 g
Aspartame	12 g
Acesulfame potassium	12 g
Fragrant materials	2 g

Example 2.5

Capsules

The following ingredients were prepared as fast release granules and slow release granules through regular methods, and capsule-filled to give an amount of 225 mg (fast release granules: 75 mg, slow release granules: 150 mg) per one capsules.

Fast release granules	
Meloxicam	60 g
Ambroxol hydrochloride	120 g
Dihydrocodeine phosphate	64 g
dl-Methylephedrine hydrochloride	160 g
Noscapine	128 g
Microcrystalline cellulose	668 g
Slow release granules	
Ambroxol hydrochloride	240 g
Dihydrocodeine phosphate	128 g
dl-Methylephedrine hydrochloride	320 g
Noscapine	256 g
Fumaric acid	240 g
Microcrystalline cellulose	1000 g
Ethylcellulose (coating layer)	128 g
Hydroxypropylmethylcellulose (coating layer)	32 g
Glycerol esters of fatty acids (coating layer)	44 g
Talc (coating layer)	12 g

Example 2.6

Capsules

The following ingredients were prepared as fast release granules and slow release granules through regular methods, and capsule-filled to give an amount of 350 mg (fast release granules: 115 mg, slow release granules: 235 mg) per one capsules.

Fast release granules	
Meloxicam	60 g
Guaifenesin	666.4 g
dl-Methylephedrine hydrochloride	160 g
Anhydrous caffeine	200 g
Microcrystalline cellulose	753.6 g
Slow release granules	
Guaifenesin	1333.6 g
dl-Methylephedrine hydrochloride	320 g
Anhydrous caffeine	400 g
Fumaric acid	480 g
Microcrystalline cellulose	714.4 g
Methacrylic acid copolymer S (coating layer)	360 g
Glycerol esters of fatty acids (coating layer)	104 g
Talc (coating layer)	48 g

Example 3.1

Two layer tablet

The following ingredients of the layer A and the layer B are processed through a regular method to provide mixed particles, respectively, and the particles are compressed to form two layer tablets at 300 mg (layer A 100 mg, layer B 200 mg) each.

Layer A:	
Meloxicam	45 g
Diphenhydramine hydrochloride	150 g
Ambroxol hydrochloride	90 g
Dihydrocodeine phosphate	48 g
dl-Methylephedrine hydrochloride	120 g

Anhydrous caffeine	300 g
Lactose	435 g
Microcrystalline cellulose	558 g
Sodium lauryl sulfate	18 g
Light anhydrous silicic acid	18 g
Talc	9 g
Magnesium stearate	9 g
Layer B:	
Diphenhydramine hydrochloride	300 g
Ambroxol hydrochloride	180 g
Dihydrocodeine phosphate	96 g
dl-methylephedrine hydrochloride	240 g
Anhydrous caffeine	600 g
Lactose	168 g
Fumaric acid	300 g
Succinic acid	60 g
Hydroxypropylmethylcellulose 2208	540 g
Hydrogenated oil	360 g
Stearic acid	360 g
Glycerol esters of fatty acids	360 g
Magnesium stearate	36 g

Example 3.2

Two layer tablet

The following ingredients of the layer A and the layer B are processed through a regular method to provide mixed particles, respectively, and the particles are compressed to form two layer tablets at 200 mg (layer A 80 mg, layer B 120 mg) each.

Layer A:	
Meloxicam	45.0 g
Diphenylpyraline hydrochloride	8.0 g
Noscapine	60.0 g

dl-Methylephedrine hydrochloride	60.0 g
Anhydrous caffeine	192.0 g
Lactose	491.8 g
Microcrystalline cellulose	540.0 g
Sodium lauryl sulfate	14.4 g
Light anhydrous silicic acid	14.4 g
Talc	7.2 g
Magnesium stearate	7.2 g
Layer B:	
Diphenylpyraline hydrochloride	16.0 g
Noscapine	120.0 g
dl-Methylephedrine hydrochloride	120.0 g
Anhydrous caffeine	384.0 g
Lactose	310.4 g
Fumaric acid	162.0 g
Hydroxypropylmethylcellulose 2208	180.0 g
Hydrogenated oil	282.0 g
Stearic acid	282.0 g
Glycerol esters of fatty acids	282.0 g
Magnesium stearate	21.6 g

Example 3.3

Granules

The following ingredients are prepared as granules through a regular method to prepare mixed particles, and packed to give an amount of 1000 mg per one pack of granules.

Meloxicam	37.5 g
Clemastine fumarate	6.7 g
Dihydrocodeine phosphate	40.0 g
dl-Methylephedrine hydrochloride	100.0 g
Bromhexine hydrochloride	20.0 g
Anhydrous caffeine	250.0 g

Calcium carboxymethylcellulose	500.0 g
Mannitol	3500.0 g
Corn starch	490.8 g
Aspartame	25.0 g
Acesulfame potassium	25.0 g
Fragrant materials	5.0 g

Example 3.4

Capsules

The following ingredients are prepared as fast release granules and slow release granules through regular methods, and capsule-filled to give an amount of 270 mg (fast release granules: 90 mg, slow release granules: 180 mg) per one capsule.

