PRODUCT INFORMATION

Fluticasone + Salmeterol Cipla 125/25
Fluticasone + Salmeterol Cipla 250/25

Fluticasone propionate/ Salmeterol (as xinafoate)

125 /25 microgram and 250 /25 microgram MDI

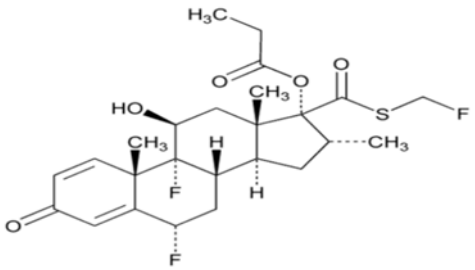
NAME OF THE MEDICINE

Fluticasone propionate/ Salmeterol (as xinafoate)

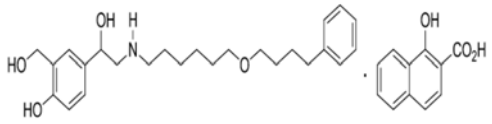
The chemical name of fluticasone propionate is S-Fluoromethyl 6α, 9α-difluoro-11ß-hydroxy-16α-methyl-3-oxo-17 α-propionyloxy-androsta-1, 4-diene-17ß-carbothioate. It has a molecular formula of $C_{25}H_{31}F_3O_5S$ and a molecular weight of 500.6.

The chemical name of salmeterol xinafoate is (±)-4-Hydroxy-α^1-[[[6-(4-phenylbutoxy)hexyl]amino]-methyl]-*m*-xylene-α, α′-diol 1-hydroxyl-2-naphthoate (salt). It has a molecular formula of $C_{25}H_{37}NO_4.C_{11}H_8O_3$ and a molecular weight of 603.8.

The structural formula of fluticasone propionate is:



The structural formula salmeterol xinafoate is:



CAS Registry Number

Fluticasone propionate: 80474-14-2

Salmeterol xinafoate: 94749-08-3

DESCRIPTION

Fluticasone + Salmeterol Cipla contains the active ingredients fluticasone propionate and salmeterol (as xinafoate).

Fluticasone propionate is a white or almost white powder. It is practically insoluble in water, sparingly soluble in methylene chloride, slightly soluble in ethanol (96 per cent).

Salmeterol (as xinafoate) is a white or almost white powder. Practically insoluble in water, soluble in methanol, slightly soluble in anhydrous ethanol.

Fluticasone + Salmeterol Cipla also contains the excipient norflurane (HFA 134a) which is a CFC-free propellant.

PHARMACOLOGY

This product contains fluticasone propionate and salmeterol (as xinafoate) which have differing modes of action. Salmeterol provides symptomatic relief, while fluticasone propionate improves lung function and prevents exacerbations of the condition. Fluticasone propionate/Salmeterol can offer a more convenient regimen for patients on concurrent long-acting beta-agonist and inhaled corticosteroid therapy. The respective mechanisms of action of both drugs are discussed below.

Fluticasone propionate
Fluticasone propionate given by inhalation at recommended doses has potent glucocorticoid activity in the airway. The potent anti-inflammatory action improves the symptomatic control of asthma, allows reduction of other drugs, such as rescue bronchodilators, and may limit the risk of decline in lung function over time. The low systemic bioavailability of fluticasone propionate provides a better risk: benefit outcome without the adverse effects that accompany systemically administered corticosteroids.

Salmeterol
Salmeterol is a selective long-acting beta-2-adrenoceptor agonist and at dosages of less than 100 microgram twice daily has little measurable cardiovascular effect. Salmeterol xinafoate is a racemate, the R-enantiomer being active.

The pharmacological properties of salmeterol offer a slower onset of action, but more effective protection against histamine-induced bronchoconstriction and a longer duration of bronchodilation (lasting for approximately 12 hours) than recommended doses of conventional short-acting beta-2 agonists. The onset of effective bronchodilation (> 15% improvement in FEV_1) occurs within 10 to 30 minutes and peak effect occurs between 3 to 4 hours.

