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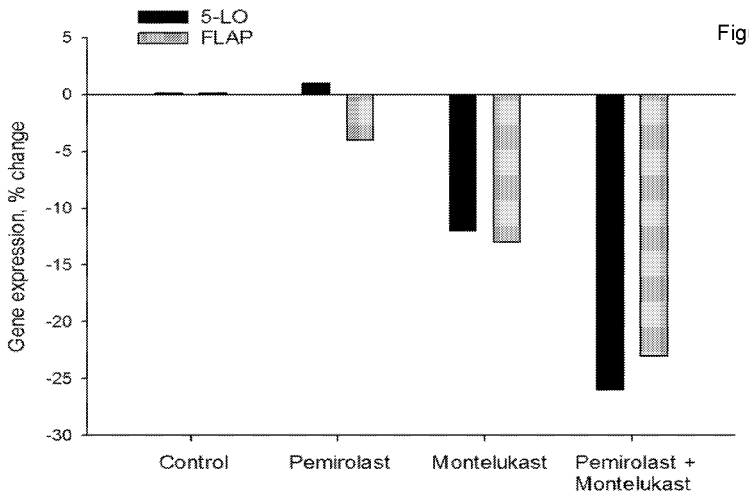


Figure 1

(57) Abstract: There is provided combination products comprising (a) pemirolast, or a pharmaceutically-acceptable salt or solvate thereof; and (b) montelukast, or a pharmaceutically-acceptable salt or solvate thereof. Such combination products5 find particular utility in asthma and related conditions.

NEW COMBINATION OF PEMIROLAST AND MONTELUKAST

Field of the Invention

This invention relates to a novel pharmaceutical combination.

Background and Prior Art

Asthma is one of the most common chronic inflammatory diseases, known to affect nearly 25 million citizens in the US alone. In childhood, it is the most common chronic disease, affecting in the region of an estimated 7 million US children.

The pathophysiology of asthma is complex and involves airway inflammation, intermittent airflow obstruction, and bronchial (airway) hyper-responsiveness, resulting in shortness of breath, wheezing, coughing, chest tightness and/or pain, as well as other non-specific symptoms in young children, including recurrent bronchitis, bronchiolitis, or pneumonia and the like.

Diagnosis may be made under guidelines from the (US) National Asthma Education and Prevention Program and include prevalence of episodic symptoms of airflow obstruction and/or at least partially reversible airflow obstruction or symptoms, followed by spirometry with post-bronchodilator response, and/or chest radiography (mainly to rule out other pulmonary diseases), as more definitive diagnostic tools.

There is presently no cure for asthma, and treatments often revolve around avoidance of known triggers, such as allergens, dust, pollutants, etc.

In the management and/or treatment of asthma, the ultimate goal is to prevent symptoms, minimize morbidity and prevent functional and psychological morbidity to provide a healthy (or near healthy) lifestyle.

However, there is also a need to reduce the numerical frequency and severity of acute asthma episodes. Such acute exacerbations of asthma are usually

commonly referred to as “asthma attacks”. Symptoms include shortness of breath, wheezing, and tightness in the chest. In severe cases, breathing may be significantly impaired such that the condition may become life-threatening.

Acute asthma attacks can often be brought on by infections, allergens, air pollution, exercise or insufficient or inappropriate medication use.

The most commonly-used active agents are presently employed to prevent asthma episodes (“preventers”). Such medications make the airways less sensitive, reduce airway inflammation and help to dry up mucus. Such preventers need to be taken every day to prevent symptoms and asthma attacks, and it may take a few weeks before they reach their full effect. Preventer medications include long-acting bronchodilators, oral theophylline, inhaled corticosteroids, leukotriene modifiers, cromones (cromolyn or nedocromil) and anti-IgE antibodies.

On the other hand, relief medications (“relievers”) are fast acting medications that give quick relief of existing asthma symptoms or “attacks” (wheeze, cough, shortness of breath). They are bronchodilators, which means that they relax the muscle around the outside of the airway, which opens the airway. Every asthmatic patient should have a reliever medication. There are three main categories of reliever medication: theophylline; short-acting beta-agonists, such as terbutaline and salbutamol; and anticholinergics, such as ipratropium.

