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V9-2012

Item Description:	FLUTIFORM INH 125-5MG 250MG-10MG 50MG-5MG PIL PH 666553		
POR No.:	5263	PMS No.:	N/A
Pack Size:	N/A	Drawing No.:	LSN-CON-30
Market(s):	PH	Prefixes:	N/A
Item Code:	666553	Dimensions:	720X200mm
Item Code:	N/A	Dimensions Folded:	40x200mm
Security Code:	Pharmacode	Unwind No.:	N/A
Security Code No.:	1157	No. of pages:	N/A
Edge Code:	N/A	Application Used:	Adobe InDesign 7.5.0.142
Barcode Type:	N/A	Created By:	lta02
Manufacturer / Packer:	SANOFI AVENTIS	Version:	2
Template No.:	720x200mm (LSN-CON-30) V1	Date Created:	27-03-17
PIL Readability code:	N/A		
Pattern Repeat (mm):	N/A		

Colour(s):
PMS 1505
PMS 280
PMS 286
Black

Non-Printing Colours
PINK
BLUE
PURPLE
BUFF

Font(s):
Helvetica Neue

APPROVED
By Anna Theresa D. Cristobal at 2:45 pm, Mar 30, 2017

APPROVED
By Carem P. Arevalo at 9:51 am, Apr 03, 2017

COUNTRY	Skyepharma - Flutiform
OPERATOR	Graham
LOGO VERSION	N/A
MINIMUM POINT SIZE	8

PACKAGING ADMINISTRATION
HOLMES CHAPEL, UK

SANOFI

JOB NUMBER	125901		
COMP. CODE	666553		
BASED ON	636474		
PROOF NO.	1	DATE	31/01/17
CPRO	1-54		
SIZE (mm)	720 x 200		
PHARMACODE	1157		

COLOURS USED
Black

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Flutiform Sales Pack - Philippines

fluticasone propionate / *formoterol fumarate*

flutiform®

Anti-Asthma

1. NAME OF THE MEDICINAL PRODUCT

fluticasone propionate/ formoterol fumarate (flutiform$^{®}$) 50mcg/5mcg per actuation metered dose inhaler (suspension)
fluticasone propionate/ formoterol fumarate (flutiform$^{®}$) 125mcg/5mcg per actuation metered dose inhaler (suspension)
fluticasone propionate/ formoterol fumarate (flutiform$^{®}$) 250mcg/10mcg per actuation metered dose inhaler (suspension)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each metered dose (ex-valve) contains:

- 50 mg of fluticasone propionate and 5 mcg of formoterol fumarate dihydrate. This is equivalent to a delivered dose (ex-actuator) of approximately 46 mcg of fluticasone propionate/4.5 mcg of formoterol fumarate dihydrate.
- 125 mg of fluticasone propionate and 5 mcg of formoterol fumarate dihydrate. This is equivalent to a delivered dose (ex-actuator) of approximately 115 mcg of fluticasone propionate/4.5 mcg of formoterol fumarate dihydrate.
- 250 mg of fluticasone propionate and 10 mcg of formoterol fumarate dihydrate. This is equivalent to a delivered dose (ex-actuator) of approximately 230 mcg of fluticasone propionate/9.0 mcg of formoterol fumarate dihydrate.

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Pressurized inhalation, suspension
The canister contains white to off white liquid suspension.
The canister is in a white actuator with a grey integrated dose indicator and a light grey mouthpiece cover.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication

This fixed-dose combination of ***fluticasone propionate/ formoterol fumarate (flutiform$^{®}$)*** inhaler is indicated in the regular treatment of asthma where the use of a combination product (an inhaled corticosteroid and a long-acting β2 agonist) is appropriate:

- For patients not adequately controlled with inhaled corticosteroids and 'as required' inhaled short-acting β2 agonist.
  or
- For patients already adequately controlled on both an inhaled corticosteroid and a long-acting β2 agonist.