In vitro tests have shown salmeterol is a potent and long-lasting inhibitor of the release of mast cell mediators, such as histamine, leukotrienes and prostaglandin D_2, from human lung fragments. In one study in man, salmeterol inhibits the early and late phase response to inhaled allergen; the latter persisting for over 30 hours after a single dose when the bronchodilator effect is no longer evident. Single dosing with salmeterol attenuates bronchial hyperresponsiveness. These properties indicate that salmeterol has additional non- bronchodilator activity, but the full clinical significance is not yet clear. The mechanism is different from the anti-inflammatory effect of corticosteroids.

Pharmacokinetics

There is no evidence in animal or human subjects that the administration of fluticasone propionate and salmeterol together by the inhaled route affects the pharmacokinetics of either component. For pharmacokinetic purposes therefore each component can be considered separately.

Even though plasma levels of fluticasone propionate/salmeterol are very low, potential interactions with other substrates and inhibitors of CYP 3A4 cannot be excluded.

Fluticasone propionate
Following oral administration 87-100% of the dose is excreted in the faeces, up to 75% as parent compound depending on the dose. There is a non-active major metabolite. Following intravenous administration there is rapid plasma clearance suggestive of extensive hepatic extraction. The plasma elimination half-life is approximately 3 hours. The volume of distribution is approximately 250 litres. Doses delivered by the dry powder inhalers and metered-dose inhalers may not have the same systemic bioavailability; however, there is no difference in clinical efficacy between the inhalers in controlled studies.

The absolute bioavailability of fluticasone propionate for each of the available inhaler devices has been estimated from within and between study comparisons of inhaled and intravenous pharmacokinetic data based on $AUC_{(0\text{-infinity})}$ data. In healthy adult subjects the absolute bioavailability has been estimated for fluticasone propionate Accuhaler (8%), fluticasone propionate

Diskhaler (9%) and fluticasone propionate Inhaler (10.9%) respectively. The absolute bioavailability from fluticasone propionate/salmeterol Accuhaler and Inhaler are approximately 6%.

Salmeterol
Salmeterol acts locally in the lung, therefore plasma levels are not predictive of therapeutic effect. In addition there are only limited data available on the pharmacokinetics of salmeterol because of the technical difficulty of assaying very low plasma concentrations (approximately 200 pg/mL or less) of the drug after inhaled dosing.

Following administration, salmeterol xinafoate is extensively bound (95-98%) to plasma proteins. Elimination of radioactivity from plasma following oral administration of radiolabelled salmeterol xinafoate is slow (mean $t_{½}$ is 67 hours). Excretion is predominantly through the faeces and to a lesser extent urine. Aliphatic hydroxylation appears to be the major route of metabolism in humans.

After regular dosing with salmeterol xinafoate, the xinafoate moiety, hydroxynaphthoic acid, can be detected in the systemic circulation, reaching steady state concentrations of approximately 100 ng/mL. These concentrations are up to 1000-fold lower than steady state levels observed in toxicity studies and in longer-term regular dosing (more than 12 months) trials in patients with airways obstruction, there have not been adverse effects attributable to hydroxynaphthoic acid reported.

In a placebo-controlled, crossover drug interaction study in 20 healthy subjects, co- administration of salmeterol (50 micrograms twice daily inhaled) and the CYP3A4 inhibitor ketoconazole (400 mg once daily orally) for 7 days resulted in a significant increase in plasma salmeterol exposure (1.4-fold C_{max} and 15-fold AUC). There was no increase in salmeterol accumulation with repeat dosing. Three subjects were withdrawn from salmeterol and ketoconazole co-administration due to QTc prolongation or palpitations with sinus tachycardia. The increase in the QTc interval observed with the co-administration of salmeterol and ketoconazole compared with salmeterol and placebo administration was not statistically significant. There were no clinically significant effects seen in heart rate or blood potassium levels, which were the primary endpoints of the study (see **PRECAUTIONS** and **INTERACTIONS WITH OTHER MEDICINES**).