A more severe condition, known as status asthmaticus or acute severe asthma, is an acute exacerbation of asthma that does not respond well to such standard treatments.

Additionally, there are drawbacks associated with all of the aforementioned drugs (particularly inhaled corticosteroids), including lack of efficacy, non-adherence to treatment regimens, tolerance dependence and safety profiles/side-effects. Accordingly, there is thus a real clinical need for safer and/or more effective treatments of asthma.

Pemirolast is an orally-active anti-allergic mast cell inhibitor that is used in the prevention of conditions such as asthma, allergic rhinitis and conjunctivitis. See, for example, US patent No. 4,122,274, European Patent Applications EP 316 174 and EP 1 285 921 and *Drugs of Today*, **28**, 29 (1992). The drug is only known for the prophylaxis (i.e. preventative treatment) of asthma, and indeed has been marketed for over 20 years in e.g. Japan as the potassium salt in 5 and 10 mg doses (equating to 4.25 and 8.5 mg of the free acid, respectively) e.g. under the trademark ALEGYSAL™.

Montelukast is an orally-active non-steroidal immunomodulating compound that is used for the maintenance treatment and prevention of symptoms of seasonal allergies (see e.g. Hon *et al*, *Drug Design, Development and Therapy*, **8**, 839 (2014)). It acts by blocking the action of, primarily, leukotriene D4 (as well as leukotrienes C4 and E4) on the cysteinal leukotriene receptor CysLT1 in the airways. It is thought not to be useful in the treatment of acute asthma attacks (see e.g. Zubairi *et al*, *BMC Pulm. Med.*, **13**, 20 (2013)).

Methods of treating infectious diseases with mast cell inhibitors are described in WO 2013/148366. The use of leukotriene receptor antagonists to treat Alzheimer's Disease is described in CN 103505731. The use of antiallergic agents that are not histamine H1 receptor antagonists to treat insect bites and stings is described in JP 2005089345.

US 2004/0180868 discloses methods of reducing systemic inflammation by administration of a leukotriene inhibitor, an antihistamine and a corticosteroid. WO 2011/058331 discloses the use of pemirolast in the treatment of systemic low grade inflammation.

US 2011/0086023 discloses topical formulations comprising combinations of antihistamines with numerous different classes of drugs, including steroids, leukotriene blockers and mast cell stabilizers for use in the treatment of allergic rhinitis.

Montelukast was found not to provide any clinically-applicable additional benefit in patients over the mast cell inhibitor, sodium cromoglycate, in relation to

inhibition of bronchoconstriction provoked by mannitol (Anderson *et al*, *Journal of Asthma*, **47**, 429 (2010)).

The use of combination products comprising, specifically, pemirolast and montelukast to treat, for example, asthma, is not specifically disclosed in any of the above-mentioned documents.

Disclosure of the Invention

According to the invention, there is provided a combination product comprising:
(a) pemirolast, or a pharmaceutically-acceptable salt or solvate thereof; and
(b) montelukast, or a pharmaceutically-acceptable salt or solvate thereof,
which combination products are referred to hereinafter as "the combination products according to the invention".

Pharmaceutically-acceptable salts that may be mentioned include acid addition salts and base addition salts. Such salts may be formed by conventional means, for example by reaction of a free acid or a free base form of an active ingredient with one or more equivalents of an appropriate acid or base, optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using standard techniques (e.g. *in vacuo*, by freeze-drying or by filtration). Salts may also be prepared by exchanging a counter-ion of an active ingredient in the form of a salt with another counter-ion, for example using a suitable ion exchange resin.

Preferred salts include, for example, hydrochloride, bisulfate, maleate, mesylate, tosylate, alkaline earth metal salts, such as calcium and magnesium, or alkali metal salts, such as sodium and potassium salts. Preferred salts of pemirolast include alkaline earth, and more particularly alkali, metal salts, such as calcium, magnesium, particularly potassium and sodium salts (see e.g. international patent application WO 2010/146348). Preferred salts of montelukast include sodium salts and dicyclohexylamine salts.

Montelukast may be employed in enantiomerically-enriched form. By "enantiomerically-enriched" we mean, respectively, any mixture of the

enantiomers of montelukast, in which one isomer is present in a greater proportion than the other. For example, enantiomers of montelukast with optical purities (enantiomeric excess; e.e.) of greater than 90% may be employed.