4.2 Posology and Method of Administration

Posology
For inhalation use.
Patients will need to be trained on the use of the inhaler and their asthma should be regularly reassessed by a doctor, so that the strength of ***fluticasone propionate/ formoterol fumarate (flutiform$^{®}$)*** inhaler they are receiving remains optimal and is only changed on medical advice. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. Once control of asthma is achieved with the lowest strength of ***fluticasone propionate/ formoterol fumarate (flutiform$^{®}$)*** inhaler administered twice daily, treatment should be reviewed and consideration given as to whether patients should be stepped down to an inhaled corticosteroid alone.
Patients should be given the strength of ***fluticasone propionate/ formoterol fumarate (flutiform$^{®}$)*** inhaler containing the appropriate fluticasone propionate dosage for the severity of their disease.
Note: fluticasone propionate/ formoterol fumarate (flutiform$^{®}$) 50 mcg/5 mcg per actuation, strength is not appropriate in adults and adolescents with severe asthma. Prescribers should be aware that, in patients with asthma, fluticasone propionate is as effective as some other inhaled steroids when administered at approximately half the total daily dose (in mcg). If an individual patient should require doses outside the recommended dose regimens, appropriate doses of the β2 agonist and the inhaled corticosteroid in separate inhalers, or appropriate doses of the inhaled corticosteroid alone, should be prescribed.
fluticasone propionate/ formoterol fumarate (flutiform$^{®}$) inhaler is delivered by a press-and-breathe pressurized metered dose inhaler (pMDI) which also contains an integrated dose indicator. Each inhaler will provide at least 120 actuations (60 doses).
Adults and adolescents aged 12 years and above:
Two inhalations (puffs) of ***fluticasone propionate/ formoterol fumarate (flutiform$^{®}$)*** 50 mcg/5 mcg inhaler twice daily.
Or
Two inhalations (puffs) of ***fluticasone propionate/ formoterol fumarate (flutiform$^{®}$)*** 125 mcg/5 mcg inhaler twice daily.
Or
For adults only:
Two inhalations (puffs) of ***fluticasone propionate/ formoterol fumarate (flutiform$^{®}$)*** 250 mcg/10 mcg inhaler twice daily.
Children under 12 years:
No data are available for this strength of ***fluticasone propionate/ formoterol fumarate (flutiform$^{®}$)*** inhaler in children.
fluticasone propionate/ formoterol fumarate (flutiform$^{®}$) inhaler should not be used in this young age group.
Special patient groups:
There are no data available for use of ***fluticasone propionate/ formoterol fumarate (flutiform$^{®}$)*** inhaler in patients with COPD. ***fluticasone propionate/ formoterol fumarate (flutiform$^{®}$)*** inhaler should not be used in patients with COPD.
There is no need to adjust the dose in elderly patients.
There are no data available for use of ***fluticasone propionate/ formoterol fumarate (flutiform$^{®}$)*** inhaler in patients with hepatic or renal impairment *(see section 5.2)*. These patients should be regularly monitored by a physician to ensure titration to the lowest dose at which effective control of symptoms is maintained. As the fractions of fluticasone and formoterol which reach systemic circulation are primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe hepatic impairment.
General information:
If asthma symptoms arise in the period between doses, an inhaled, short-acting β2 agonist should be taken for immediate relief.
For patients who are currently receiving medium to high doses of inhaled corticosteroid therapy, and whose disease severity clearly warrants treatment with two maintenance therapies, the recommended starting dose is two inhalations ***fluticasone propionate/ formoterol fumarate (flutiform$^{®}$)*** 125 mcg/5 mcg inhaler per actuation twice daily.
Use of a spacer device with ***fluticasone propionate/ formoterol fumarate (flutiform$^{®}$)*** inhaler is recommended in patients who find it difficult to synchronize aerosol actuation with inspiration of breath.
Patients should be instructed in the proper use and care of their inhaler and spacer and their technique checked to ensure optimum delivery of the inhaled drug to the lungs.
Re-titration to the lowest effective dose should always follow the introduction of a spacer device.
Patients should rinse their mouth, gargle with water or brush the teeth after inhaling and spit out the residue to minimize the risk of oral candidiasis or dysphonia.

Method of administration
To ensure proper administration of the drug, the patient should be shown how to use the inhaler correctly by a physician or other health professionals. The correct use of the pressurized metered dose inhaler (pMDI) is essential for successful treatment.
The actuator has an integrated dose indicator which counts down the number of actuations (puffs) remaining. When this is getting near to zero, the patient should be advised to contact their prescriber for a replacement inhaler. The inhaler must not be used after the dose indicator reads "0". There is a color change as the dose indicator counts down: green 120-50puffs, yellow 50-30 puffs, red less 30 puffs.

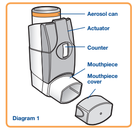

Diagram 1

Priming the inhaler
Before using the inhaler for the first time, or if the inhaler has not been used for 3 days or more, or after exposure to freezing or refrigerated conditions *(refer to section 6.4 Special precautions for storage)* the inhaler must be primed before use:

- Remove the mouthpiece cover and shake the inhaler well.
- Actuate (puff) the inhaler while pointing it away from the face. This step must be performed 4 times.
- The inhaler should always be shaken immediately before use.

Whenever possible, patients should stand or sit in an upright position when inhaling from the inhaler.
If you feel you are getting breathless or wheezy while using ***fluticasone propionate/ formoterol fumarate (flutiform$^{®}$)*** inhaler, you should continue to use ***fluticasone propionate/ formoterol fumarate (flutiform$^{®}$)*** inhaler but go to see your doctor or asthma nurse as soon as possible, as you may need additional treatment. Once your asthma is well controlled your doctor or asthma nurse may consider it appropriate to gradually reduce the dose of ***fluticasone propionate/ formoterol fumarate (flutiform$^{®}$)*** inhaler.
Steps to follow when using the inhaler:


Diagram 2

1. Remove the mouthpiece cover (see Diagram 2) and check that your inhaler is clean and free from any dust. The inhaler should be shaken immediately before releasing each puff (actuation).
2. Sit upright or stand. Breathe out as far as is comfortable and as slowly and as deeply as possible.


Diagram 3

3. Hold your inhaler upright (as shown in Diagram 3) and put the mouthpiece in your mouth with your lips tightly around it. Hold the inhaler with your thumb(s) on the base of the mouthpiece and forefinger/index finger(s) on the top of the inhaler. Do not bite the mouthpiece. Make sure that the tongue does not obstruct the mouthpiece.
4. Breathe in slowly and deeply through your mouth and, at the same time, press down on the aerosol can to release one puff (actuation). Continue to breathe in steadily and deeply.