CLINICAL TRIALS

Asthma

Two 12 week, double blind, double dummy, randomised, parallel group clinical studies were performed in 1006 adult and adolescent patients aged ≥ 12 years. The first study compared the 50/25 micrograms strength fluticasone propionate/salmeterol metered dose inhaler (MDI; 165 patients) with the corresponding 100/50 micrograms Accuhaler (167 patients), while the second study compared the 250/25 micrograms strength MDI (176 patients) with the 500/50 micrograms Accuhaler (161 patients). The dosing regimen for the MDI is two inhalations twice daily whilst the Accuhaler is one inhalation twice daily, ensuring the total daily dose of each active ingredient is the same for both formulations. Both studies also included a comparison with CFC fluticasone propionate MDI alone, at the same fluticasone propionate dose as the combination, to reaffirm the superiority of the combination over fluticasone propionate alone despite the change in formulation. All patients had reversible obstructive airways disease and were symptomatic on inhaled corticosteroids, with room for improvement in lung function. No clinical trial was performed with the 125/25 micrograms MDI strength because pharmaceutical and clinical pharmacology data have demonstrated dose proportionality across the three strengths of the fluticasone propionate component.

The primary efficacy variable was change in mean morning PEF over weeks 1–12, and this met the criterion for clinical equivalence between the MDI and Accuhaler combination formulations (95% confidence limits for the difference between treatments contained within ±15 L/min) in both studies. Comparable results were also seen for other time points in both studies, with almost all 95% confidence intervals falling within ±15 L/min. In no cases were the confidence intervals greater than ±16L/min. Large increases in mean PEF were seen over weeks 1-12 in both the MDI and the Accuhaler

combination groups.

In both studies, fluticasone propionate/salmeterol MDI was significantly more effective than fluticasone propionate MDI alone in change from baseline in mean morning PEF throughout the treatment period. This was manifest as early as week 1 ($p<0.001$). Mean treatment differences were greater than 15L/min. These results demonstrate clinical superiority of the MDI combination over the FP CFC formulation alone, reaffirming the superiority of the combination over fluticasone propionate alone, despite the change in formulation. While a statistical comparison of fluticasone/salmeterol Accuhaler was not conducted, the differences between these 2 treatment groups were of similar magnitude to those observed for the combination MDI.

Both the fluticasone propionate/salmeterol MDI and Accuhaler formulations improved symptoms scores, decreased rescue salbutamol usage and increased the percentage of symptom free days and nights. Effects of the two treatments on these parameters were similar.

Chronic Obstructive Pulmonary Disease (COPD)

Three randomised, double blind, placebo-controlled trials have investigated the safety and efficacy of fluticasone propionate/salmeterol Accuhaler in the treatment of patients with COPD. The studies used two fluticasone propionate/salmeterol dose strengths (250/50 micrograms and 500/50 micrograms). All studies comprised four treatment arms: fluticasone propionate/salmeterol, salmeterol, fluticasone propionate, placebo. Salmeterol is currently registered for the treatment of COPD.

Fluticasone propionate/salmeterol vs salmeterol alone: The primary efficacy variable for the three studies was mean change in morning pre-dose FEV_1. In the ITT analysis, a statistically significant difference in the primary endpoint in favour of fluticasone propionate/salmeterol was seen across all three studies. For multiple measured secondary endpoints, fluticasone propionate/salmeterol 500/50 micrograms was superior by a clinically significant degree only for dyspnoea vs salmeterol alone. In addition, fluticasone propionate/salmeterol 250/50 micrograms was statistically significantly superior to salmeterol for % days without use of reliever medication and % of nights without awakening.

Post-hoc subgroup analyses were performed for those patients with severe COPD ($FEV_1<50\%$ predicted normal). There were 1724 patients in the severe subgroup, of whom 415 received fluticasone propionate/salmeterol. A statistically significant treatment difference in favour of fluticasone propionate/salmeterol (both doses) was seen in the primary endpoint in two of the three studies. The clinical significance of these results is uncertain. For multiple measured secondary endpoints, fluticasone propionate/salmeterol 500/50 micrograms produced a clinically significant improvement in breathlessness and a clinically significant reduction in % of days without use of reliever medication (1 time per day) compared with salmeterol alone.

INDICATIONS

For the regular treatment of asthma, where the use of a combination product is appropriate. This may include the following:

- Patients on effective maintenance doses of long-acting beta-2 agonists and inhaled corticosteroids
- Patients who are symptomatic on current inhaled corticosteroid therapy

For the symptomatic treatment of patients with severe COPD ($FEV_1<50\%$ predicted normal) and a history of repeated exacerbations who have significant symptoms despite regular beta-2 agonist bronchodilator therapy. Fluticasone propionate/salmeterol (125/25 microgram and 250 /25 microgram) is not indicated for the initiation of bronchodilator therapy in COPD.