Fast release granules:	
Meloxicam	60.0 g
Triprolidine hydrochloride	9.6 g
Tipepidine hibenzate	160.0 g
dl-Methylephedrine hydrochloride	160.0 g
Anhydrous caffeine	240.0 g
Microcrystalline cellulose	810.4 g
Slow release granules:	
Triprolidine hydrochloride	19.2 g
Tipepidine hibenzate	320.0 g
dl-Methylephedrine hydrochloride	320.0 g
Anhydrous caffeine	480.0 g
Fumaric acid	288.0 g
Microcrystalline cellulose	1236.8 g
Ethylcellulose (coating layer)	136.0 g
Hydroxypropylmethylcellulose (coating layer)	24.0 g
Glycerol esters of fatty acids (coating layer)	44.0 g
Talc (coating layer)	12.0 g

Example 3.5

Capsules

The following ingredients are prepared as fast release granules and slow release granules through regular methods, and capsule-filled to give an amount of 350 mg (fast release granules: 115 mg, slow release granules: 235 mg) per one capsules.

Fast release granules:	
Meloxicam	60.0 g
Isothipendyl hydrochloride	24.0 g
Guaifenesin	666.4 g
dl-Methylephedrine hydrochloride	160.0 g
Anhydrous caffeine	200.0 g
Microcrystalline cellulose	729.6 g
Slow release granules:	
Isothipendyl hydrochloride	32.0 g
Guaifenesin	1333.6 g
dl-Methylephedrine hydrochloride	320.0 g
Anhydrous caffeine	400.0 g
Fumaric acid	400.0 g
Succinic acid	80.0 g
Microcrystalline cellulose	682.4 g
Methacrylic acid copolymer S (coating layer)	360.0 g
Glycerol esters of fatty acids (coating layer)	104.0 g
Talc (coating layer)	48.0 g

Example 3.6

Tablet

The following ingredients are homogeneously mixed. The resulted mixed particles are compressed with a mold to prepare tablets at 250 mg each.

Meloxicam	15 g
Ebastine	10 g
Noscapine	40 g
Anhydrous caffeine	100 g

Ascorbic acid	200 g
Lactose	200 g
Microcrystalline cellulose	420 g
Light anhydrous silicic acid	5 g
Talc	6 g
Magnesium stearate	4 g

Claims

1. A pharmaceutical composition comprising meloxicam or a pharmaceutically acceptable salt thereof and a second pharmaceutically active compound selected from the group consisting of antitussive agents, expectorants and anti-H1-histamines.

2. The pharmaceutical composition according to claim 1 comprising meloxicam or a pharmaceutically acceptable salt thereof and at least one antitussive agent.

3. The pharmaceutical composition according to claim 1 comprising meloxicam or a pharmaceutically acceptable salt thereof and at least one expectorant.

4. The pharmaceutical composition according to claim 1 comprising meloxicam or a pharmaceutically acceptable salt thereof and at least one anti-H1-histamine.

5. The pharmaceutical composition according to claim 3 further comprising at least one antitussive agent.

6. The pharmaceutical composition according to claim 4 further comprising at least one antitussive agent.

7. The pharmaceutical composition according to claim 4 or 6 further comprising at least one expectorant.

8. The pharmaceutical composition according to claim 4, 6 or 7 further comprising at least one vitamin.

9. The pharmaceutical composition according to one or more of the previous claims further comprising one or more antacids.

10. The pharmaceutical composition according to one or more of the previous further comprising one or more central nervous system stimulants.

11. The pharmaceutical composition according to one or more of the previous claims further comprising at least one pharmaceutically acceptable carrier and/or excipient.

12. The pharmaceutical composition according to the previous claims, wherein the antitussive agent is selected from the group consisting of alloclamide hydrochloride, chloperastine hydrochloride, cloperastine fendizoate, pentoxyverine citrate, tipepidine citrate, tipepidine hibenzate, dibunate sodium, dextromethorphan hydrobromide, dextromethorphan phenolphthalein, codeine phosphate, dihydrocodeine phosphate, noscapine hydrochloride, noscapine, *dl*-methylephedrine hydrochloride, dl-methylephedrine saccharinate, ephedrine hydrochloride, ephedrine sulfate, dimemorfan phosphate, eprazinone hydrobromide, clofedanol hydrochloride, benproperine phosphate, pholcodine, fominoben hydrochloride, ephedra herb and nandina fruit.

13. The pharmaceutical composition according to the previous claims, wherein the expectorant is selected from the group consisting of potassium guaiacolsulfonate, guaifenesin, potassium cresolsulfonate, bromhexine hydrochloride, ambroxol hydrochloride, L-carbocisteine, L-methylcysteine hydrochloride, ethyl L-cysteine hydrochloride, fudosteine, ipecac (*Ipecacuanhae radix*), lycoris bulb (*Lycoridis bulbus*), fritillaria bulb (*Fritillariae bulbus*), cherry bark (*Pruni cortex*), platycodon root (*Platycodi radix*), senega (*Senegae radix*), apricot kernel (*Armeniacae semen*), polygala root (*Polygalae radix*), glycyrrhiza (*Glycyrrhizae radix*), plantago seed (*Plantaginis semen*), plantago herb (*Plantaginis herba*).