Combination products according to the invention provide for the administration of pemirolast in conjunction with montelukast, and may thus be presented either as separate formulations, wherein at least one of those formulations comprises pemirolast, and at least one comprises montelukast, or may be presented (i.e. formulated) as a combined preparation (i.e. presented as a single formulation including pemirolast and montelukast).

Thus, there is further provided:

(1) a pharmaceutical formulation including pemirolast, or a pharmaceutically-acceptable salt or solvate thereof; montelukast, or a pharmaceutically-acceptable salt or solvate thereof; and a pharmaceutically-acceptable adjuvant, diluent or carrier (which formulation is hereinafter referred to as a "combined preparation"); and

(2) a kit of parts comprising components:

(A) a pharmaceutical formulation including pemirolast, or a pharmaceutically-acceptable salt or solvate thereof, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(B) a pharmaceutical formulation including montelukast, or a pharmaceutically-acceptable salt or solvate thereof, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier,

which components (A) and (B) are each provided in a form that is suitable for administration in conjunction with the other.

According to a further aspect of the invention, there is provided a method of making a kit of parts as defined above, which method comprises bringing component (A), as defined above, into association with a component (B), as defined above, thus rendering the two components suitable for administration in conjunction with each other.

By bringing the two components "into association with" each other, we include that components (A) and (B) of the kit of parts may be:

(i) provided as separate formulations (i.e. independently of one another), which are subsequently brought together for use in conjunction with each other in combination therapy; or

(ii) packaged and presented together as separate components of a "combination pack" for use in conjunction with each other in combination therapy.

Thus, there is further provided a kit of parts comprising:

(I) one of components (A) and (B) as defined herein; together with

(II) instructions to use that component in conjunction with the other of the two components.

The kits of parts described herein may comprise more than one formulation including an appropriate quantity/dose of pemirolast/salt/solvate, and/or more than one formulation including an appropriate quantity/dose of montelukast/salt/solvate, in order to provide for repeat dosing. If more than one formulation (comprising either active compound) is present, such formulations may be the same, or may be different in terms of the dose of either compound, chemical composition(s) and/or physical form(s).

With respect to the kits of parts as described herein, by "administration in conjunction with", we include that respective formulations comprising pemirolast (or salt/solvate thereof) and montelukast (or salt/solvate thereof) are administered, sequentially, separately and/or simultaneously, over the course of treatment of the relevant condition.

Thus, in respect of the combination product according to the invention, the term "administration in conjunction with" includes that the two components of the combination product (pemirolast and montelukast) are administered (optionally repeatedly), either together, or sufficiently closely in time, to enable a beneficial effect for the patient, that is greater, over the course of the treatment of the relevant condition, than if either a formulation comprising pemirolast, or a formulation comprising montelukast, are administered (optionally repeatedly) alone, in the absence of the other component, over the same course of treatment.

Determination of whether a combination provides a greater beneficial effect in respect of, and over the course of treatment of, a particular condition will depend upon the condition to be treated or prevented, but may be achieved routinely by the skilled person.

Further, in the context of a kit of parts according to the invention, the term "in conjunction with" includes that one or other of the two formulations may be administered (optionally repeatedly) prior to, after, and/or at the same time as, administration of the other component. When used in this context, the terms "administered simultaneously" and "administered at the same time as" include that individual doses of pemirolast and montelukast are administered within 48 hours (e.g. 24 hours) of each other.

The combination products according to the invention find utility in the treatment of inflammatory conditions. Inflammatory conditions are typically characterized by activation of immune defence mechanisms, resulting in an effect that is more harmful than beneficial to the host. Such conditions are generally associated with varying degrees of tissue redness or hyperemia, swelling, hyperthermia, pain, itching, cell death and tissue destruction, cell proliferation, and/or loss of function.

