

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
21 April 2011 (21.04.2011)

PCT

(10) International Publication Number
WO 2011/045429 A1

(51) International Patent Classification:
A61K 9/00 (2006.01) *A61K 31/00* (2006.01)

(21) International Application Number:
PCT/EP2010/065569

(22) International Filing Date:
15 October 2010 (15.10.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0918150.4 16 October 2009 (16.10.2009) GB

(71) Applicant (*for all designated States except US*):
JAGOTEC AG [CH/CH]; Eptingerstrasse 61, CH-4132
Muttenz (CH).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **MUELLER-
WALZ, Rudi** [DE/DE]; Hans-Vetter-Strasse 108, 79650
Schopfheim (DE). **FUEG, Lise-Marie** [CH/CH]; Neu-
mattstrasse 58, CH-4144 Arlesheim (CH).

(74) Agent: **HAILE, Alison Victoria**; Mintz Levin Cohn Fer-
ris Glovsky & Popeo Intellectual Property LLP, Alder
Castle, 10 Noble Street, London, London EC2V 7JX
(GB).

(81) Designated States (*unless otherwise indicated, for every
kind of national protection available*): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ,
CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO,
DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP,
KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD,
ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI,
NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD,
SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR,
TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every
kind of regional protection available*): ARIPO (BW, GH,
GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG,
ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ,
TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU,
LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK,
SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: IMPROVED FORMULATIONS

(57) Abstract: In a metered dose inhaler, comprising a canister and metering valve, containing a suspension aerosol formulation comprising particles of formoterol fumarate dihydrate and fluticasone propionate suspended in an HFA propellant, a method of reducing deposition of particles on the surfaces of the canister and the metering valve, the method comprising the step of adding a wetting agent to the formulation.



WO 2011/045429 A1

Improved formulations

The present invention relates to pharmaceutical suspension aerosol formulations for use in
5 metered dose inhalers.

Pharmaceutical aerosol formulations typically comprise a drug substance suspended or
dissolved in a liquefied gas propellant. A metered dose inhaler typically consists of a canister
for storing an aerosol formulation under pressure, which is sealed at one end with a metering
10 valve. The canister and valve are held in an actuator, which comprises means for actuating the
metering valve through which may be dispensed a precisely fixed dose of the aerosol
formulation, and a mouth-piece through which a dispensed dose of the aerosol formulation is
directed into the mouth of a patient.

15 Each dose of drug released from a metered dose inhaler should be metered with very narrow
tolerance of dose variance set by regulatory authorities. Furthermore, as metered dose inhalers
usually contain multiple doses of a drug substance, accuracy in dosing must be assured
throughout the life of the inhaler, which may be up to one month or even longer.

20 When a metered dose inhaler contains a suspension aerosol formulation, i.e. an aerosol
formulation in which particles of drug substance are suspended in a liquefied gas propellant, it
is often a problem that the particles tend to deposit on the inner surfaces of the canister and
metering valve. This can result in unacceptable variance in the delivered dose and reduction in
delivered dose. Deposition can be a particular problem when a drug substance is used in very
25 low concentrations. If the concentration of drug substance delivered per actuation is very low,
then any loss of dose because of deposition could result in serious dosing problems.
Formoterol fumarate dihydrate particularly, but also fluticasone propionate are potent
materials and are consequently intended for use in very low concentrations.

30 The prior art has addressed the problem of particle deposition. WO96/32099 discloses a
canister that is coated with certain non-stick polymers, such as fluorocarbons, see also for
example WO-A-96/32150 and US-A-6,596,260. Draw backs with such polymers include the
risk of partial solubility of some of their constituents in some aerosol propellants, and that
such coatings themselves need to undergo safety tests and product formulation development

in order to ensure a safe and stable product. These polymers and the testing required can add to production costs.

WO 0224552 discloses a method of applying multiple layers of fluoro polymers to canisters with heating. Not only is this laborious and costly, but problems can arise with regard to certain metals used in the production of canisters. The most commonly used metals for forming canisters are aluminium alloys. The polymer coatings must undergo heat treatment in order to be cured, which can result in the strength of canisters being compromised because the metal can become softer and malleable from the application of heat.

The polymer coating materials themselves can also be incompatible with some components of certain aerosol formulations and can lead to contamination because there is the potential for leachable compounds to find their way into formulations. Such leachable compounds can lead to degradation of drug substances and also result in less effective and less robust products.

In the field of suspension aerosol formulations there remains a need to reduce or eliminate drug particle deposition without the need to resort to the use of coated canisters.

Surprisingly the applicant has found that a wetting agent employed in a suspension aerosol formulation can act to reduce drug particle deposition and improve delivered dose uniformity and the aerodynamic particle size distribution of the delivered dose. This effect is observed with canisters having no surface coating or coatings.

In one aspect of the invention there is provided in a metered dose inhaler containing a suspension aerosol formulation comprising particles of formoterol fumarate dihydrate and fluticasone propionate suspended in an HFA propellant, the use of a wetting agent to reduce deposition of particles on the canister wall and the metering valve.

In another aspect of the present invention there is provided in a metered dose inhaler containing a suspension aerosol formulation comprising particles of formoterol fumarate dihydrate and fluticasone propionate suspended in a HFA propellant, a method of reducing deposition of particles on the canister wall and the metering valve, said method comprising the step of adding a wetting agent to said formulation.

The wetting agent may be selected from alcohols, more particularly ethanol, diols or polyols, such as propylene glycol, glycerol, butandiol or mixtures thereof. In a particularly preferred embodiment, the wetting agent is, ethanol, and more particularly dehydrated ethanol.

- 5 The skilled person will be able to optimise the amount of wetting agent employed having regard to the concentration of the drug substances employed, the nature of the propellant and also the nature of any other adjuvants or excipients employed in the suspension aerosol formulation. If a wetting agent is a solvent for one or both of the drug substances, the wetting agent should be employed in an amount that avoids solubilisation or partial solubilisation of
10 the drug substances or any excipients intended to be held in suspension.

The wetting agent is thought to facilitate the wetting of the particles of the drug substance suspended in the liquefied propellant preventing the drug substance from becoming partially solubilised. Partial solubilisation of a drug substance can cause Ostwald ripening, particle
15 growth, and eventually formulation stability failure. Partial solubilisation would be particularly detrimental in formulations employing drug substances in very low concentrations, as the loss of even the slightest amount of drug substance to these effects would have an exaggerated effect in terms of variance of the dose emitted from an inhaler.

- 20 The balance a formulator needs to achieve in providing sufficient wetting agent to achieved a desired effect whilst at the same time avoiding solubilisation can be particularly fine when one employs high potency materials such as formoterol fumarate dihydrate and fluticasone propionate in low or very low concentrations. The balance is made yet more complicated by the presence of two drug substances each having their unique physical properties, such as
25 solubility.

The wetting agent may be employed in an amount of less than 2% by weight, more particularly 1.99 to 0.01% by weight, still more particularly 1.5 to 0.01 % by weight, still more particularly 1.5% to 1.0% by weight based on the total weight of the suspension aerosol
30 formulation.

When a metered dose inhaler is actuated, propellant containing suspended drug substance is expelled under pressure from a metering valve on the metered dose inhaler. The propellant boils off as it leaves the valve and the drug substance particles are released as a stream of

micro-fine powder into the oral cavity of a patient. In order that the formulation can be inhaled deep into the lungs to exert a therapeutic effect, the particles of the aerosol formulation need to be micro-fine with a mean aerodynamic particle diameter (measured as Mass Median Aerodynamic Diameter (MMAD)) of about 1 to 10 μ m, and preferably 1 to 6 μ m.

- 5 Micronised particles of this size can be obtained by various methods known in the art, for example mechanical grinding or spray drying. In a preferred method, size reduction of drug particles is carried out by an air jet mill.