Diagram 4

5. Once the lungs are full, hold your breath for as long as is comfortable (ideally about 10 seconds). Finally, remove the inhaler from your mouth and breathe out slowly. Do not breathe out into the inhaler.
6. Keep the inhaler in a vertical position for about half a minute and then shake the inhaler prior to slowly repeating steps 2 to 5.
7. Replace the mouthpiece cover.

IMPORTANT: Do not perform steps 2 to 5 too quickly.
Patients may be advised to practice their technique in front of a mirror. If a mist appears following inhalation, either from the inhaler or from the sides of the mouth, the procedure should be repeated from step 2.
For patients with weak hands, it may be easier to hold the inhaler with both hands. Therefore, the index fingers should be placed on the top of the inhaler canister and both thumbs on the base of the inhaler.
Patients should always rinse their mouth, gargle with water or brush the teeth after inhaling and spit out the residue to minimize the risk of oral candidiasis or dysphonia.

Cleaning:
The inhaler should be cleaned once a week.

- Remove the mouthpiece cover.
- Do not remove the canister from the plastic casing.
- Wipe the inside and outside of the mouthpiece and the plastic casing with a dry cloth or tissue.
- Replace the mouthpiece cover in the correct orientation.
- Do not put the metal canister into water.

4.3 Contraindications

Hypersensitivity to any of the active substances or to any of the excipients *(see section 6.1)*.

4.4 Special Warnings and Precautions for Use

fluticasone propionate/ formoterol fumarate (flutiform$^{®}$) inhaler should not be used to treat acute asthma symptoms for which a fast and short-acting bronchodilator is required. Patients should be advised to have their medicine to be used for relief in an acute asthma attack available at all times.
The prophylactic use of ***fluticasone propionate/ formoterol fumarate (flutiform$^{®}$)*** inhaler in exercise-induced asthma has not been studied. For such use, a separate rapid-acting bronchodilator should be considered.
Patients should not be initiated on ***fluticasone propionate/ formoterol fumarate (flutiform$^{®}$)*** inhaler during an exacerbation, or if they have significantly worsening or acutely deteriorating asthma.
Serious asthma-related adverse events and exacerbations may occur during treatment with ***fluticasone propionate/ formoterol fumarate (flutiform$^{®}$)*** inhaler. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on ***fluticasone propionate/ formoterol fumarate (flutiform$^{®}$)*** inhaler.
fluticasone propionate/ formoterol fumarate (flutiform$^{®}$) inhaler should not be used as the first treatment for asthma.
If increasing use of short-acting bronchodilators to relieve asthma is required, if short-acting bronchodilators become less effective, or ineffective or if asthma symptoms persist, the patient should be reviewed by their doctor as soon as possible as any of these may indicate a deterioration in asthma control and their treatment may need to be changed.
The lowest effective dose of ***fluticasone propionate/ formoterol fumarate (flutiform$^{®}$)*** inhaler should be used (see *section 4.2*).
Treatment with ***fluticasone propionate/ formoterol fumarate (flutiform$^{®}$)*** inhaler should not be stopped abruptly in patients with asthma due to risk of exacerbation. Therapy should be down-titrated under the supervision of a prescriber.
An exacerbation of the clinical symptoms of asthma may be due to an acute respiratory tract bacterial infection and treatment may require appropriate antibiotics, increased inhaled corticosteroids and a short course of oral corticosteroids. A rapid-acting inhaled bronchodilator should be used as rescue medication. As with all inhaled medication containing corticosteroids, ***fluticasone propionate/ formoterol fumarate (flutiform$^{®}$)*** inhaler should be administered with caution in patients with pulmonary tuberculosis, quiescent tuberculosis or patients with fungal, viral or other infections of the airway. Any such infections must always be adequately treated if ***fluticasone propionate/ formoterol fumarate (flutiform$^{®}$)*** inhaler is being used.
fluticasone propionate/ formoterol fumarate (flutiform$^{®}$) inhaler should be used with caution in patients with thyrotoxicosis, pheochromocytoma, diabetes mellitus, uncorrected hypokalemia or patients predisposed to low levels of serum potassium, hypertrophic obstructive cardiomyopathy, idiopathic subvalvular aortic stenosis, severe hypertension, aneurysm or other severe cardiovascular disorders, such as ischemic heart disease, cardiac arrhythmias or severe heart failure.
Potentially serious hypokalemia may result from high doses of β_2 agonists. Concomitant treatment of β_2 agonists with drugs which can induce hypokalemia or potentiate a hypokalemic effect, e.g. xanthine derivatives, steroids and diuretics, may add to a possible hypokalemic effect of the β_2 agonist. Particular caution is recommended in unstable asthma with variable use of rescue bronchodilators, in acute severe asthma as the associated risk may be augmented by hypoxia and in other conditions when the likelihood for hypokalemia adverse effects is increased. It is recommended that serum potassium levels are monitored during these circumstances.
Caution must be observed when treating patients with existing prolongation of the QTc interval. Formoterol itself may induce prolongation of the QTc interval.
As for all β_2 agonists, additional blood sugar controls should be considered in diabetic patients.
Care should be taken when transferring patients to ***fluticasone propionate/ formoterol fumarate (flutiform$^{®}$)*** inhaler therapy, particularly if there is any reason to suppose that adrenal function is impaired from previous systemic steroid therapy.
As with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing.
Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). It is important, therefore, that the patient is reviewed regularly and the dose of inhaled corticosteroid is reduced to the lowest dose at which effective control of asthma is maintained.
Prolonged treatment of patients with high doses of inhaled corticosteroids may result in adrenal suppression and acute adrenal crisis.
In situations of possible impaired adrenal function hypothalamic pituitary adrenocortical (HPA) axis function should be monitored regularly.
There is an increased risk of systemic side effects when combining fluticasone propionate with potent CYP3A4 inhibitors *(see section 4.5)*.
As the fractions of fluticasone and formoterol which reach systemic circulation are primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe hepatic impairment.
Pediatric population
It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of inhaled corticosteroid, if possible, to the lowest dose at which effective control of asthma is maintained. In addition, consideration should be given to referring the patient to a pediatric respiratory specialist.
Only limited data are available in respect of the use of *fluticasone propionate/ formoterol fumarate (flutiform$^{®}$)* inhaler in children under 12 years of age. *fluticasone propionate/ formoterol fumarate (flutiform$^{®}$)* inhaler is NOT recommended for use in children under 12 years of age until further data become available.