Inflammatory conditions that may be mentioned include arteritis, diabetes mellitus, metabolic syndrome, acne, skin burns, rosacea, seborrheic dermatitis, skin ulcers, preferably asthma and allergy (including allergic conjunctivitis and allergic rhinitis and food allergy), ankylosing spondylitis, atopic dermatitis, chronic obstructive pulmonary disease, contact dermatitis, cystitis, gouty arthritis, inflammatory bowel disease (such as Crohn's disease and ulcerative colitis), multiple sclerosis, osteoarthritis, pancreatitis, prostatitis, psoriasis, psoriatic arthritis, rheumatoid arthritis, tendinitis, bursitis, Sjogren's syndrome, systemic lupus erythematosus, uveitis, urticaria, vasculitis, mastocytosis, diabetic vascular complications, migraine, atherosclerosis and associated cardiovascular disorders. Conditions that may be mentioned include atopic dermatitis, migraine, asthma, chronic obstructive pulmonary disease, asthma-COPD overlap syndrome (ACOS), Crohn's disease, multiple sclerosis, psoriasis, rheumatoid arthritis, systemic lupus erythematosus, ulcerative colitis and atherosclerosis and associated cardiovascular disorders.

Conditions that may be mentioned include asthma, mastocytosis and allergic/atopic diseases, such as rhinitis, conjunctivitis, dermatitis, urticaria, food allergy and anaphylaxis. Particular conditions that may be mentioned include asthma.

According to a further aspect of the invention there is provided a method of treatment of an inflammatory disorder, and in particular asthma, which method comprises the administration of a combination product according to the invention to a patient in need of such treatment.

For the avoidance of doubt, in the context of the present invention, the terms "treatment", "therapy" and "therapy method" include the therapeutic, or palliative, treatment of patients in need of, as well as the prophylactic treatment and/or diagnosis of patients which are susceptible to, inflammatory disorders, such as asthma.

"Patients" include mammalian (particularly human) patients.

The term "asthma" will be understood to include any condition characterized by episodes of an apparent or measurable decrease in airflow and/or symptoms, including wheezing, coughing, difficulty in breathing etc. The term "treatment of asthma" thus includes both prophylactic treatment of chronic asthma, as well as the therapeutic treatment of acute asthma. "Acute" asthma may be characterized by peak expiratory flow (PEF) and/or spirometry (ratio of forced expiratory volume in one second (FEV1) to forced vital capacity (FVC)) that are reduced by ≥10%. The term thus includes the conditions variously known as acute asthmatic episodes, asthmatic bronchoconstriction, exercise-induced bronchoconstriction, asthma/asthmatic exacerbations, severe asthma, acute severe asthma, status asthmaticus, brittle asthma (including Type 1 and Type 2 brittle asthma).

In accordance with the invention, pemirolast and montelukast are preferably administered locally or systemically, for example orally, intravenously or intraarterially (including by intravascular and other perivascular devices/dosage forms (e.g. stents)), intramuscularly, cutaneously, subcutaneously,

transmucosally (e.g. sublingually or buccally), rectally, transdermally, nasally, pulmonarily (e.g. tracheally or bronchially), topically, or by any other parenteral route, in the form of a pharmaceutical preparation comprising the compound(s) in pharmaceutically acceptable dosage form(s). Preferred modes of delivery include oral (particularly), intravenous, cutaneous or subcutaneous, nasal, intramuscular, or intraperitoneal delivery.

Pemirolast and montelukast will generally be administered together or separately in the form of one or more pharmaceutical formulations in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier, which may be selected with due regard to the intended route of administration and standard pharmaceutical practice. Such pharmaceutically acceptable carriers may be chemically inert to the active compounds and may have no detrimental side effects or toxicity under the conditions of use. Such pharmaceutically acceptable carriers may also impart an immediate, or a modified, release of either active ingredient, whether administered together in a combined preparation or in the form of a kit of parts.

Suitable pharmaceutical formulations may be commercially available or otherwise are described in the literature, for example, Remington *The Science and Practice of Pharmacy*, 19th ed., Mack Printing Company, Easton, Pennsylvania (1995) and *Martindale – The Complete Drug Reference* (35th Edition) and the documents referred to therein, the relevant disclosures in all of which documents are hereby incorporated by reference. Otherwise, the preparation of suitable formulations, and in particular combined preparations including both pemirolast and montelukast may be achieved non-inventively by the skilled person using routine techniques.