- 10 The quantity of drug substance delivered in fine, inhalable particles having a MMAD in the range stated above and which is considered able to penetrate and deposit in the lung is known as the fine particle dose (FPD), or expressed as a portion of the delivered dose, the fine particle fraction (FPF). Both of these parameters can be calculated from the measurement of the aerodynamic particle size distribution of a delivered dose with a cascade impactor or liquid impinger. These are routine tests for which the methods and apparatus are described in
15 the pharmacopoeia, see for example Chapter <601> of the United States Pharmacopoeia (USP) 32 or in the inhalants monograph 2.9.18 of the European Pharmacopoeia (Ph.Eur.), 6th edition 2009.

- 20 Whereas the micro-fine nature of the drug particles is desirable and necessary for them to penetrate deep into the lung and exert a therapeutic effect, fine particles, owing to their large surface area and therefore an unfavourable ratio of surface area to volume or mass, can exhibit adhesive forces, which can cause particles to deposit on the surfaces of the canister and metering valve surfaces.

- 25 The use of a wetting agent in accordance with the present invention minimises these adhesive interactions and reduces the amount of deposition ensuring acceptable delivered dose uniformity and an aerodynamic particle size distribution of the delivered dose that translates to a high fine particle dose and fine particle fraction.

- 30 Deposition of particles inside a canister and valve can be measured by assaying the drug substances remaining in exhausted inhalers.

Delivered dose uniformity and aerodynamic particle size distribution may be measured at initial testing. Initial testing as used herein refers to a test of filled canisters at time $t = 0$ after

an initial equilibration storage condition of at least 2 weeks and at ambient temperature and humidity, e.g. about 17 to 25 degrees centigrade and a relative humidity of about 29 to 63%.

Testing proceeds with the repeated actuation of an equilibrated canister to exhaustion and the delivered dose, its variance and the aerodynamic particle size distribution is measured by

5 techniques known in the art. Testing a product at “initial” is an important benchmark for formulators. If a product fails to meet acceptable levels for variance of delivered dose or aerodynamic particle size distribution at this stage, then it is an indication that a formulation would fail under conditions of accelerated storage, which is predictive of the performance of a formulation under normal storage and usage conditions e.g. for 2 years or longer at a
10 temperature of 25 degrees centigrade and a relative humidity of 60 % to 75 % or preferably at 30 degrees centigrade and a relative humidity of about 65 %.

Assaying the amount of drug substance deposited on the canister and valve at initial testing is an important aspect of aerosol formulation development. Drug loss is observed to some extent
15 in all parts of manufacturing and application before the drug reaches the patient’s lung. There is usually some loss in the manufacturing vessel, pipes and filling line. Furthermore, during storage, one can expect to observe a certain amount of deposition in the canister and closure system. Still further, during application or actuation there is an amount of drug retained on the valve and on the actuator. All this is taken into consideration when determining how much
20 drug should be filled into a canister to achieve the desired dose to be delivered to the patient.

As there are a multitude of deposition sites for drug substance throughout manufacture, filling, storage and application, one must ensure tight control during all aspects of manufacture and storage of a formulation. A very important control is the assay for deposited
25 drug within the canister and closure system (including the valve) at “initial”. If the deposition is too high at this stage of the process, then there is no realistic possibility that the formulation will be delivered to a patient with the correct delivered dose, or fine particle fraction.

In the assay for deposition of drug substance, it is important that for both formoterol fumarate
30 dihydrate and for fluticasone propionate, the extent of deposition is below about 12% of the nominal content of the canister, more particularly deposition should be within the range of about 4 to 10% of the nominal content. By “nominal content” is meant, the amount of drug that is weighed into the batch manufacturing vessel divided by number of canisters to be filled with the given amount of bulk suspension formulation.

Accordingly, the invention provides in another of its aspects a canister for use in a metered dose inhaler containing a suspension aerosol formulation as described herein, which canister after filling and being stored for at least two weeks at a temperature of about 17 to about 25
5 degrees centigrade and a relative humidity of about 29 to 63% contains a residue of formoterol fumarate dihydrate of not more than about 12%, more particularly in a range of about 4 to 10% based on the amount of formoterol fumarate dihydrate filled into the canister.

In another aspect the invention provides a canister for use in a metered dose inhaler containing
10 a suspension aerosol formulation as described herein, which canister after filling and being stored for at least two weeks at a temperature of about 17 to about 25 degrees centigrade and a relative humidity of about 29 to 63% contains a residue of fluticasone propionate of not more than about 12%, more particularly in a range of about 4 to 10% based on the amount fluticasone propionate filled into the canister.

15 The amount of deposition is remarkably low considering that these values can be achieved using canisters whose internal surfaces are not treated with non-stick substances such as fluoropolymers. Canisters for use in the present invention in fact can be of standard aluminium or aluminium alloy, typically of cylindrical cross section that are commonly used
20 in drug aerosol applications. In the assay described above, a suitable canister is sealed by crimping with a suitable metering valve, which valves are commonly known in the art.

It is also desirable that the suspended drug substance particles have a particle size distribution such that D10 (10 % of the volume distribution) is in the range of 0.2 to 2 micro-metres, D50
25 in the range of 1 to 4 micro-metres and D90 in the range of 2 to 6 micro-metres when measured by laser diffraction either in suspension or as a dispersed dry powder.

The invention provides in another of its aspects a suspension aerosol formulation comprising particles of formoterol fumarate dihydrate and fluticasone propionate suspended in an HFA
30 propellant, and a wetting agent, wherein the particles have a particle size distribution wherein D10 (10 % of the volume distribution) is in the range of 0.2 to 2 micro-metres, D50 in the range of 1 to 4 micro-metres and D90 in the range of 2 to 6 micro-metres when measured by laser diffraction either in suspension or as a dispersed dry powder.

Still more particularly, D10 is about 0.2-1.8, D50 is about 1.0-3.0 and D90 is about 2.0-6.0 micro-metres for formoterol fumarate dihydrate, and for fluticasone propionate D10 is about 0.2-1.8, D50 is about 1.2-3.5 and D90 is about 2.0-6.0 micro-metres.

- 5 The delivered dose uniformity and aerodynamic particle size distribution of the delivered dose are important parameters that determine the therapeutic effectiveness of formulations from metered dose inhalers. These parameters can be measured in vitro. The delivered dose (sometimes referred to as the “emitted dose”) is the amount of drug substance that is substantially released from an actuator mouthpiece and available for inhalation by a patient.
- 10 The delivered dose can be different to the dose actually dispensed from an inhaler by the metering valve upon actuation (often referred to as the metered dose). This is because a tiny amount of the metered dose can be deposited on the valve stem and the actuator of the metered dose inhaler.
- 15 Delivered dose uniformity is a measure of the variance of the delivered dose and can be used to test the reproducibility of dosing from batch to batch, or for a particular metered dose inhaler, the variability from actuation to actuation through life of the inhaler. Some variance in delivered dose is to be expected, but it must fall within limits proscribed by regulatory authorities if a product is to gain market authorisation.
- 20 The aerodynamic particle size distribution informs the formulator of the amount of drug substance particles contained in the delivered dose that are of small enough aerodynamic diameter in order to reach the deep lung upon inhalation, and the fine particle dose and fine particle fraction can be derived from this measurement.
- 25 The variance of the delivered dose (the delivered dose uniformity) can be measured using a Dosage Unit Sampling Apparatus (DUSA). The FPF can be determined from measurements of particle size distribution by a cascade impactor or a liquid impinger, for example an Andersen Cascade Impactor (ACI). The measurement methodology and the apparatus
- 30 employed are well known in the art, and are described in the United States Pharmacopoeia Chapter < 601 > , or in the inhalants monograph of the European Pharmacopoeia, both of which documents are hereby incorporated by reference for this purpose. The USP suggests that the Apparatus 1 can be used for the measurement of FPF. The USP also suggests that delivered dose uniformity can be measured with DUSA or its equivalent. Alternatively,

however, the delivered dose and delivered dose uniformity may be measured using the Funnel Method, which is well known in the art.