CONTRAINDICATIONS

Fluticasone propionate/salmeterol is contraindicated in patients with a history of hypersensitivity to any ingredients of the preparation (see **DESCRIPTION**).

PRECAUTIONS

Use in asthma management plan

The management of asthma should normally follow a stepwise program and patient response should be monitored clinically and by lung function tests. Treatment of asthma should be in accordance with current National asthma treatment guidelines.

Fluticasone propionate/salmeterol is not for relief of acute symptoms for which a fast- and short-acting inhaled bronchodilator (e.g. salbutamol) is required. Patients should be advised to have their relief medication available at all times.

Increasing use of short-acting bronchodilators to relieve symptoms indicates deterioration of control and patients should be reviewed by a physician.

Sudden and progressive deterioration in control of asthma is potentially life threatening and the patient should be reviewed by a physician. Consideration should be given to increasing corticosteroid therapy. Also, where the current dosage of fluticasone propionate/salmeterol has failed to give adequate control of asthma, the patient should be reviewed by a physician. For patients with asthma or COPD, consideration should be given to additional corticosteroid therapies and administration of antibiotics if an exacerbation is associated with infection.

Treatment should not be stopped abruptly in patients with asthma due to risk of exacerbation; therapy should be titrated-down under physician supervision. For patients with COPD cessation of therapy may be associated with symptomatic decompensation and should be supervised by a physician.

Pneumonia in COPD

There was an increased reporting of pneumonia in studies of patients with COPD receiving fluticasone propionate/salmeterol (see **ADVERSE EFFECTS**). Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbation frequently overlap.

As with all medications containing corticosteroids, fluticasone propionate/salmeterol should be administered with caution in patients with active or quiescent pulmonary tuberculosis.

Fluticasone propionate/salmeterol should be administered with caution in patients with thyrotoxicosis.

Cardiovascular effects

Cardiovascular effects, such as increases in systolic blood pressure and heart rate, may occasionally be seen with all sympathomimetic drugs, especially at higher than therapeutic doses. For this reason, fluticasone propionate/salmeterol should be used with caution in patients with pre-existing cardiovascular disease.

Hypokalaemia

A transient decrease in serum potassium may occur with all sympathomimetic drugs at higher therapeutic doses. Therefore, fluticasone propionate/salmeterol should be used with caution in patients predisposed to low levels of serum potassium.

Ocular complications

Rare instances of glaucoma and increased intraocular pressure have been reported following administration of inhaled corticosteroids.

Care should be taken when transferring patients to fluticasone propionate/salmeterol therapy, particularly if there is any reason to suppose that adrenal function is impaired from previous systemic steroid therapy.

Risks associated with salmeterol

Fluticasone propionate/salmeterol should not be initiated in patients with unstable or acutely deteriorating asthma, which may be a life-threatening condition. Serious acute respiratory events, including fatalities, have been reported when salmeterol has been initiated in this situation. Although it is not possible from these reports to determine whether salmeterol contributed to these adverse events or failed to relieve the deteriorating asthma, the use of salmeterol in this setting is inappropriate.

Fluticasone propionate/salmeterol should not be used to transfer patients from oral to inhaled steroids.

In rare cases inhaled therapy may unmask underlying eosinophilic conditions (e.g. Churg Strauss syndrome). These cases have usually been associated with reduction or withdrawal of oral corticosteroid therapy. A direct causal relationship has not been established.

There have been very rare reports of increases in blood glucose levels (see **ADVERSE EFFECTS**) and this should be considered when prescribing to patients with a history of diabetes mellitus.

Data from a large US study (SMART) comparing the safety of salmeterol (a component of fluticasone propionate/salmeterol) or placebo added to usual therapy showed a significant increase in asthma-related deaths in patients receiving salmeterol. Data from this study suggested that African-American patients may be at greater risk of serious respiratory-related events or deaths when using salmeterol compared to placebo. It is not known if this was due to pharmacogenetic or other factors. The SMART study was not designed to determine whether concurrent use of inhaled corticosteroids modifies the risk of asthma-related death.