Administration of active ingredients may be continuous or intermittent (e.g. by bolus injection). The mode of administration may also be determined by the timing and frequency of administration, but is also dependent, in the case of the therapeutic treatment of asthma, on the severity of the condition. For example in the case of a mild to moderate asthma attack (e.g. exercise-induced asthma), pemirolast/montelukast/salt of either may be administered perorally. In case of more severe asthma attacks, pemirolast/montelukast/salt may administered

perorally, intravenously or by inhalation, and in the case of a severe asthma attack, in which, for example, a patient may be hospitalized, a bolus injection may be administered.

Depending on the disorder, and the patient, to be treated, as well as the route of administration, active ingredients may be administered at varying therapeutically effective doses to a patient in need thereof.

Similarly, the amount of active ingredients in a formulation will depend on the severity of the condition, and on the patient, to be treated, but may be determined by the skilled person.

Suitable doses of active ingredients include those referred to in the medical literature, such as *Martindale – The Complete Drug Reference* (35th Edition) and the documents referred to therein, the relevant disclosures in all of which documents are hereby incorporated by reference. Suitable doses of active ingredients are therefore in the range of about 0.01 mg/kg of body weight to about 1,000 mg/kg of body weight. More preferred ranges are about 0.1 mg/kg to about 20 mg/kg on a daily basis, when given orally.

However, suitable doses of pemirolast are known to those skilled in the art. For example suitable lower limits of daily dose ranges (calculated as the free acid), irrespective of the route of administration are about 1 (for example about 2) mg, for example about 5 mg, such as about 10 mg, more preferably about 20 mg. Suitable upper limits of peroral daily dose ranges may be about 1,000 mg, such as about 800 mg, including about 600 mg, for example about 400 mg, such as about 300 mg. Suitable upper limits for inhalation may be about 200 mg. Suitable upper limits for injectable bolus administration (e.g. subcutaneous or intravenous administration) may be about 5 g, for example about 2 g, such as about 0.8 g per day. (All of the above doses are calculated as the free acid.)

In any event, the medical practitioner, or other skilled person, will be able to determine routinely the actual dosage, which will be most suitable for an individual patient, depending on the severity of the condition and route of administration. The above-mentioned dosages are exemplary of the average

case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

Peroral and inhaled doses may be given between once and four times daily, preferably three times daily and more preferably twice daily.

Calculated as the free acid, suitable lower dose limits of pemirolast/salt are about 1.5 mg of body weight per day (calculated as the free acid), irrespective of the mode of administration. Again, calculated as the free acid, suitable upper limits of peroral daily dose ranges may be about 15 mg/kg of body weight, for inhalation may be up to about 3 mg/kg of body weight; and for injectable bolus administration may be up to about 75 mg/kg of body weight.

Suitable doses of montelukast are known to those skilled in the art and include those listed for the drugs in question to in the medical literature, such as *Martindale – The Complete Drug Reference* (35th Edition) and the documents referred to therein, the relevant disclosures in all of which documents are hereby incorporated by reference.

For example, suitable peroral doses of montelukast that may be mentioned are in the range of about 0.25 mg to about 600 mg, such as about 0.4 mg to about 200 mg, preferably about 5 mg to about 100 mg, for example about 7 mg (e.g. about 8 mg) to about 25 mg (e.g. about 12 mg) per day, irrespective of whether the formulation employed is a combined preparation or a kit of parts as hereinbefore described.

In any event, in respect of either active ingredient, the dose administered to a mammal, particularly a human, in the context of the present invention should be sufficient to effect a therapeutic response in the mammal over a reasonable timeframe (as described hereinbefore). One skilled in the art will recognize that the selection of the exact dose and composition and the most appropriate delivery regimen will also be influenced by *inter alia* the pharmacological properties of the formulation, the nature and severity of the condition being treated, and the physical condition and mental acuity of the recipient, as well as the age, condition, body weight, sex and response of the patient to be treated,

and the stage/severity of the disease, as well as genetic differences between patients.

Wherever the word "about" is employed herein, for example in the context of doses of active ingredients, it will be appreciated that such variables are approximate and as such may vary by ± 10%, for example ± 5% and preferably ± 2% (e.g. ± 1%) from the numbers specified herein.

The combination products/methods described herein may have the advantage that, in the treatment of the conditions mentioned hereinbefore, they may be more convenient for the physician and/or patient than, be more efficacious than, be less toxic than, have a broader range of activity than, be more potent than, produce fewer side effects than, or that it/they may have other useful pharmacological properties over, similar methods (treatments) known in the prior art for use in the treatment of inflammatory disorders (such as asthma) or otherwise.