The Funnel Method is described in Drug Delivery to the Lungs, VIII p116 to 119, which is hereby incorporated by reference. In summary, the Funnel Method consists of discharging a formulation from a metered dose inhaler into a Funnel Apparatus, which basically consists of a standard Buchner Funnel. The discharged dose is captured on a glass sinter located within the Funnel, and can be washed off, and the dose is determined using HPLC analysis. The Funnel Method gives comparable results to the standard USP apparatus, and is generally considered to be an equivalent of the DUSA apparatus.

Accordingly, in another aspect of the invention there is provided in a metered dose inhaler, a suspension aerosol formulation comprising particles of formoterol fumarate dihydrate and fluticasone propionate suspended in a HFA propellant, and a wetting agent, which formulation when stored for at least 2 weeks at about 17 to 25 degrees centigrade and a relative humidity of about 29 to 63% has a mean delivered dose through life of the inhaler of about 40 to 500 micrograms fluticasone propionate and 4 to 20 micrograms formoterol fumarate dihydrate.

In yet another aspect of the invention there is provided in a metered dose inhaler a suspension aerosol formulation comprising particles of formoterol fumarate dihydrate and fluticasone propionate suspended in a HFA propellant and a wetting agent, which when stored for at least 2 weeks at about 17 to 25 degrees centigrade and a relative humidity of about 29 to 63% has a mean fine particle fraction of 30 to 60 % of the labelled dose.

In preferred suspension aerosol formulations described herein the particles of formoterol fumarate dihydrate and of fluticasone propionate display a particle size distribution wherein D10 (10 % of the volume distribution) is in the range of 0.2 to 2 micro-metres, D50 in the range of 1 to 4 micro-metres and D90 in the range of 2 to 6 micro-metres when measured by laser diffraction either in suspension or as a dispersed dry powder.

Still more particularly, D10 is about 0.2-1.8, D50 is about 1.0-3.0 and D90 is about 2.0-6.0 micro-metres for formoterol fumarate dihydrate, and for fluticasone propionate D10 is about 0.2-1.8, D50 is about 1.2-3.5 and D90 is about 2.0-6.0 micro-metres.

In preferred suspension aerosol formulations described herein the wetting agent is selected from the group consisting of ethanol, diols or polyols, such as propylene glycol, glycerol, butandiol and mixtures thereof.

- 5 In preferred suspension aerosol formulations described herein the wetting agent is employed in an amount of less than 2% by weight, more particularly 1.99 to 0.01% by weight, still more particularly 1.5 to 0.01 % by weight, still more particularly 1.5% to 1.0% by weight based on the total weight of the suspension aerosol formulation.
- 10 In preferred suspension aerosol formulations described herein formoterol fumarate dihydrate may be employed in an amount of 0.003-0.04% by weight; preferably 0.004-0.03% by weight; and more preferably 0.005-0.02% by weight, based on the total weight of the formulation. In a preferred embodiment, formoterol fumarate dihydrate may be employed in an amount of 0.003-0.008% by weight, based on the total weight of the formulation. In an
15 alternative preferred embodiment, formoterol fumarate dihydrate may be employed in an amount of 0.01 to 0.04% by weight, based on the total weight of the formulation.

- In preferred suspension aerosol formulations described herein fluticasone propionate may be present in an amount of 0.01-0.6% by weight; preferably between 0.02 -0.5% by weight; and
20 more preferably 0.03-0.4 % by weight, based on the total weight of the formulation.

- Formoterol fumarate dihydrate and fluticasone propionate can be employed in suspension aerosol formulations in varying doses in order that physicians can have flexibility in the manner in which they treat patients. Nominal doses of formoterol fumarate dihydrate may
25 range from about 5 to about 20 micrograms, whereas nominal doses of fluticasone propionate may range from about 50 to about 500 micrograms. The term "nominal dose" is essentially a target dose for a drug substance contained in a metered dose inhaler. Metered dose inhalers of the present invention typically will contain a plurality of nominal doses such that a single inhaler may treat patients over several days or weeks depending on the total number of
30 nominal doses loaded into a canister. The actual dose metered from a metered dose inhaler and the delivered dose are expected to be slightly lower than the nominal dose, but within strictly regulated limits.

Examples of doses in metered dose inhalers according to the present invention are set forth in table 1:

Table 1: Concentrations of formoterol fumarate dihydrate (FF) and Fluticasone propionate (FP) (%w/w) deployed in different dosage strengths of Flutiform.

Product	Flutiform 25/5	Flutiform 50/5	Flutiform 125/5	Flutiform 250/5
Nominal dose	50 mcg FP and 10 mcg FF	100 mcg FP and 10 mcg FF	250 mcg FP and 10 mcg FF	500 mcg FP and 10 mcg FF
Fluticasone	0.0357	0.0714	0.1785	0.3570
Formoterol	0.0071	0.0071	0.0071	0.0071

Table 1 (Continued):

Product	Flutiform 250/10
Nominal dose	500 mcg FP and 20 mcg FF
Fluticasone	0.3570
Formoterol	0.0142

In table 1, the term “Flutiform” relates to the formulation in clinical development by Skyepharma AG. “mcg” is an abbreviation of “micrograms”.

The Flutiform product is under development in multiple dosage strengths as shown in the table 1. The Flutiform product 25/5 for example, represents a formulation that dispenses 25 mcg Fluticasone propionate and 5 mcg formoterol fumarate dihydrate per actuation. The inhaler is actuated twice to give the required delivered dose, hence Flutiform 25/5 actually dispenses a dose of 50 mcg Fluticasone propionate and 10 mcg formoterol fumarate dihydrate.

In addition to the components referred to hereinabove, suspension aerosol formulations of the present invention may contain other excipients, which may assist in the manufacture, stabilisation, ease of administration of the formulation, or which are deemed useful or desirable in any other way.

Surfactants may be employed if desired. Surfactants include oleic acid, lecithin, sorbitan trioleate, cetylpyridinium chloride, benzalkonium chloride, polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan monostearate, polyoxyethylene (20) sorbitan monooleate, polyoxypropylene/polyoxyethylene block copolymers,

polyoxypropylene/polyoxyethylene/ethylenediamine block copolymers, ethoxylated castor oil and the like, where the proportion of surface-active agents, if present, can preferably be approximately 0.0001 to 1% by weight, in particular approximately 0.001 to 0.1% by weight, based on the total formulation.

5

Furthermore, if desired, the aerosol formulations according to the invention can contain buffer substances or stabilizers such as citric acid, ascorbic acid, sodium EDTA, vitamin E, N-acetylcysteine and the like. In general, such substances, if present, are used in amounts of not more than approximately 1% by weight, for example in an amount of from approximately

10

0.0001 to 1% by weight, based on the total formulation.

Formulations according to the invention may contain a carrier material. The salts of nedocromil or cromoglycic acid, such as sodium cromoglycate (sometimes referred to as DSCG), are both therapeutically active substances, but their use as moisture-scavenging

15

The salts of nedocromil or cromoglycic acid, and particularly DSCG may be employed in an amount of 0.01-0.1% by weight, preferably 0.016-0.09% by weight, more preferably 0.02-0.08% by weight, more preferably 0.025-0.07%, more preferably 0.03-0.05% and more

20

preferably 0.03-0.04% by weight, based on the total weight of the formulation.