4.5 Interaction with other Medicinal Products and other Forms of Interaction

No formal drug interaction studies have been performed with ***fluticasone propionate/ formoterol fumarate (flutiform$^{®}$)*** inhaler.
fluticasone propionate/ formoterol fumarate (flutiform$^{®}$) inhaler contains sodium cromoglicate at non-pharmacological levels. Patients should not discontinue any cromoglicate containing medication.
Fluticasone propionate, an individual component of ***fluticasone propionate/ formoterol fumarate (flutiform$^{®}$)*** inhaler, is a substrate of CYP3A4. The effects of short-term co-administration of strong CYP3A4 inhibitors (e.g. ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nelfinavir, saquinavir, ketoconazole, telithromycin) together with ***fluticasone propionate/ formoterol fumarate (flutiform$^{®}$)*** inhaler is of minor clinical relevance, but caution needs to be taken in long-term treatment and co-administration with such drugs should be avoided if possible. Particularly co-medication of ritonavir should be avoided unless the benefit outweighs the increased risk of systemic glucocorticoid side-effects. Information about this interaction is lacking for inhaled fluticasone propionate, but a marked increase in fluticasone propionate plasma levels is expected. Cases of Cushing's syndrome and adrenal suppression have been reported.
The ECG changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by β agonists, especially when the recommended dose of the β agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the co-administration of a β agonist with non-potassium sparing diuretics. Xanthine derivatives and glucocorticosteroids may add to a possible hypokalemic effect of the β agonists.
In addition L-Dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards β_2 sympathomimetics.
Concomitant treatment with monoamine oxidase inhibitors, including agents with similar properties such as furazolidone and procarbazine, may precipitate hypertensive reactions.
There is an elevated risk of arrhythmias in patients receiving concomitant anesthesia with halogenated hydrocarbons.
Concomitant use of other β adrenergic drugs can have a potentially additive effect.
Hypokalemia may increase the risk of arrhythmias in patients who are treated with digitalis glycosides.
Formoterol fumarate, as with other β_2 agonists, should be administered with caution to patients being treated with tricyclic antidepressants or monoamine oxidase inhibitors, and during the immediate two week period following their discontinuation, or other drugs known to prolong the QTc interval such as antipsychotics (including phenothiazines), quinidine, disopyramide, procainamide, and antihistamines. Drugs that are known to prolong the QTc interval can increase the risk of ventricular arrhythmias *(see section 4.4)*.
If additional adrenergic drugs are to be administered by any route, they should be used with caution, because the pharmacologically predictable sympathetic effects of formoterol may be potentiated.
Beta adrenergic receptor antagonists (β blockers) and formoterol fumarate may inhibit the effect of each other when administered concurrently. Beta blockers may also produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with β blockers and this includes β blockers used as eye drops for treatment of glaucoma. However, under certain circumstances, e.g. as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of β blockers in patients with asthma. In this setting, cardioselective β blockers could be considered, although they should be administered with caution.

4.6 Fertility, Pregnancy and Lactation

Pregnancy
There are limited data on the use of fluticasone propionate and formoterol fumarate, either administered alone or together but administered from separate inhalers, or on the use of this fixed-dose combination, ***fluticasone propionate/ formoterol fumarate (flutiform$^{®}$)*** inhaler in pregnant women. Studies in animals have shown reproductive toxicity *(see section 5.3)*.
Administration of ***fluticasone propionate/ formoterol fumarate (flutiform$^{®}$)*** inhaler is not recommended during pregnancy, and should only be considered if expected benefit to the mother is greater than any possible risk to the fetus. If this is the case, then the lowest effective dose needed to maintain adequate asthma control should be used.
Because of the potential for β agonist interference with uterine contractility, use of ***fluticasone propionate/ formoterol fumarate (flutiform$^{®}$)*** inhaler for management of asthma during labor should be restricted to those patients in whom the benefit outweighs the risks.