The invention is illustrated by the following examples, in which Figure 1 shows 5-lipoxygenase (5-LO), and 5-lipoxygenase activating protein (FLAP) gene expression levels after different drug treatments (untreated control, pemirolast and montelukast seperately, and in combination).

Examples

Example 1

Inhibition of 5-Lipoxygenase Gene Expression by Pemirolast and Montelukast

5-Lipoxygenase (5-LO) is an enzyme that catalyzes steps in biosynthesis of leukotrienes, a group of lipid mediators of inflammation derived from arachidonic acid.

Cells from the human monocytic cell-lineTHP-1 (American Type Culture Collection, ATCC) were cultured (37°C/10% CO_2) in RPMI-1640 medium supplemented with 2 mM Glutamine, 100 units/mL penicillin, 100 µg/mL streptomycin and 10% (v/v) fetal bovine serum. At the start of the experiment,

THP-1 cells were seeded in 12-well plates at a density of $1x10^6$ cells/mL (1 mL per well). Directly after the cells were seeded, 100 ng/mL of PMA (Sigma-Aldrich, P1585, dissolved in DMSO) was added to the wells (for macrophage differentiation). The cells were then incubated at 37°C 10% CO_2 for 48 hours. After 48 hours, 20 µM of pemirolast (potassium salt; American Custom Chemicals Corporation, San Diego, USA), 20 µM montelukast (sodium salt; Sigma-Aldrich) or a combination of pemirolast and montelukast was added to the wells.

The cells were then incubated at 37°C 10% CO_2 for 30 min, and after that 1 µg/mL of LPS (Sigma-Aldrich; L2630, 0111:B4) was added to the wells and the cells were incubated at 37°C 10% CO_2 for a further 5 hours. The cells were then gently scraped from the wells using a plastic cell scraper and transferred to Eppendorf tubes. The cells were spun down and as much liquid as possible was removed. This was repeated once. The samples were snap frozen on dry ice and stored at -80°C until RNA isolation and microarray experiments were performed.

Total RNA from the cell pellets was isolated with QIAgen RNeasy Mini Kit. The RNA quality was checked with Agilent Bioanalyzer. 200 ng total RNA was used as input for amplification and labeling using the Gene Chip 3'IVT Express Kit (Affymetrix P/N 901229) according to manufacturers protocols.

The fragmented cRNA was hybridized for 16 hr at 45°C on GeneChip Human Genome U133 Plus 2.0 Arrays in Affymetrix Gene Chip Hybridization Oven 645. Then the Gene Chips were washed and stained in the Affymetrix Fluidics Station 450, following the standard protocol.

GeneChips were scanned using the Affymetrix GeneChip Scanner 3000 7G

5-LO gene expression levels after different drug treatments were compared by comparing the normalized 5-LO probe-set signal intensity ("5-LO signal intensity") of each of the conditions (signal is a quantitative metric calculated for each probe set, which represents the relative level of expression of a gene, and the detection p-value for each individual probe-set signal for 5-LO was less than 0.006).

In the untreated control group, the 5-LO signal intensity was 653. In animals treated with both montelukast and pemirolast, the corresponding 5-LO signal intensity was 485. For comparison, the corresponding 5-LO signal intensity was 572 in the group treated with montelukast alone and 657 the group treated with pemirolast alone. Figure 1 illustrates these results as percentage change. Thus, montelukast and pemirolast in combination synergistically inhibited the 5-LO gene expression.

With a second probe-set for 5-LO, in the untreated control group, the 5-LO signal intensity was 70. In animals treated with both montelukast and pemirolast, the corresponding 5-LO signal intensity was 53. For comparison, the corresponding 5-LO signal intensity was 68 in the group treated with montelukast alone and 137 the group treated with pemirolast alone.

Example 2

Inhibition of 5-Lipoxygenase-Activating Protein Gene Expression by Pemirolast and Montelukast

5-Lipoxygenase Activating Protein (FLAP) is necessary for the activation of 5-lipoxygenase and therefore for the production of leukotrienes.

Preparation and incubations of THP-1 cells and microarray experiments were as in Example 1 above.