DSCG has been used for administration via the inhalation route and has been demonstrated to be clinically safe. For providing maximum absorption capacity for water molecules that may enter a metered dose inhaler, the specific surface area of DSCG is preferably increased by

25

reducing the particle size by air jet milling. The preferred moisture scavenging material has a D10 in the range of about 0.2 to 2 micro-metres, D50 in the range of about 1 to 4 micro-metres and D90 in the range of about 2 to 6 micro-metres when measured by a laser diffraction instrument either in suspension or as a dispersed dry powder. More particularly, D10 is not more than 1 micro-metre, D50 is not more than 3 micro-metres and D90 is not

30

more than 5 micro-metres.

It is believed that DSCG acts to aid stabilisation of the aerosol formulations, particularly against hydrolysis by competitive water absorption. DSCG exists as a single crystal form that is non-stoichiometric with regard to water content and adsorbs or desorbs water rapidly in

response to changes in relative humidity. DSCG crystals are universal in the extent of reversible water absorption without collapse of the crystal lattice and can absorb up to 9 molecules of water per mol, which is about 24 % w/w. The crystal structure analysis by X-ray diffraction reveals the existence of channels that are capable of reversibly accommodating a variable number of water molecules (depending on the ambient relative humidity) with only small dimensional changes within the lattice. Despite its large moisture adsorption capacity DSCG is not deliquescent (like, for example, sodium sulphate) but is solid in the range of 10 to 90 % r.h..

It is believed that DSCG acts to stabilize the formulation. In particular, it is believed to have a beneficial effect on fine particle fraction (FPF) by competitively binding free (i.e. molecular dissolved) water present within the propellant phase. This assists in stabilising the fine particle fraction by preventing agglomeration of suspended particles (i.e. formation of liquid and/or crystal bridges) and particle growth (i.e. Ostwald ripening) on stability. This allows for a more robust product during storage and use as the formulation has improved tolerance to the presence of internal water. For example, up to 600ppm of total internal water may be tolerated. Furthermore this allows for a much longer 'use period' once the product is in the patients hands.

The moisture-scavenging properties are particularly important when one employs bronchodilator β_2 -agonists, such as formoterol fumarate dihydrate owing to their susceptibility to oxidative and hydrolytic conditions. Hydrolysis is one of the major identified factors affecting degradation of formoterol fumarate dihydrate under stress conditions (e.g. 40°C/ 75% relative humidity) because such formulations are usually sensitive to moisture and is susceptible to the ingress of moisture from the surrounding air.

Slight concentration changes or changes in the physical stability of suspension aerosol formulations, which may occur during storage due to temperature changes and/or moisture ingress may lead to significant reductions or variance in the delivered dose and fine particle dose.

DSCG is also acts as a suspension enabling agent when used in aerosol formulations of the present invention. DSCG itself consists of particles which encourage and allow the formation of heterogeneous floccules with particles, and this is believed to produce better suspensions

with lower tendency to cream or to sediment. This in turn leads to improvements in the stability and robustness of the formulations of the present invention.

DSCG therefore is an advantageous excipient to ensure through-life robustness and stability to aerosol formulations of the present invention. Furthermore, having regard to the foregoing, aerosol formulations containing a wetting agent and DSCG in the amounts referred to herein are particularly preferred formulations as the wetting agent ensures good dose uniformity at initial testing and the DSCG ensures that the performance in this parameter and others is stable and robust through life of the container.

The invention therefore provides in yet another aspect, in a suspension aerosol formulation as hereinabove described, the use of a wetting agent and DSCG in the amounts referred to hereinabove to provide dose uniformity throughout the life of the formulation.

Examples of particularly preferred dosage strengths of suspension aerosol formulations useful in the present invention may be found in the following table.

Table 2: Composition of examples of dosage strengths of the formulation %w/w.

	Flutiform 25/5	Flutiform 50/5	Flutiform 125/5	Flutiform 250/5
Nominal dose	50 mcg FP and 10 mcg FF	100 mcg FP and 10 mcg FF	250 mcg FP and 10 mcg FF	500 mcg FP and 10 mcg FF
Fluticasone	0.0357	0.0714	0.1785	0.3570
Formoterol	0.0071	0.0071	0.0071	0.0071
Cromolyn sodium	0.0343	0.0343	0.0343	0.0343
Ethanol	1.43	1.43	1.43	1.43
HFA 227	qs ad 100.0	qs ad 100.0	qs ad 100.0	qs ad 100.0

	Flutiform 250/10	Flutiform 250/10
Nominal dose	500 mcg FP and 20 mcg FF	500 mcg FP and 20 mcg FF
Fluticasone	0.3570	0.3570
Formoterol	0.0142	0.0142
Cromolyn sodium	0.0343	0.0686
Ethanol	1.43	1.43
HFA 227	qs ad 100.0	qs ad 100.0

The suspension aerosol formulations described herein can be loaded into metered dose inhalers and deliver consistent doses of the drug substances through the life of the inhalers.

The formulations of the present invention meet compendial requirements regarding delivered dose uniformity as set forth, by way of example, the United States and European pharmacopoeias. More particularly, the formulations of the present invention meet the requirements as set out in the USP26-NF21 chapter 601 "dose uniformity".

5

Accordingly, the invention provides in another of its aspects a suspension aerosol formulation as hereinabove described, wherein the formulation, when dispensed from a metered dose inhaler delivers a dose of both the formoterol fumarate dihydrate and fluticasone propionate that has a variance of no more than $\pm 15\%$ of the target mean dose (and not more than 1 value outside $\pm 25\%$ of target and none outside $\pm 30\%$ of target) when the formulation is stored at 25 degrees centigrade and 60% relative humidity, more particularly 40 degrees centigrade and 75% relative humidity for a period of up to 1 month, more particularly up to 3 months, still more particularly up to 6 months.

10

15 There is provided in another aspect of the invention a method of treating asthma, chronic obstructive pulmonary disease (COPD) or allergic rhinitis comprising the step of administering to a patient in need thereof a suspension aerosol formulation comprising formoterol fumarate dihydrate and fluticasone propionate.

20

A suspension aerosol formulation comprising formoterol fumarate dihydrate and fluticasone propionate as drug substances is intended as a therapy for controlling the symptoms of asthma and COPD. Such formulations, for this reason, can be referred to as controller medications. An adequately controlled patient should not require any other therapy for the treatment of asthma or COPD symptoms. However, it is possible that between receiving doses of the suspension aerosol formulation a patient may experience an exacerbation of symptoms, in which case the patient may receive a dose of a short-acting beta 2 agonist. Examples of such beta-2- agonists include albuterol, salbutamol, terbutaline, fenoterol, levalbuterol, reproterol and pirbuterol.

25

30 In another aspect the invention provides a method of treating asthma or chronic obstructive pulmonary disease (COPD) comprising the step of administering to a patient in need thereof a suspension aerosol formulation comprising formoterol fumarate dihydrate and fluticasone propionate, and a short-acting beta-2-agonist selected from the group consisting of albuterol, salbutamol, terbutaline, fenoterol, levalbuterol, reproterol and pirbuterol.

Patients receiving or indicated to receive a controller medication comprising a suspension aerosol formulation comprising formoterol fumarate dihydrate and fluticasone propionate may be receiving alternative controller medications or no medications at all. A typical controller medication may be an inhaled corticosteroid. Typical inhaled corticosteroids include beclamethasone dipropionate, budesonide, ciclesonide, flunisolide, fluticasone propionate, mometasone furoate and triamcinolone acetonide. The dosages of these materials that a patient may be receiving will depend on the particular steroid employed.

A low dose beclamethasone dipropionate product may meter 80 to 240 micrograms, whereas a medium dose product may meter greater than 240 to about 480 micrograms, and a high dose product may meter greater than 480 micrograms.

A low dose budesonide product may meter 180 to 600 micrograms, whereas a medium dose product may meter greater than 600 to about 1200 micrograms and a high dose product may meter greater than 1200 micrograms.

A low dose ciclesonide product may meter 80 to 160 micrograms, whereas a medium dose product may meter greater than 160 up to 320 micrograms and a high dose product may meter greater than 320 up to 1280 micrograms.