It was observed in a drug interaction study that concomitant use of systemic ketoconazole increases exposure to salmeterol. This may lead to prolongation in the QTc interval. Due to the potential increased risk of cardiovascular adverse events, the concomitant use of salmeterol with strong CYP3A4 inhibitors (e.g. ketoconazole, atazanavir, ritonavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir) is nor recommended (see **INTERACTIONS WITH OTHER MEDICINES** and **Pharmacokinetics**).

Risks associated with fluticasone propionate

A drug interaction study in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can greatly increase fluticasone propionate plasma concentrations, resulting in markedly reduced serum cortisol concentrations. During post- marketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Therefore, concomitant use of fluticasone propionate and ritonavir should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side-effects.

Paradoxical bronchospasm

As with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. This should be treated immediately with a fast-acting inhaled bronchodilator. Fluticasone propionate/salmeterol should be discontinued immediately, the patient assessed, and if

necessary alternative therapy instituted.

The pharmacological side-effects of beta-2 agonist treatment, such as tremor, subjective palpitations and headache, have been reported, but tend to be transient and may reduce with regular therapy.

Spacer devices

Most patients will benefit from the consistent use of a spacer device with their metered dose inhaler (MDI or 'puffer'), particularly those with poor inhaler technique. Use of a spacer will also decrease the amount of drug deposited in the mouth and back of the throat, and therefore reduce the incidence of local side effects such as 'thrush' and a hoarse voice.

A change in the make of spacer may be associated with alterations in the amount of drug delivered to the lungs. The clinical significance of these alterations is uncertain. However, in these situations, the person should be monitored for any loss of asthma control.

If using a spacer, the patient should be instructed to actuate the inhaler into the spacer and then slowly breathe in as far as possible. Hold your breath for as long as comfortable, before breathing out slowly. This should be repeated for each actuation of the drug into the spacer. Any delays between actuation and inhalation should be kept to a minimum.

Static on the walls of the spacer may cause variability in drug delivery. Patients should be instructed to wash the spacer in warm water and detergent and allow it to air dry without rinsing or drying with a cloth. This should be performed before initial use of the spacer and at least monthly thereafter.

Possible systemic effects, including adrenocortical function, bone density and growth

Inhaled steroids are designed to direct glucocorticoid delivery to the lungs in order to reduce overall systemic glucocorticoid exposure and side effects. With sufficient doses however, all inhaled steroids can have adverse effects; possible systemic effects include Cushing's syndrome, Cushingoid features, depression of the hypothalamic-pituitary adrenal (HPA) axis, reduction of bone mineral density, cataract, glaucoma and retardation of growth rate in children and adolescents (see **OVERDOSAGE**).

The lowest dose of inhaled fluticasone that causes suppression of the HPA axis (as indicated by the 24 hour urinary cortisol concentrations), effects on bone mineral density or growth retardation in children has not yet been established. Some depression of plasma cortisol may occur in a small number of adult patients on higher doses (e.g. >1 mg/day). However, adrenal function and adrenal reserve usually remain within normal range on inhaled fluticasone propionate therapy. To minimise the systemic effects of inhaled corticosteroids, including fluticasone propionate, each patient should be titrated down to the lowest dose that effectively controls his/her asthma (see **DOSAGE AND ADMINISTRATION**).

Data regarding the effect of long term use of inhaled fluticasone on bone mineral density in elderly patients are limited.

Patients in a medical or surgical emergency, who in the past have required high doses of inhaled steroids and/or intermittent treatment with oral steroids, remain at risk of impaired adrenal reserve for a considerable time. The extent of the adrenal impairment may require specialist advice before elective procedures. The possibility of residual impaired adrenal response should always be borne in mind in emergency and elective situations likely to produce stress and appropriate corticosteroid treatment must be considered (see **OVERDOSAGE**).

Effects on fertility

Neither fluticasone propionate nor salmeterol alone show significant effects on fertility. Studies to detect such effects with co-administration have not been conducted.