Lactation

It is not known whether fluticasone propionate or formoterol fumarate is excreted in human breast milk. A risk to the suckling child cannot be excluded. Therefore, a decision must be made whether to discontinue breastfeeding or to discontinue/abstain from ***fluticasone propionate/ formoterol fumarate (flutiform®)*** inhaler therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility

There are no data available on effects on fertility following administration of ***fluticasone propionate/ formoterol fumarate (flutiform®)*** inhaler. In animal studies, no effects on fertility have been seen following administration of the individual active substances at clinically relevant doses *(see section 5.3)*.

4.7 Effects on Ability to Drive and Use Machines

fluticasone propionate/ formoterol fumarate (flutiform®) inhaler has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable Effects

Undesirable effects which have been associated with ***fluticasone propionate/ formoterol fumarate (flutiform®)*** inhaler during clinical development are given in the table below, listed by system organ class.

The following frequency categories form the basis for classification of the undesirable effects as:

Very common (≥1/10)
Common (≥1/100 and <1/10)
Uncommon (≥1/1,000 and <1/100)
Rare (≥1/10,000, < 1/1,000)
Very rare (<1/10,000) and not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Adverse Event	Frequency
Infections and Infestations	Oral candidiasis	Rare
	Oral fungal infection	
	Sinusitis	
Metabolism and Nutrition Disorders	Hyperglycemia	Rare
Psychiatric Disorders	Sleep disorders including Insomnia	Uncommon
	Abnormal dreams	Rare
	Agitation	
	Psychomotor hyperactivity	Not known
	Anxiety	
	Depression	
	Aggression	
	Behavioral changes (predominantly in children)	
Nervous System Disorders	Headache	Uncommon
	Tremor	
	Dizziness	
	Dysgeusia	Rare
Ear and labyrinth disorders	Vertigo	Rare
Cardiac Disorders	Palpitations	Uncommon
	Ventricular extrasystoles	
	Angina pectoris	Rare
	Tachycardia	
Vascular disorders	Hypertension	Rare
Respiratory, Thoracic and Mediastinal Disorders	Exacerbation of asthma	Uncommon
	Dysphonia	
	Throat irritation	
	Dyspnea	Rare
	Cough	
Gastrointestinal disorders	Dry mouth	Uncommon
	Diarrhea	Rare
	Dyspepsia	
Skin and subcutaneous tissue disorders	Rash	Uncommon
	Pruritus	Rare
Musculoskeletal and Connective Tissue Disorders	Muscle spasms	Rare
General disorders and administration site conditions	Peripheral edema	Uncommon
	Asthenia	Rare

As with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing.

Since ***fluticasone propionate/ formoterol fumarate (flutiform®)*** inhaler contains both fluticasone propionate and formoterol fumarate, the same pattern of undesirable effects as reported for these substances may occur.

4.9 Overdose

There are no data available from clinical trials on overdose with ***fluticasone propionate/ formoterol fumarate (flutiform®)*** inhaler, however, data on overdose with both single drugs are given below:

Formoterol fumarate:

An overdose of formoterol would likely lead to an exaggeration of effects that are typical for β_2 agonists; in which case the following adverse experiences may occur: angina, hypertension or hypotension, palpitations, tachycardia, arrhythmia, prolonged QTc interval, headache, tremor, nervousness, muscle cramps, dry mouth, insomnia, fatigue, malaise, seizures, metabolic acidosis, hypokalemia, hyperglycemia, nausea and vomiting.

Treatment of formoterol overdose consists of discontinuation of the medication together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of cardio selective β receptor blockers may be considered, bearing in mind that such medication can induce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial in cases of formoterol overdose. Cardiac monitoring is recommended.

If ***fluticasone propionate/ formoterol fumarate (flutiform®)*** inhaler therapy has to be withdrawn due to overdose of the β agonist component of the drug, provision of appropriate replacement steroid therapy should be considered. Serum potassium levels should be monitored as hypokalemia can occur. Potassium replacement should be considered.

Fluticasone propionate:

Acute overdose with fluticasone propionate usually does not constitute a clinical problem. The only harmful effect after inhalation of a large amount of the drug over a short period is suppression of hypothalamic pituitary adrenocortical (HPA) axis function. HPA axis function usually recovers in a few days, as verified by plasma cortisol measurements. Treatment with the inhaled corticosteroid should be continued at the recommended dose to control asthma.

There are reports of rare cases of acute adrenal crisis. Children and adolescents<16 years taking high doses of fluticasone propionate: (typically ≥1000mcg/day) may be at particular risk. Presenting symptoms can be vague (anorexia, abdominal pain, weight loss, tiredness, headache, nausea, vomiting and hypotension). Typical symptoms of an adrenal crisis are decreased level of consciousness, hypoglycemia and/or seizures.

Following chronic use of very high doses a degree of atrophy of the adrenal cortex and HPA axis suppression may occur. Monitoring of adrenal reserve may be necessary. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma *(see section 4.4)*.

In the management of chronic overdose, oral or systemic corticosteroids may be required in situations of stress. All patients deemed to be chronically overdosed should be treated as if steroid dependent with a suitable maintenance dose of a systemic corticosteroid. When stabilized, treatment should be continued with an inhaled corticosteroid at the recommended dose for symptom control.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic Group: Drugs for obstructive airways diseases, Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics

ATC code: R03AK11

Mechanism of Action and Pharmacodynamic Effects

fluticasone propionate/ formoterol fumarate (flutiform®) inhaler contains both fluticasone propionate and formoterol fumarate. These drugs represent two classes of medications (a synthetic corticosteroid and a selective, long-acting β_2 adrenergic receptor agonist).