A low dose flunisolide product may meter 500 to 1000 micrograms, whereas a medium dose product may meter greater than 1000 up to 2000 micrograms and a high dose product may meter greater than 2000 micrograms. In the alternative, a low dose flunisolide product may meter 320 micrograms, whereas a medium dose product may meter greater than 320 to about 640 micrograms, and a high dose product may meter greater than 640 micrograms.

A low dose fluticasone propionate product may meter 100 to 300 micrograms, whereas a medium dose product may meter greater than 300 up to 500 micrograms and a high dose product may meter greater than 500 micrograms. In the alternative, a low dose product may meter 88 to 264 micrograms, whereas a medium dose product may meter greater than 260 to about 440 micrograms, and a high dose product may meter greater than 440 micrograms.

A low dose mometasone furoate product may meter 200 micrograms, whereas a medium dose product may meter 400 micrograms and a high dose product greater than 400 micrograms.

5 A low dose triamcinolone acetonide product may meter 300 to 750 micrograms, whereas a medium dose product may meter greater than 750 up to 1500 micrograms and a high dose product greater than 1500 micrograms.

10 In a patient receiving no or low to medium dose inhaled corticosteroids, the invention provides in another aspect a method of treating asthma or COPD comprising the step of providing to said patient a metered dose inhaler containing a suspension aerosol formulation comprising a dose of 10 micrograms formoterol fumarate dihydrate and 50 to 100 micrograms fluticasone propionate BID.

15 In a patient receiving medium to high dose inhaled corticosteroids, the invention provides in yet another aspect a method of treating asthma or COPD comprising the step of providing to said patient a metered dose inhaler containing a suspension aerosol formulation comprising a dose 10 micrograms formoterol fumarate dihydrate and 250 to 500 micrograms fluticasone propionate BID.

20 The invention is particularly concerned with methods of treating patients that are receiving, but are not adequately controlled with, inhaled corticosteroids, and also patients that are indicated to receive inhaled corticosteroids.

25 Thus the invention provides in another aspect, in a patient receiving, but not adequately controlled by inhaled corticosteroids at low, medium or high dose, or in a patient indicated to receive inhaled corticosteroids, a method of treating asthma or COPD in a patient in need thereof, said method comprising the step of providing said patient with a metered dose inhaler containing a suspension aerosol formulation comprising formoterol fumarate dihydrate and fluticasone propionate.

30

The suspension aerosol formulation may comprise a dose of 10 to 20 micrograms formoterol fumarate dihydrate and 50 to 100 micrograms fluticasone propionate BID, or 10 micrograms formoterol fumarate dihydrate and 250 to 500 micrograms fluticasone propionate BID

depending on the whether the patient is receiving low, medium or high dose inhaled corticosteroid as described above.

In the event of asthma or COPD deteriorating over time, the doses of formoterol fumarate dihydrate and fluticasone propionate employed in the suspension aerosol formulations may be increased or additional controller medications may be added to a patient's therapy. Additional therapies may include leukotriene modifiers or sustained release methylxanthine formulations.

In the methods of the present invention, the suspension aerosol formulations containing formoterol fumarate dihydrate and fluticasone propionate are preferably those described hereinabove.

The suspension aerosol formulations describe for use in the treatments describe above are intended as BID, that is, twice daily administration on a regular basis as part of a therapy for controlling the symptoms of asthma and COPD. Physicians will assess the condition of patients receiving such treatment and adjust the dosage according to need

Each dosage administration may be delivered with a single actuation of a metered dose inhaler, or the dose may be administered in two or more actuations. Preferably, each dose is delivered in two actuations of a metered dose inhaler.

There now follows a series of examples that serve to illustrate the invention

Example 1

The following compositions shown below in Table 3 were prepared.

Table 3: Compositions of pharmaceutical formulations.

	Flutiform 25/5	Flutiform 50/5	Flutiform 125/5	Flutiform 250/5	Flutiform 250/10
Nominal dose	50 mcg FP and 10 mcg FF	100 mcg FP and 10 mcg FF	250 mcg FP and 10 mcg FF	500 mcg FP and 10 mcg FF	500 mcg FP and 20 mcg FF
Fluticasone	0.0357	0.0714	0.1785	0.3570	0.3570
Formoterol	0.0071	0.0071	0.0071	0.0071	0.0142
Cromolyn sodium	0.0343	0.0343	0.0343	0.0343	0.0343

Ethanol	1.43	1.43	1.43	1.43	1.43
HFA 227	qs ad 100.0	qs ad 100.0	qs ad 100.0	qs ad 100.0	qs ad 100.0

The appropriate amounts of the micronised active substances were weighed and transferred into the batching vessel. The appropriate amount of micronised sodium cromolyn, (DSCG) was added and the vessel closed. The propellant mixture of HFA 227 (apafurane) with 1.43 % alcohol was made in a separate vessel and transferred into the batching vessel. The solid materials were dispersed in the liquefied propellant by use of a rotor-stator homogenizer at 2900 rpm for 30 min. The homogeneous bulk suspension was cooled to 4 °C and re-circulated between the vessel and the Pamasol aerosol filling machine P2001.

Pharmaceutical aerosol canisters with 14 ml brim full volume were crimped with 50 mcl metering valves using a Pamasol P2005 crimping machine. Aliquots of 11 g suspension were filled into the crimped canisters by the P2001 filling machine. The weight of each filled canister was checked; all filled canisters were subjected to a heat stress test at about 50 to 60 °C and stored one month prior to assembly with an actuator for testing.

Example 2

The Flutiform 50/5 composition shown in Table 2 above, was tested against a comparator product identical to the 50/5 formulation but for the ethanol being removed from the comparator product.

MDI canisters filled with these compositions were tested for assay of both drugs in the canister, dose uniformity through inhaler life up to the last nominal dose, aerodynamic particle size distribution of the aerosol medication by Andersen Cascade Impactor, and for drug deposition on the internal surfaces of the canister and valve (CCS).

The results are shown in Table 3:

Table 3: Effect of Ethanol on dose uniformity and Aerodynamic Particle Size Distribution (APSD). Results at initial.

	Flutiform 50/5	Comparator
Total drug content per container		

	Flutiform 50/5	Comparator
FP assay % of target (RSD[%]); n=3	95.1(0.4)	95.4(1.0)
FF assay % of target (RSD[%]); n=3	95.5 (0.4)	100.8 (1.1)
dose uniformity through container life (intra inhaler)		
Mean FP dose µg/actuation (RSD[%]); n=9	45 (8.0)	31 (13.7)
Mean FF dose µg/actuation (RSD[%]); n=9	4.4 (7.7)	3.5 (13.5)
APSD by Anderson cascade impactor		
Mean metered FP dose µg/actuation (n=5)	44.9	34.2
Mean FP dose µg/actuation (n=5)	42.5	30.3
Mean fine particle dose FP µg/actuation (n=5)	16.7	12.5
Mean metered FF dose µg/actuation (n=5)	4.6	4.4
Mean FF dose µg/actuation (n=5)	4.2	3.4
Mean fine particle dose FF µg/actuation (n=5)	2.13	1.55
Residue in CCS*		
FP assay % of target (RSD[%]); n=3	7.8 (13.6)	14.5 (12.8)
FF assay % of target (RSD[%]); n=3	8.1 (13.8)	14.7 (14.1)
Cromolyn sodium assay % of target (RSD[%]); n=3	7.7 (15.1)	15.9 (13.3)

The purpose of this experiment was to test the effect of a wetting agent, in this case dehydrated ethanol, on critical parameters such as dose uniformity and particle size distribution. The results show that at initial (results at t= 0, after at least 2 weeks storage at ambient conditions of 17 to 25 degrees centigrade and 29 to 63% relative humidity for the formulation without ethanol, the mean dose and fine particle dose was reduced. Furthermore, the assay of residual material in exhausted containers indicated a marked increase in deposition on internal surfaces of the container closure system for the formulation not containing ethanol.