FLAP gene expression levels after different drug treatments were compared by comparing the normalized FLAP probe-set signal intensity ("FLAP signal intensity") of each of the conditions (signal is a quantitative metric calculated for each probe set, which represents the relative level of expression of a gene, and the detection p-value for each individual probe-set signal for 5-LO was less than 0.001).

In the untreated control group, the FLAP signal intensity was 2129. In animals treated with both montelukast and pemirolast, the corresponding FLAP signal intensity was 1632. For comparison, the corresponding FLAP signal intensity was 1857 in the group treated with montelukast alone and 2053 the group treated

with pemirolast alone. These results are also illustrated in Figure 1 as percentage change. Thus, montelukast and pemirolast in combination synergistically inhibited the FLAP gene expression.

One or more of the above-described examples demonstrate a clear synergistic effect for the combination of pemirolast and montelukast.

Claims

1. A combination product comprising:
(a) pemirolast, or a pharmaceutically-acceptable salt or solvate thereof; and
(b) montelukast, or a pharmaceutically-acceptable salt or solvate thereof.

2. A combination product as claimed in Claim 1 which comprises a pharmaceutical formulation including pemirolast, or a pharmaceutically-acceptable salt or solvate thereof; montelukast, or a pharmaceutically-acceptable salt or solvate thereof; and a pharmaceutically-acceptable adjuvant, diluent or carrier.

3. A combination product as claimed in Claim 1, which comprises a kit of parts comprising components:
(A) a pharmaceutical formulation including pemirolast, or a pharmaceutically-acceptable salt or solvate thereof, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and
(B) a pharmaceutical formulation including montelukast, or a pharmaceutically-acceptable salt or solvate thereof, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier,
which components (A) and (B) are each provided in a form that is suitable for administration in conjunction with the other.

4. A method of making a kit of parts as defined in Claim 3, which method comprises bringing component (A) into association with a component (B), thus rendering the two components suitable for administration in conjunction with each other.

5. A kit of parts comprising:
(I) one of components (A) and (B) as defined in Claim 3; together with
(II) instructions to use that component in conjunction with the other of the two components.

6. A kit of parts as claimed in Claim 3 or Claim 5, wherein components (A) and (B) are suitable for sequential, separate and/or simultaneous use in the treatment of an inflammatory disorder.

7. The use of a combination product as defined in any one of Claims 1 to 3, 5 or 6, for the manufacture of a medicament for the treatment of an inflammatory disorder.