Use in pregnancy

Pregnancy Category B3

There are limited data from clinical trials in pregnant women. However, extensive clinical experience with drugs in this class has revealed no evidence of adverse effects on the mother or foetus at relevant therapeutic doses of ICS. As with any medication, administration during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

An observational retrospective epidemiological cohort study utilising electronic health records from the United Kingdom was conducted to evaluate the risk of major congenital malformations (MCMs) following first trimester exposure to inhaled fluticasone propionate alone and salmeterol-fluticasone propionate relative to non-fluticasone propionate containing inhaled corticosteroids. No placebo comparator was included in this study.

Within the asthma cohort of 5362 first trimester inhaled corticosteroid-exposed pregnancies, 131 diagnosed MCMs were identified; 1612 (30%) were exposed to fluticasone propionate or salmeterol-fluticasone propionate of which 42 diagnosed MCMs were identified. The adjusted odds ratio for MCMs diagnosed by 1 year was 1.1 (95% CI: 0.5 – 2.3) for fluticasone propionate exposed versus non-fluticasone propionate inhaled corticosteroid exposed women with moderate asthma and 1.2 (95% CI: 0.7 – 2.0) for women with considerable to severe asthma. No difference in the risk of MCMs was identified following first trimester exposure to fluticasone propionate alone versus salmeterol-fluticasone propionate. Absolute risks of MCM across the asthma severity strata ranged from 2.0 to 2.9 per 100 fluticasone propionate-exposed pregnancies which is comparable to results from a study of 15,840 pregnancies unexposed to asthma therapies in the General Practice Research Database (2.8 MCM events per 100 pregnancies).

Results from the retrospective epidemiological study did not find an increased risk of MCMs following exposure to fluticasone propionate when compared to other inhaler corticosteroids, during the first trimester of pregnancy.

Reproductive toxicity studies in animals, either with single drug or in combination, revealed the foetal effects expected at excessive systemic exposure levels of a potent beta-2-adrenoceptor agonist and glucocorticosteroid – however these findings may not be relevant to humans taking inhaled steroids and beta-2 agonist at the recommended dose.

Use in lactation

Fluticasone propionate and salmeterol concentrations in plasma after inhaled doses are very low and therefore concentrations in human breast milk are likely to be correspondingly low. Studies in lactating animals support this for salmeterol xinafoate, although after subcutaneous administration of radiolabelled fluticasone propionate to lactating rats, levels of radioactivity in milk were 3 to 7 times plasma levels. There are no data available for human breast milk.

Administration during lactation should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

Paediatric use

Use in children less than 12 years is not recommended for this product. If the 50/25 microgram strength formulation is required, an alternative brand may be used.

The growth of paediatric patients receiving corticosteroids, including fluticasone propionate, should be monitored. The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained. To minimise the systemic effects of inhaled corticosteroids, including fluticasone propionate, each patient should be titrated down to the lowest dose that effectively controls

his/her asthma (see **DOSAGE AND ADMINISTRATION**).

In children taking recommended doses of inhaled fluticasone propionate, adrenal function and adrenal reserve usually remain within the normal range. However, the possible effects of previous or intermittent treatment with oral steroids should not be discounted. Nevertheless, the benefits of inhaled fluticasone propionate should minimise the need for oral steroids.

Genotoxicity

Neither fluticasone propionate nor salmeterol showed evidence of mutagenic potential when tested alone in a standard battery of genotoxicity assays. No studies examining the potential interaction of fluticasone propionate and salmeterol to cause genetic toxicity when co-administered have been conducted.

The non-CFC propellant, norflurane (HFA134a), has been shown to have no toxic effect at very high vapour concentrations, far in excess of those likely to be experienced by patients, in a wide range of animal species exposed daily for periods of two years.

Carcinogenicity

No studies on the carcinogenic potential of the combined formulation of fluticasone propionate: salmeterol have been conducted in animals. With fluticasone alone, no evidence of a tumorigenic effect was observed in either a 2 year study in rats receiving doses of fluticasone propionate up to 57 mg/kg/day by inhalation or in an 18 month study in mice receiving oral doses of fluticasone propionate up to 1 mg/kg/day. With salmeterol alone, oral administration to mice at 0.2, 1.4 or 10 mg/kg/day for 18 months resulted in the development of smooth muscle tumours (leiomyomas and possibly leiomyosarcomas) in the uterus. In rats, combined oral / inhalational administration for 24 months at total dose levels of 0.2, 0.7 and 2.6 mg/kg/day resulted in leiomyomas in the suspensory ligament of the ovaries, as well as an increased incidence of benign pituitary tumours. The smooth muscle tumours in both species are thought to result from chronic stimulation of beta-adrenoceptors in these tissues, whereas the mechanism involved in the development of the pituitary tumours is unknown.