Testing a product at initial is an important benchmark for formulators. If a product fails in key parameters such as dose and aerodynamic particle size distribution at this stage, it is extremely unlikely that the product will be stable under conditions of accelerated storage.

Example 3.

The following batches were made up using the process described in Example 1:

5 Table 14:

Description	Fluticasone/formoterol formulation (nominal dose 500 µg fluticasone /20 µg formoterol)	Fluticasone/formoterol formulation (nominal dose 500 µg fluticasone /10 µg formoterol)
Composition	% w/w	% w/w
Fluticasone propionate	0.3571	0.3571
Formoterol fumarate dihydrate	0.0143	0.0071
DSCG	0.0343	0.0343
Ethanol	1.43	1.43
HFA 227	qs to 100.0	qs to 100.0

10 The results of the stability investigation up to 12 months demonstrated good product quality
and robustness of both formulations, as shown by the results displayed in Tables 15 and 16,
below.

15

Table 15: Summary of ACI results of fluticasone/formoterol formulation Flutiform 250/10 up to 12 months at 25 °C / 60 %RH and 40 °C / 75 %RH. Each result is the mean of 6 determinations (beginning and end of 3 canisters).

Fluticasone	25 °C / 60 %RH						40 °C / 75 %RH					
	Initial	3 months	6 months	12 months	1 month	3 months	6 months	12 months	1 month	3 months	6 months	12 months
Metered dose [µg]	428.9	419.8	426.8	425.9	454.8	429.3	437.1	412.6	442.3	449.8	430.0	431.2
Delivered dose [µg]	407.5	400.9	407.3	408.5	434.2	413.5	417.0	392.2	423.2	417.3	415.6	414.1
FPD (Stage 3 - Filter) [µg]	173.6	184.0	179.1	181.8	184.0	177.0	180.1	177.0	193.2	183.1	174.7	181.0
Group 1 (Mouthpiece – USP throat) [µg]	186.2	172.6	185.2	179.5	180.3	182.6	185.6	164.9	179.9	206.5	182.6	179.6
Group 2 (Stage 0 - Stage 2) [µg]	60.2	52.3	52.6	56.7	53.5	60.8	60.7	61.3	59.7	52.5	63.3	61.5
Group 3 (Stage 3 - Stage 5) [µg]	168.8	178.5	174.2	177.1	179.2	172.1	175.1	172.4	188.6	178.1	170.7	176.6
Group 4 (Stage 6 - Filter) [µg]	4.9	5.5	5.0	4.7	4.8	4.8	5.0	4.6	4.7	5.0	3.9	4.4
3.7												
Formoterol												
Metered dose [µg]	18.50	18.27	18.12	18.22	18.00	17.60	18.15	17.51	18.59	19.05	18.42	18.21
Delivered dose [µg]	16.89	16.71	16.47	16.89	16.57	16.34	16.76	16.05	17.13	16.56	17.04	16.76
FPD (Stage 3 - Filter) [µg]	8.40	8.87	8.66	8.90	9.04	8.29	8.61	8.48	9.23	8.92	8.64	9.00
8.23												
Group 1 (Mouthpiece – USP throat) [µg]	8.06	7.61	7.67	7.42	7.21	7.30	7.49	7.01	7.42	8.44	7.72	7.23
Group 2 (Stage 0 - Stage 2) [µg]	1.75	1.41	1.45	1.57	1.45	1.68	1.68	1.70	1.61	1.42	1.74	1.67
Group 3 (Stage 3 - Stage 5) [µg]	8.18	8.60	8.43	8.68	8.81	8.08	8.36	8.27	9.00	8.69	8.44	8.79
Group 4 (Stage 6 - Filter) [µg]	0.22	0.27	0.23	0.23	0.23	0.21	0.25	0.21	0.23	0.23	0.20	0.21
0.18												

Table 16: Summary of ACI results of fluticasone/formoterol formulation Fluiform 250/5 up to 12 months at 25 °C / 60 %RH and 40 °C / 75 %RH. Each result is the mean of 6 determinations (beginning and end of 3 canisters).

Fluticasone	Initial	25 °C / 60 %RH			40 °C / 75 %RH		
		6 months	12 months	1 month	6 months	12 months	12 months
Metered dose [µg]	402.2	432.1	426.9	433.0	420.3	417.1	417.9
Delivered dose [µg]	378.4	413.9	411.6	416.2	405.5	401.0	402.7
FPD (Stage 3 - Filter) [µg]	181.0	203.2	195.1	193.6	185.6	185.0	178.9
Group 1 (Mouthpiece – USP throat) [µg]	171.5	175.9	180.1	175.6	178.9	181.4	171.2
Group 2 (Stage 0 - Stage 2) [µg]	42.1	46.3	46.2	54.2	47.8	43.6	58.1
Group 3 (Stage 3 - Stage 5) [µg]	177.1	199.1	190.8	189.9	182.0	181.0	175.7
Group 4 (Stage 6 - Filter) [µg]	3.8	4.0	4.4	3.7	3.6	4.0	3.2
Formoterol							
Metered dose [µg]	8.47	9.28	9.22	9.22	8.78	9.09	8.49
Delivered dose [µg]	7.62	8.38	8.40	8.45	8.03	8.36	7.76
FPD (Stage 3 - Filter) [µg]	3.81	4.42	4.28	4.27	4.04	4.08	3.82
Group 1 (Mouthpiece – USP throat) [µg]	3.78	3.91	4.01	3.84	3.79	4.04	3.59
Group 2 (Stage 0 - Stage 2) [µg]	0.75	0.82	0.81	0.92	0.81	0.79	0.92
Group 3 (Stage 3 - Stage 5) [µg]	3.75	4.34	4.19	4.17	3.97	3.96	3.75
Group 4 (Stage 6 - Filter) [µg]	0.06	0.08	0.10	0.10	0.08	0.11	0.07

Claims:

- 5 1. In a metered dose inhaler, comprising a canister and metering valve, containing a suspension aerosol formulation comprising particles of formoterol fumarate dihydrate and fluticasone propionate suspended in an HFA propellant, a method of reducing deposition of particles on the surfaces of the canister and the metering valve, the method comprising the step of adding a wetting agent to the formulation.
- 10 2. A method according to claim 1, wherein the wetting agent is selected from the group consisting of ethanol, diols or polyols, such as propylene glycol, glycerol, butandiol and mixtures thereof.
- 15 3. A method according to claim 1 wherein the wetting agent is ethanol.
4. A method according to claim 1 wherein the wetting agent is employed in an amount of less than 2% by weight based on the total weight of the suspension aerosol formulation.
- 20 5. A method according to claim 4 wherein the wetting agent is employed in an amount of 1.99 to 0.01% by weight based on the total weight of the suspension aerosol formulation.
- 25 6. A method according to claim 4 wherein the wetting agent is employed in an amount of 1.5% to 1.0% by weight based on the total weight of the suspension aerosol formulation.
- 30 7. A method according to claim 1 wherein the HFA propellant is HFA 227.

8. A method according to claim 1 wherein the formoterol fumarate dihydrate is employed in an amount of 0.003-0.04% by weight.
9. A method according to claim 1 wherein fluticasone propionate is employed in an amount of 0.01-0.6% by weight.
10. A method according to claim 1 wherein the suspension aerosol formulation comprises a salt selected from the group consisting of nedocromil and cromoglycic acid.
11. A method according to claim 10 wherein the salt is sodium cromoglycate (DSCG).
12. A method according to claim 11 wherein the sodium cromoglycate is employed in an amount of 0.01-0.1% by weight based on the total weight of the formulation.
13. A suspension aerosol formulation comprising particles of formoterol fumarate dihydrate and fluticasone propionate suspended in an HFA propellant and a wetting agent wherein the particles have a particle size distribution wherein D10 (10 % of the volume distribution) is in the range of 0.2 to 2 micro-metres, D50 in the range of 1 to 4 micro-metres and D90 in the range of 2 to 6 micro-metres when measured by a laser diffraction instrument either in suspension or as a dispersed dry powder.
14. A suspension aerosol formulation according to claim 13 wherein the wetting agent is selected from the group consisting of ethanol, diols or polyols, such as propylene glycol, glycerol, butandiol and mixtures thereof.
15. A suspension aerosol formulation according to claim 14 wherein the wetting agent is ethanol.