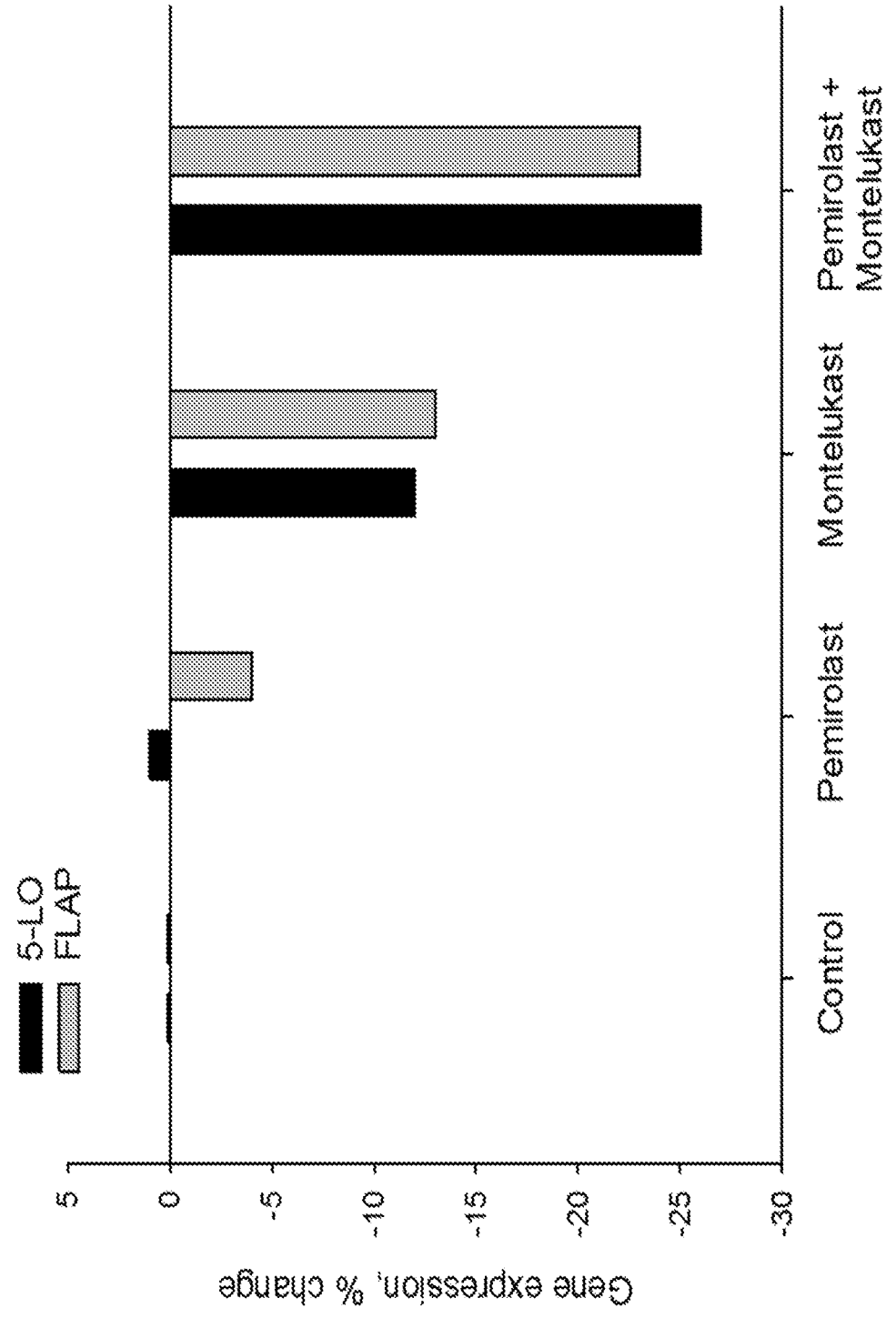
8. A combination product as defined in any one of Claims 1 to 3, 5 or 6, for use in a method for the treatment of an inflammatory disorder.

9. A method of treatment of an inflammatory disorder, which method comprises the administration of a combination product as defined in any one of Claims 1 to 3, 5 or 6, to a patient in need of such treatment.

10. A kit of parts as claimed in Claim 6, a use as claimed in Claim 7, a combination product for use as claimed in Claim 8, or a method as claimed in Claim 9, wherein the disorder is selected from asthma, mastocytosis, rhinitis, conjunctivitis, dermatitis, urticaria, food allergy and anaphylaxis.

11. A kit of parts, use, combination product for use or method as claimed in Claim 10, wherein the disorder is asthma.

Figure 1


Gene expression, % change
5
0
-5
-10
-15
-20
-25
-30
Control
Pemirolast
Montelukast
Pemirolast + Montelukast
5-LO
FLAP

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2015/054100

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/47 A61K31/519 A61P29/00 A61P37/08 A61P11/06
ADD.

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)
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 practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	"PEMIROLAST POTASSIUM", DRUGS OF TODAY / MEDICAMENTOS DE ACTUALIDAD, J.R. PROUS SS.A. INTERNATIONAL PUBLISHERS, ES, vol. 28, no. 1, 1 January 1992 (1992-01-01), pages 29-31, XP008066535, ISSN: 0025-7656 cited in the application	5-11
A	chapter Clinical Evaluation	1-4

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[X] Further documents are listed in the continuation of Box C. [ ] See patent family 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 application or patent 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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 March 2016	16/03/2016

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2015/054100

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NAYAK A: "A REVIEW OF MONTELUKAST IN THE TREATMENT OF ASTHMA AND ALLERGIC RHINITIS", EXPERT OPINION ON PHARMACOTHERAPY, ASHLEY PUBLICATIONS LTD, LONDON, UK, vol. 5, no. 3, 1 March 2004 (2004-03-01), pages 679-686, XP009058759, ISSN: 1465-6566, DOI: 10.1517/14656566.5.3.679	5-11
A	chapter 4. Clinical efficacy -----	1-4