14. The pharmaceutical composition according to the previous claims, wherein the anti-H1-histamine is selected from the group consisting of diphenhydramine, diphenylpyraline, clemastine, triprolidine, promethazine, alimemazine, isothipendyl, iproheptine, difeterol, tripelennamine, thonzylamine, fenethazine, methdilazine, mebhydroline, cyproheptadine, homochlorcyclizine, hydroxyzine, ebastine, cetirizine, emedastine, bepotastine, azelastine, oxatomide,

fexofenadine, olopatadine, loratadine, acrivastine, brompheniramine and doxylamin, including pharmaceutically acceptable salts thereof.

15. The pharmaceutical composition according to claim 14, wherein the anti-H1-histamine is selected from the group consisting of diphenhydramine hydrochloride, diphenhydramine salicylate, diphenhydramine tannate, diphenylpyraline hydrochloride, diphenylpyraline teoclate, clemastine fumarate, triprolidine hydrochloride, promethazine hydrochloride, promethazine methylenedisalicylate, alimemazine tartrate, isothipendyl hydrochloride, iproheptine hydrochloride, difeterol hydrochloride, difeterol phosphate, tripelennamine hydrochloride, thonzylamine hydrochloride, fenethazine hydrochloride, methdilazine hydrochloride and mebhydroline napadisylate.

16. An oral pharmaceutical dosage form comprising a pharmaceutical composition according to one or more of the claims 1 to 15.

17. The oral pharmaceutical dosage form according to claim 16 wherein the amount of meloxicam or a pharmaceutically acceptable salt thereof is in the range of 1 to 30 mg.

18. The oral pharmaceutical dosage form according to claim 16 or 17 wherein the amount of the second pharmaceutically active compound is:

a) in the range from 1 to 12000 mg in case the second pharmaceutically active compound is one or more antitussive agents;

b) in the range from 0.1 to 12000 mg in case the second pharmaceutically active compound is one or more expectorants;

c) in the range from 0.1 to 450 mg in case the second pharmaceutically active compound is one or more anti-H1-histamines.

19. Use of an oral pharmaceutical dosage form according to one or more of the claims 16 to 18 as an analgesic, an antipyretic, antitussive, expectorant and/or antihistaminic.

20. Use of an oral pharmaceutical dosage form according to one or more of the claims 16 to 18 for the treatment or alleviation of a cold, including various symptoms thereof such as fever, sore throat, chills, headache, joint pain, muscular pain, cough, runny nose, stuffy nose, sputum and/or sneezing.

21. Use of a pharmaceutical composition according to one or more of the claims 1 to 15 for the manufacture of a medicament for the treatment or alleviation of a cold, including various symptoms thereof such as fever, sore throat, chills, headache, joint pain, muscular pain, runny nose, stuffy nose, sputum and/or sneezing.

22. A method of treating or alleviating of a cold, including various symptoms thereof such as fever, sore throat, chills, headache, joint pain, muscular pain, runny nose, stuffy nose, sputum and/or sneezing, in a patient in need of such treatment, which comprises orally administering to the patient a pharmaceutical composition according to one or more of the claims 1 to 15.

23. The method according to claim 22 characterized by orally administering to the patient an amount of 1 to 30 mg of meloxicam or a pharmaceutically acceptable salt thereof and

a) in case the second pharmaceutically active compound is an antitussive agent, an amount of 1 to 12000 mg of an anitussive agent;

b) in case the second pharmaceutically active compound is an expectorant, an amount of 0.1 to 12000 mg of an expectorant;

c) in case the second pharmaceutically active compound is a anit-H1-histamine , an amount of 0.1 to 450 mg of an anti-H1-histamine.

24. Use of meloxicam or a pharmaceutically acceptable salt thereof for the manufacture of an oral pharmaceutical dosage form according to one or more of the claims 16 to 18.

25. Use of a pharmaceutically active compound selected from the group consisting of antitussive agents, expectorants and anti-H1-histamines, for the

manufacture of an oral pharmaceutical dosage form according to one or more of the claims 16 to 18.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/003231

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/541 A61P11/00 A61P19/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/070251 A (ADCOCK INGRAM LIMITED; NORRIS, MICHAEL, CHRISTIAN) 28 August 2003 (2003-08-28) page 3, paragraph 4; claims 7,28,29; table 1	1,2, 5-12, 16-25
X	US 2003/171391 A1 (GAIDA WOLFRAM ET AL) 11 September 2003 (2003-09-11) paragraph '0017!	1,3,5, 7-11,13, 16-25
P,X	WO 2005/000297 A (PHARMACIA CORPORATION; SIEBERT, KAREN) 6 January 2005 (2005-01-06) paragraphs '0437!, '0444! page 130, lines 2,4,7; table 4c	1,4,11, 16,19, 24,25

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 August 2005	26/08/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Loher, F

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2005/003231

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 19, 20, 22, 23 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/003231

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