Fluticasone propionate

Fluticasone propionate is a synthetic, trifluorinated glucocorticoid with potent anti-inflammatory activity in the lungs when given by inhalation. Fluticasone propionate reduces symptoms and exacerbations of asthma with less adverse effects than when corticosteroids are administered systemically.

Formoterol fumarate

Formoterol fumarate is a long-acting selective β_2 adrenergic receptor agonist. Inhaled formoterol fumarate acts locally in the lung as a bronchodilator. The onset of bronchodilating effect is rapid, within 1 - 3 minutes, and the duration of effect is at least 12 hours after a single dose.

fluticasone propionate/ formoterol fumarate (flutiform®) inhaler

In 12-week clinical trials in adults and adolescents, the addition of formoterol to fluticasone propionate improved asthma symptoms and lung function and reduced exacerbations. Therapeutic effect of ***fluticasone propionate/ formoterol fumarate (flutiform®)*** inhaler exceeded that of fluticasone propionate alone. There are no long-term data comparing ***fluticasone propionate/ formoterol fumarate (flutiform®)*** inhaler with fluticasone propionate.

In an 8-week clinical trial, the effect on lung function with ***fluticasone propionate/ formoterol fumarate (flutiform®)*** inhaler was at least equal to that of the combination of fluticasone propionate and formoterol fumarate when administered as separate inhalers. Long-term comparative data of ***fluticasone propionate/ formoterol fumarate (flutiform®)*** inhaler versus fluticasone propionate and formoterol fumarate are not available. There were no signs of attenuation of therapeutic effects of ***fluticasone propionate/ formoterol fumarate (flutiform®)*** inhaler in trials lasting up to 12 months including adult and adolescent patients.

Dose-response trends for ***fluticasone propionate/ formoterol fumarate (flutiform®)*** inhaler were evident for symptom-based endpoints, with incremental benefits from high versus low dose ***fluticasone propionate/ formoterol fumarate (flutiform®)*** inhaler being most likely in patients with more severe asthma.

Pediatric population

In a 12-week pediatric study including a 6-month extension phase for long-term safety 210 children aged 4 - 12 years were treated with a maintenance dose of ***fluticasone propionate/ formoterol fumarate (flutiform®)*** inhaler (2 inhalations of 50/5 mcg twice daily) or with a fixed combination comparator drug. Lung function was at least equal to that of the fixed combination comparator drug during the 12-week study duration. Following the 12-week core phase, patients could enter into a 6-month extension phase. Two hundred and five patients treated with ***fluticasone propionate/ formoterol fumarate (flutiform®)*** inhaler completed the 6-month extension phase during which ***fluticasone propionate/ formoterol fumarate (flutiform®)*** inhaler was safe and well tolerated.

5.2 Pharmacokinetic properties

Fluticasone propionate:

Absorption

Following inhalation, systemic absorption of fluticasone propionate occurs mainly through the lungs and has been shown to be linearly related to dose over the dose range 500 to 2000 mcg. Absorption is initially rapid then prolonged.

Published studies using oral dosing of labeled and unlabeled drug have demonstrated that the absolute oral systemic bioavailability of fluticasone propionate is negligible (<1%) due to a combination of incomplete absorption from the GI tract and extensive first-pass metabolism.

Distribution

Following intravenous administration, fluticasone propionate is extensively distributed in the body. The initial disposition phase for fluticasone propionate is rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averages 4.2 L/kg. The percentage of fluticasone propionate bound to human plasma proteins averages 91%. Fluticasone propionate is weakly and reversibly bound to erythrocytes and is not significantly bound to human transcortin.

Metabolism

The total clearance of fluticasone propionate is high (average, 1,093 mL/min), with renal clearance accounting for less than 0.02% of the total. The very high clearance rate indicates extensive hepatic clearance. The only circulating metabolite detected in man is the 17β-carboxylic acid derivative of fluticasone propionate, which is formed through the cytochrome P450 3A4 isoform subfamily (CYP3A4) pathway. This metabolite has less affinity (approximately 1/2000) than the parent drug for the glucocorticoid receptor of human lung cytosol *in vitro*. Other metabolites detected *in vitro* using cultured human hepatoma cells have not been detected in man.

Elimination

87 - 100% of an oral dose is excreted in the feces, up to 75% as parent compound. There is also a non-active major metabolite.

Following intravenous dosing, fluticasone propionate shows polyexponential kinetics and has a terminal elimination half-life of approximately 7.8 hours. Less than 5% of a radiolabelled dose is excreted in the urine as metabolites, and the remainder is excreted in the feces as parent drug and metabolites.

Formoterol fumarate:

Data on the plasma pharmacokinetics of formoterol were collected in healthy volunteers after inhalation of doses higher than the recommended range and in COPD patients after inhalation of therapeutic doses.