Preclinical safety data

Fluticasone propionate and salmeterol have been extensively evaluated in animal toxicity tests. Significant toxicities occurred only at doses in excess of those recommended for human use and were those expected for a potent beta-2-adrenoreceptor agonist and glucocorticosteroid.

Co-administration of fluticasone propionate and salmeterol resulted in some cardiovascular lesions not seen upon dosing with the individual drugs (mild atrial myocarditis and focal coronary arteritis in rats and papillary muscle necrosis in dogs). However, these high dose changes were not consistently observed across studies and are unlikely to be of clinical relevance.

Co-administration did not modify other class-related toxicities in animals.

Effects on ability to drive and use machinery

Fluticasone propionate/salmeterol is unlikely to produce an effect.

INTERACTIONS WITH OTHER MEDICINES

Both non-selective and selective beta-blockers should be avoided unless there are compelling reasons for their use.

Under normal circumstances, low plasma concentrations of fluticasone propionate are achieved after

inhaled dosing, due to extensive first pass metabolism and high systemic clearance mediated by cytochrome P450 3A4 in the gut and liver. Hence, clinically significant drug interactions mediated by fluticasone propionate are unlikely.

A drug interaction study in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can greatly increase fluticasone propionate plasma concentrations, resulting in markedly reduced serum cortisol concentrations. During post- marketing use, there have been reports of clinically significant drug interactions in patients receiving intranasal or inhaled fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Therefore, concomitant use of fluticasone propionate and ritonavir should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side-effects.

Studies have shown that other inhibitors of cytochrome P450 3A4 produce negligible (erythromycin) and minor (ketoconazole) increases in systemic exposure to fluticasone propionate without notable reductions in serum cortisol concentrations. Nevertheless, care is advised when co-administering potent cytochrome P450 3A4 inhibitors (e.g. ketoconazole) as there is potential for increased systemic exposure to fluticasone propionate.

Co-administration of ketoconazole and salmeterol resulted in a significant increase in plasma salmeterol exposure (1.4-fold C_{max} and 15-fold AUC). This increase in plasma salmeterol may cause a prolongation of QTc interval (see **PRECAUTIONS** and **Pharmacokinetics**).

ADVERSE EFFECTS

As this product contains fluticasone propionate and salmeterol the type and severity of adverse reactions associated with each of the compounds may be expected. There is no evidence of additional adverse events following concurrent administration of the two compounds.

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥ 1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000) and very rare (<1/10,000).

Clinical trial data

Infections and infestations

Common: Candidiasis of mouth and throat, pneumonia (in COPD patients).

Such patients may find it helpful to rinse out their mouth with water after inhalation. Symptomatic candidiasis can be treated with topical anti-fungal therapy whilst still continuing with the fluticasone propionate.

Rare: Oesophageal candidiasis

Immune system disorders

Hypersensitivity reactions:

Uncommon: Cutaneous hypersensitivity reactions, dyspnoea.

Rare: Anaphylactic reactions

Endocrine disorders

Possible systemic effects include (see **PRECAUTIONS**):

Uncommon: Cataract

Rare: Glaucoma

Metabolism and nutrition disorders

Uncommon: Hyperglycaemia.

Psychiatric disorders

Uncommon: Anxiety, sleep disorders.

Rare: Behavioural changes, including hyperactivity and irritability (predominantly in children).

Nervous system disorders

Very common: Headache (see **PRECAUTIONS**).

Uncommon: Tremor (see **PRECAUTIONS**).

Cardiac disorders

Common: Palpitations (see **PRECAUTIONS**),

Uncommon: Tachycardia, atrial fibrillation.

Rare: Cardiac arrhythmias including supraventricular tachycardia and extrasystoles.