16. A suspension aerosol formulation according to claim 13 wherein the wetting agent is employed in an amount of less than 2% by weight based on the total weight of the suspension aerosol formulation.
- 5 17. A suspension aerosol formulation according to claim 13 wherein the wetting agent is employed in an amount of 1.99 to 0.01% by weight based on the total weight of the suspension aerosol formulation.
- 10 18. A suspension aerosol formulation according to claim 13 wherein the wetting agent is employed in an amount of 1.5% to 1.0% by weight based on the total weight of the suspension aerosol formulation.
- 15 19. A suspension aerosol formulation according to claim 13 wherein the HFA propellant is HFA 227.
- 20 20. A suspension aerosol formulation according to claim 13 wherein the formoterol fumarate dihydrate is employed in an amount of 0.003-0.04% by weight.
- 25 21. A suspension aerosol formulation according to claim 13 wherein fluticasone propionate is employed in an amount of 0.01-0.6% by weight.
- 30 22. A suspension aerosol formulation according to claim 13 wherein the suspension aerosol formulation comprises a salt selected from the group consisting of nedocromil and cromoglicic acid.
23. A suspension aerosol formulation according to claim 22 wherein the salt is sodium cromoglycate (DSCG).
24. A suspension aerosol formulation according to claim 23 wherein the sodium cromoglycate is employed in an amount of 0.01-0.1% by weight based on the total weight of the formulation.

25. A suspension aerosol formulation according to claim 13 when dispensed from a metered dose inhaler delivers a dose of both the formoterol fumarate dihydrate and fluticasone propionate that has a variance of no more than $\pm 15\%$ of the target mean delivered dose (and not more than 1 value outside $\pm 25\%$ of target and none outside $\pm 30\%$ of target) when the formulation is stored at 25 degrees centigrade and 60% relative humidity, more particularly 40 degrees centigrade and 75% relative humidity for a period of up to 1 month, more particularly up to 3 months, still more particularly up to 6 months.
26. A suspension aerosol formulation according to claim 13 when stored in a metered dose inhaler for at least 2 weeks and a temperature of 17 to 25 degrees centigrade and a relative humidity of 29 to 63% has a mean fine particle fraction of 30 to 60 % of the labelled dose as in-vitro representation of the aerodynamic particle size distribution.
27. A suspension aerosol formulation according to claim 13 contained in a metered dose inhaler comprising 0.035% fluticasone propionate, 0.007% formoterol fumarate, 0.034% sodium cromoglycate, 1.4% ethanol and HFA 227 qs ad 100 wherein all percentages are based on the total weight of the composition, and wherein the nominal dose of fluticasone propionate is 50 micrograms, and for formoterol fumarate 10 micrograms, two times per day (BID).
28. A suspension aerosol formulation according to claim 13 contained in a metered dose inhaler comprising 0.071% fluticasone propionate, 0.007% formoterol fumarate, 0.034% sodium cromoglycate, 1.4% ethanol and HFA 227 qs ad 100 wherein all percentages are based on the total weight of the composition, and wherein the nominal dose of fluticasone propionate is 100 micrograms and for formoterol fumarate 10 micrograms, two times per day (BID).
29. A suspension aerosol formulation according to claim 13 contained in a metered dose inhaler comprising 0.178% fluticasone propionate, 0.007% formoterol fumarate, 0.034% sodium cromoglycate, 1.4% ethanol and HFA 227 qs ad 100 wherein all

percentages are based on the total weight of the composition, and wherein the nominal dose of fluticasone propionate is 250 micrograms, and for formoterol fumarate 10 micrograms two times per day (BID).

5 30. A suspension aerosol formulation according to claim 13 contained in a metered dose inhaler comprising 0.357% fluticasone propionate, 0.007% formoterol fumarate, 0.034% sodium cromoglycate, 1.4% ethanol and HFA 227 qs ad 100 wherein all percentages are based on the total weight of the composition, and wherein the nominal dose of fluticasone propionate is 500 micrograms, and for formoterol fumarate 10
10 micrograms, two times per day (BID).

31. A suspension aerosol formulation according to claim 13 contained in a metered dose inhaler comprising 0.357% fluticasone propionate, 0.014% formoterol fumarate, 0.068% sodium cromoglycate, 1.4% ethanol and HFA 227 qs ad 100 wherein all
15 percentages are based on the total weight of the composition, and wherein the nominal dose of fluticasone propionate is 500 micrograms and for formoterol fumarate 20 micrograms, two times per day.

32. A suspension aerosol formulation according to claim 13 contained in a metered
20 dose inhaler comprising 0.357% fluticasone propionate, 0.014% formoterol fumarate, 0.034% sodium cromoglycate, 1.4% ethanol and HFA 227 qs ad 100 wherein all percentages are based on the total weight of the composition, and wherein the nominal dose of fluticasone propionate is 500 micrograms and for formoterol fumarate 20 micrograms, two times per day.

25 33. A method of treating asthma, allergic rhinitis or chronic obstructive pulmonary disease (COPD) comprising administering to a patient in need thereof a suspension aerosol formulation defined in claim 13.

30 34. A method according to claim 33 wherein the suspension aerosol formulation is dosed BID.

35. A method according to claim 33 wherein the suspension aerosol formulation is delivered two actuations per dose.
- 5 36. A method according to claim 33 comprising the step of administering simultaneously, sequentially or separately a short-acting beta-2-agonist.
37. A method according to claim 36 wherein the short-acting beta-2-agonist is selected from the group consisting of albuterol, salbutamol, terbutaline, fenoterol,
10 levalbuterol, reproterol and pirbuterol.
38. A method of treating asthma or chronic obstructive pulmonary disease (COPD) comprising the step of administering to a patient in need thereof a suspension aerosol formulation comprising formoterol fumarate dihydrate and fluticasone propionate, and a
15 short-acting beta-2-agonist selected from the group consisting of albuterol, salbutamol, terbutaline, fenoterol, levalbuterol, reproterol and pirbuterol.
39. A method according to claim 38 in a patient receiving no or low to medium dose inhaled corticosteroids comprising the step of providing to said patient a metered dose
20 inhaler containing a suspension aerosol formulation comprising a nominal dose of 10 micrograms formoterol fumarate dihydrate and 100 micrograms fluticasone propionate BID.
40. A method according to claim 38, in a patient receiving medium to high dose
25 inhaled corticosteroids, or in a patient indicated to receive medium to high dose inhaled corticosteroids, comprising the step of providing to said patient a metered dose inhaler containing a suspension aerosol formulation comprising a nominal dose of 10 micrograms formoterol fumarate dihydrate and 250 to 500 micrograms fluticasone propionate BID.