Absorption

Following inhalation of a single 120 mcg dose of formoterol fumarate by healthy volunteers, formoterol was rapidly absorbed into plasma, reaching a maximum concentration of 91.6pg/mL within 5 minutes of inhalation. In COPD patients treated for 12 weeks with formoterol fumarate 12 or 24 mcg b.i.d. the plasma concentrations of formoterol ranged between 4.0 and 8.9 pg/mL and 8.0 and 17.3 pg/mL respectively at 10 minutes, 2 hours and 6 hours post inhalation.

Studies investigating the cumulative urinary excretion of formoterol and/or its (RR) and (SS)-enantiomers, after inhalation of dry powder (12 - 96 mcg) or aerosol formulations (12-96 mcg), showed that absorption increased linearly with the dose.

After 12 weeks administration of 12 mcg or 24 mcg formoterol powder b.i.d., the urinary excretion of unchanged formoterol increased by 63 - 73% in adult patients with asthma, by 19 - 38% in adult patients with COPD and by 18 - 84% in children, suggesting a modest and self-limiting accumulation of formoterol in plasma after repeated dosing.

Distribution

The plasma protein binding of formoterol is 61 - 64% (34% primarily to albumin).

There is no saturation of binding sites in the concentration range reached with therapeutic doses.

The concentrations of formoterol used to assess the plasma protein binding were higher than those achieved in plasma following inhalation of a single 120 mcg dose.

Metabolism

Formoterol is eliminated primarily by metabolism, direct glucuronidation being the major pathway of biotransformation, with O-demethylation followed by further glucuronidation being another pathway. Minor pathways involve sulfate conjugation of formoterol and deformylation followed by sulfate conjugation. Multiple isozymes catalyze the glucuronidation (UGT1A1, 1A3, 1A6, 1A7, 1A8, 1A9, 1A10, 2B7 and 2B15) and O-demethylation (CYP 2D6, 2C19, 2C9 and 2A6) of formoterol, and so consequently the potential for metabolic drug-drug interaction is low. Formoterol did not inhibit cytochrome P450 isozymes at therapeutically relevant concentrations. The kinetics of formoterol is similar after single and repeated administration, indicating no auto-induction or inhibition of metabolism.

Elimination

In asthmatic and COPD patients treated for 12 weeks with 12 or 24 mcg formoterol fumarate b.i.d., approximately 10% and 7% of the dose, respectively, were recovered in the urine as unchanged formoterol. In asthmatic children, approximately 9% of the dose was recovered in the urine as unchanged formoterol after multiple dosing of 12 and 24 mcg. The (R,R) and (S,S)-enantiomers accounted for 40% and 60% respectively of urinary recovery of unchanged formoterol, after single doses (12 to 120 mcg) in healthy volunteers and after single and repeated doses in asthma patients. After a single oral dose of 3H-formoterol, 59 - 62% of the dose was recovered in the urine and 32 - 34% in the feces. Renal clearance of formoterol is 150 mL/min.

After inhalation, plasma formoterol kinetics and urinary excretion rate data in healthy volunteers indicate a biphasic elimination, with the terminal elimination half-lives of the (R, R) - and (S, S)-enantiomers being 13.9 and 12.3 hours, respectively. Peak excretion occurs rapidly, within 1.5 hours. Approximately 6.4 - 8% of the dose was recovered in the urine as unchanged formoterol, with the (R, R) and (S, S)-enantiomers contributing 40% and 60%, respectively.

flutiform® - fluticasone propionate/ formoterol fumarate combination

A number of studies have examined the pharmacokinetic characteristics of fluticasone propionate and formoterol fumarate from ***fluticasone propionate/ formoterol fumarate (flutiform®)*** inhaler compared with the individual components, given both together and separately.

There is a high variability both within and between the pharmacokinetic studies however, in general there is a trend for the systemic exposure of fluticasone and formoterol to be less from this fixed combination of fluticasone propionate and formoterol fumarate than from the individual components given together.

Pharmacokinetic equivalence between ***fluticasone propionate/ formoterol fumarate (flutiform®)*** inhaler and the constituent monoproducts has not been demonstrated. Long-term comparative data of ***fluticasone propionate/ formoterol fumarate (flutiform®)*** inhaler versus fluticasone propionate and formoterol fumarate are not available *(see section 5.1)*.

Absorption

flutiform® – fluticasone propionate

Following inhalation of a single 250 mcg dose of fluticasone propionate from 2 actuations of ***fluticasone propionate/ formoterol fumarate (flutiform®)*** 125 mcg/10 mcg inhaler by healthy volunteers, fluticasone propionate was rapidly absorbed into the plasma, reaching a mean maximum plasma fluticasone concentration of 32.8 pg/mL within 45 minutes of inhalation. In asthma patients who received single doses of fluticasone propionate from ***fluticasone propionate/ formoterol fumarate (flutiform®)*** inhaler, mean maximum plasma concentrations of 15.4 pg/mL and 27.4 pg/mL were achieved within 20 minutes and 30 minutes for 100 mcg/10 mcg (2 actuations of ***fluticasone propionate/ formoterol fumarate (flutiform®)*** 50 mcg/5 mcg inhaler) and 250 mcg/10 mcg (2 actuations of ***fluticasone propionate/ formoterol fumarate (flutiform®)*** 125 mcg/5 mcg inhaler) doses respectively.