30

41. A method according to claim 38, in a patient receiving, but not adequately controlled by inhaled corticosteroids at low, medium or high dose, or in a patient indicated to receive inhaled corticosteroids, comprising the step of providing said patient with a metered dose inhaler containing a suspension aerosol formulation comprising
5 formoterol fumarate dihydrate and fluticasone propionate.
42. A method according to claim 41 wherein the metered dose inhaler contains a nominal dose of 10 micrograms formoterol fumarate dihydrate and 250 to 500 micrograms fluticasone propionate BID, or 10 micrograms formoterol fumarate dihydrate
10 and 250 to 500 micrograms fluticasone propionate BID.
43. A method according to claim 38 wherein the suspension aerosol formulation is as defined in claim 13.
- 15 44. A canister for use in a metered dose inhaler containing a suspension aerosol formulation as hereinabove described, which canister after filling and being stored for at least two weeks at a temperature of about 17 to about 25 degrees centigrade and a relative humidity of about 29 to 63% contains a residue of formoterol fumarate dihydrate of not more than about 12%, more particularly in a range of about 4 to 10% based on the
20 amount of formoterol fumarate dihydrate filled into the canister.
45. A canister for use in a metered dose inhaler containing a suspension aerosol formulation as hereinabove described, which canister after filling and being stored for at least two weeks at a temperature of about 17 to about 25 degrees centigrade and a relative
25 humidity of about 29 to 63% contains a residue of fluticasone propionate of not more than about 12%, more particularly in a range of about 4 to 10% based on the amount fluticasone propionate filled into the canister.
46. A canister according to claim 44 or 45 wherein the suspension aerosol
30 formulation is as defined in any of the claims 13 to 32.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/065569

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K31/00
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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/019985 A1 (CIPLA LTD [IN]; LULLA AMAR [IN]; MALHOTRA GEENA [IN]; WAIN CHRISTOPHER) 11 March 2004 (2004-03-11) the whole document * abstract claims 1-33; examples 1-43	1-46
X	US 2002/025299 A1 (LEWIS DAVID [IT] ET AL) 28 February 2002 (2002-02-28) the whole document claims 1-12	1-46
X	WO 02/078671 A1 (JAGO RES AG [CH]; MUELLER-WALZ RUDI [DE]; NIEDERLAENDER CARSTEN [CH]) 10 October 2002 (2002-10-10) * abstract claims 1-52; examples 1-6	1-46
	-/--	



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 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

23 December 2010

Date of mailing of the international search report

07/01/2011

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Felder, Christian

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/065569

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/034911 A1 (JAGOTEC AG [CH]; MUELLER-WALZ RUDI [DE]) 21 April 2005 (2005-04-21) the whole document claims 1-28 -----	1-46
X	WO 02/30394 A2 (3M INNOVATIVE PROPERTIES CO [US]; JINKS PHILIP A [GB]; MCKENZIE LESLEY) 18 April 2002 (2002-04-18) the whole document claims 1-43; examples 1-18 -----	1-46
X	US 2006/257324 A1 (LEWIS DAVID A [IT] ET AL) 16 November 2006 (2006-11-16) the whole document claims 1-26; examples 1-7 -----	1-46
A	GUPTA R K ET AL: "AN EVALUATION OF SALMETEROL IN THE TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASES", INDIAN JOURNAL OF CHEST DISEASES AND ALLIED SCIENCES, VALLABHBHAI PATEL CHEST INSTITUTE, NEW DELHI, IN, vol. 44, no. 3, 1 January 2002 (2002-01-01), pages 165-172, XP008018997, ISSN: 0377-9343 the whole document -----	1-46
A	MIRAVITLLES M ET AL: "TREATMENT AND QUALITY OF LIFE IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE", QUALITY OF LIFE RESEARCH, RAPID COMMUNICATIONS OF OXFORD, OXFORD, GB, vol. 11, no. 4, 1 January 2002 (2002-01-01), pages 329-338, XP008018999, ISSN: 0962-9343, DOI: DOI:10.1023/A:1015520110663 the whole document -----	1-46
A	BOWEN P: "Particle Size Distribution Measurement from Millimeters to Nanometers and from Rods to Platelets", JOURNAL OF DISPERSION SCIENCE AND TECHNOLOGY, TAYLOR AND FRANCIS GROUP, NEW YORK, NY, US, vol. 23, no. 5, 1 January 2002 (2002-01-01), pages 631-662, XP009102859, ISSN: 0193-2691, DOI: DOI:10.1081/DIS-120015368 the whole document -----	1-46

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2010/065569

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004019985	A1	11-03-2004	
		AU 2003260754 A1	19-03-2004
		CA 2496699 A1	11-03-2004
		EP 1531866 A1	25-05-2005
		JP 2005539046 T	22-12-2005
		NZ 538493 A	26-10-2007
		RU 2327450 C2	27-06-2008
		US 2006035874 A1	16-02-2006
US 2002025299	A1	28-02-2002	
		AR 029523 A1	02-07-2003
		AT 419832 T	15-01-2009
		AT 415945 T	15-12-2008
		AU 5070100 A	03-12-2001
		AU 2000250701 B2	01-07-2004
		BG 107256 A	30-06-2003
		BR 0015884 A	08-07-2003
		CA 2411047 A1	29-11-2001
		CN 1452479 A	29-10-2003
		CZ 20023835 A3	16-04-2003
		DE 122009000035 I1	05-11-2009
		DK 1157689 T3	16-03-2009
		DK 1466594 T3	02-03-2009
		EE 200200649 A	15-06-2004
		WO 0189480 A1	29-11-2001
		EP 1157689 A1	28-11-2001
		EP 1466594 A2	13-10-2004
		EP 1787639 A2	23-05-2007
		EP 2223682 A1	01-09-2010
		ES 2320194 T3	20-05-2009
		ES 2318217 T3	01-05-2009
		HK 1058900 A1	27-01-2006
		HR 20021025 A2	29-02-2004
		HU 0302007 A2	29-09-2003
		IL 152955 A	17-02-2010
		JP 2003534266 T	18-11-2003
		MX PA02011414 A	06-06-2003
		NL 300393 I1	01-09-2009
		NO 20025568 A	20-11-2002
		PL 359149 A1	23-08-2004
		PT 1157689 E	23-03-2009
		PT 1466594 E	13-02-2009
		SI 1466594 T1	30-06-2009
		SI 1157689 T1	30-06-2009
		SK 16522002 A3	01-04-2003
		TW 284047 B	21-07-2007
		UA 73986 C2	17-03-2003
WO 02078671	A1	10-10-2002	
		AT 375142 T	15-10-2007
		AU 2002234476 B2	27-04-2006
		CA 2442415 A1	10-10-2002
		CN 1499958 A	26-05-2004
		CZ 20032915 A3	16-06-2004
		DK 1372608 T3	27-12-2007
		EP 1372608 A1	02-01-2004
		ES 2292713 T3	16-03-2008
		HK 1064295 A1	09-04-2010
		HU 0401250 A2	29-11-2004
		JP 2004525148 T	19-08-2004

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2010/065569

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		NO 20034323 A	26-09-2003
		NZ 528640 A	25-06-2004
		PL 362797 A1	02-11-2004
		PT 1372608 E	04-01-2008
		RO 121172 B1	30-01-2007
		RU 2294737 C2	10-03-2007
		SK 13342003 A3	03-08-2004
		US 2004101483 A1	27-05-2004
W0 2005034911 A1	21-04-2005	CA 2540038 A1	21-04-2005
		EP 1670432 A1	21-06-2006
		US 2007256685 A1	08-11-2007
W0 0230394 A2	18-04-2002	AR 030862 A1	03-09-2003
		AT 320242 T	15-04-2006
		AU 1131102 A	22-04-2002
		AU 2002211311 B2	31-08-2006
		CA 2425035 A1	18-04-2002
		CN 1635870 A	06-07-2005
		CZ 20030983 A3	17-09-2003
		DE 60118021 T2	26-10-2006
		EP 1324749 A2	09-07-2003
		ES 2260299 T3	01-11-2006
		HU 0302311 A2	28-10-2003
		JP 2004510808 T	08-04-2004
		MX PA03002991 A	05-05-2004
		NO 20031597 A	30-05-2003
		NZ 525054 A	26-11-2004
		PL 361135 A1	20-09-2004
US 2006257324 A1	16-11-2006	NONE	