In multiple dose studies in healthy volunteers, ***fluticasone propionate/ formoterol fumarate (flutiform®)*** inhaler doses of 100 mcg/10 mcg, 250 mcg/10 mcg and 500 mcg/20 mcg resulted in mean maximum plasma fluticasone concentrations of 21.4, 25.9 to 34.2 and 178 pg/mL respectively. The data for the 100 mcg/10 mcg and 250 mcg/10 mcg doses were generated by use of a device without a spacer and the data for the 500 mcg/20 mcg dose were generated by use of a device with a spacer.

flutiform® – formoterol fumarate

Following a single dose of ***fluticasone propionate/ formoterol fumarate (flutiform®)*** inhaler in healthy volunteers, a dose of 20 mcg of formoterol fumarate from 2 actuations of ***fluticasone propionate/ formoterol fumarate (flutiform®)*** 250 mcg/10 mcg inhaler resulted in a mean maximum plasma formoterol concentration of 9.92 pg/mL within 6 minutes of inhalation. Following multiple doses, 20 mcg of formoterol fumarate from 2 actuations of ***fluticasone propionate/ formoterol fumarate (flutiform®)*** 250 mcg/10 mcg inhaler resulted in a mean maximum plasma formoterol concentration of 34.4 pg/mL.

Distribution

There is currently no plasma protein binding information specific to fluticasone propionate or formoterol fumarate from ***fluticasone propionate/ formoterol fumarate (flutiform®)*** inhaler.

Metabolism

There are currently no data relating to the metabolism of fluticasone propionate or formoterol fumarate specifically from the inhalation of ***fluticasone propionate/ formoterol fumarate (flutiform®)*** inhaler.

Elimination

Fluticasone propionate

Following inhalation of fluticasone propionate from 2 actuations of ***fluticasone propionate/ formoterol fumarate (flutiform®)*** 250 mcg/10 mcg inhaler, fluticasone propionate has a terminal elimination half-life of approximately 14.2 h.

Formoterol fumarate

Following inhalation of formoterol fumarate from 2 actuations of ***fluticasone propionate/ formoterol fumarate (flutiform®)*** 250 mcg/10 mcg inhaler, formoterol fumarate has a terminal elimination half-life of approximately 6.5 h. Less than 2% of a single dose of formoterol fumarate from ***fluticasone propionate/ formoterol fumarate (flutiform®)*** inhaler is excreted in the urine.

5.3 Preclinical safety data

General safety

The toxicity observed in animal studies with formoterol fumarate and fluticasone propionate, given in combination or separately consisted mainly of effects associated with exaggerated pharmacological activity. Effects on the cardiovascular system are related to formoterol administration and included hyperemia, tachycardia, arrhythmias and myocardial lesions. There was no increase in toxicity and no unexpected findings upon administration of the combination of formoterol fumarate and fluticasone propionate compared to administration of the separate components.

Reproductive and developmental toxicity

Reproduction studies in rats and rabbits with ***fluticasone propionate/ formoterol fumarate (flutiform®)*** inhaler confirmed the known embryo-fetal effects of the two individual components including fetal growth retardation, incomplete ossification, embryo-lethality, cleft palate, edema and skeletal variations. These effects were seen at lower exposures than those expected by using the clinical maximum recommended dose. A reduced fertility in male rats was observed at very high systemic exposure to formoterol.

Genotoxicity and carcinogenicity

Neither formoterol fumarate nor fluticasone propionate was found to be genotoxic in standard *in vitro* and *in vivo* tests, when tested individually.

No carcinogenicity studies have been performed with the combination. No carcinogenic potential has been identified for fluticasone propionate. A slight increase in the incidence of benign tumors was observed in the reproductive tract of female mice and rats following administration of formoterol. This effect is looked upon as a class effect in rodents after long exposure to high doses of β2 agonists and does not suggest any potential risk of carcinogenicity in man.

HFA 227

Pre-clinical studies with HFA 227 reveal no special hazard for man based on studies of repeated-dose toxicity, genotoxicity, carcinogenicity and reproductive toxicity studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Cromoglicate
Ethanol Anhydrous
Apaflurane HFA 227

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 Years
In use shelf – life: 3 months after opening the foil pouch.

6.4 Special precautions for storage

Store at temperatures not exceeding 30°C. Do not refrigerate or freeze. If the inhaler is exposed to freezing conditions then the patient must be advised to allow the inhaler to warm at room temperature for 30 minutes then re prime the inhaler *(see section 4.2)*.

The canister contains a pressurized liquid. Do not expose to temperatures higher than 50°C. Do not puncture, break or burn, even when apparently empty.

6.5 Nature and contents of container

120 actuations per inhaler

The suspension is contained in an aluminum pressurized canister crimped with a standard metering valve. This canister is inserted into a press-and-breathe actuator fitted with a mouthpiece cover (both made of polypropylene) and an integrated dose indicator which indicates the number of actuations (puffs) remaining. The actuator is white with a grey integrated dose indicator and a light grey mouthpiece cover. The assembled MDI inhaler is pouched in an aluminum foil laminate and is packed in a cardboard carton.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

KEEP DRUGS OUT OF CHILDREN'S REACH.

CAUTION: Foods, Drugs, Devices and Cosmetics Act prohibit dispensing without prescription.

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Date of revision: 7 July 2015 based on CCDS
v. 2 25 February 2014 and CC1503001.

PH-FLU-1031-V1-0715

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