Peripheral vasodilation and a compensatory small increase in heart rate may occur in some patients.

Respiratory, thoracic and mediastinal disorders

Common: Hoarseness/dysphonia, throat irritation.

Skin and subcutaneous tissue disorders

Uncommon: Contusions.

Musculoskeletal and connective tissue disorders

Common: Muscle cramps, arthralgia.

Post-marketing data

Immune system disorders

Hypersensitivity reactions manifesting as:

Uncommon: Cutaneous hypersensitivity reactions.

Rare: Angioedema (mainly facial and oropharyngeal oedema) and respiratory symptoms (dyspnoea and/or bronchospasm), anaphylactic reactions

Endocrine disorders

Possible systemic effects include (see **PRECAUTIONS**):

Rare: Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decreased bone mineral density.

Metabolism and nutrition disorders

Uncommon: Hyperglycaemia.

Psychiatric disorders

Uncommon: Anxiety, sleep disorders.

Rare: Behavioural changes, including hyperactivity and irritability (predominantly in children).

Respiratory, thoracic and mediastinal disorders

Rare: Paradoxical bronchospasm (see **PRECAUTIONS**)

DOSAGE AND ADMINISTRATION

Note: Fluticasone + Salmeterol Cipla is not for use in patients aged under 12 years. A lower strength fluticasone and salmeterol (50/25 microgram) inhalation can be available from other brand/s.

Fluticasone + Salmeterol Cipla is for inhalation only.

Fluticasone + Salmeterol Cipla must be used regularly for optimum benefit, even when asymptomatic.

Patients should be regularly assessed by a doctor, so the dose of Fluticasone + Salmeterol Cipla they are receiving remains optimal. Strength of dose should only be increased or decreased on medical advice.

The use of one puff bd of the MDI has not been investigated in clinical trials.

Asthma

The dose of fluticasone propionate should be titrated to the lowest dose at which effective control of symptoms is maintained.

Patients should be given the dose of Fluticasone + Salmeterol Cipla containing the appropriate fluticasone propionate dosage for the severity of their disease.

Note: Salmeterol + Fluticasone Cipla is only available in two strengths (fluticasone propionate and salmeterol 125/25 microgram and 250/25 microgram). It is not available in a lower strength product containing salmeterol 25 microgram and fluticasone propionate 50 microgram. Therefore, when it is appropriate to titrate down to a dose of inhaled corticosteroid below 125 micrograms, a change to an alternative fixed-dose combination of salmeterol and fluticasone propionate containing a lower dose of the inhaled corticosteroid is required.

Adults and adolescents over 12 years

The recommended dose for regular asthma management is 100/50 microgram to 500/50 microgram fluticasone propionate/salmeterol twice daily.

Two inhalations (50/25 micrograms 125/25 micrograms or 250/25 micrograms) twice daily.

(Patients requiring dose below 250 micrograms of fluticasone will need to be prescribed an alternative brand.)

Special patient groups

There is no need to adjust the dose in elderly patients or in those with renal or hepatic impairment.

COPD

Adults

Two inhalations 250/25 micrograms twice daily.

OR

Two inhalations 125/25 micrograms twice daily may be a consideration in patients who are at a greater risk of inhaled corticosteroid adverse effects (see **CLINICAL TRIALS** and **DOSAGE AND ADMINISTRATION**).

Use of the device

Fluticasone + Salmeterol Cipla is available with a dose indicator. The MDI comprises a suspension of fluticasone propionate and salmeterol in a CFC-free propellant. The suspension is contained in an aluminium canister with a suitable metering valve and a polypropylene actuator having dose indicator and a dust cap in a sealed pouch containing desiccant.

The dose indicator will show number of actuations left in the canister through a window in the plastic actuator.

Shake the inhaler well before use.

The patient should be instructed to prime four sprays before using it for the first time and two sprays whenever it is not used for a week or more.

Inhaler should be cleaned at least once a week as follows.
- 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.

For more detailed instructions for use refer to the patient information leaflet.

OVERDOSAGE

For information on the management of overdose contact the Poison Information Centre on 131126 (Australia)

The available information on overdose with fluticasone propionate/salmeterol, fluticasone and/or salmeterol is given below:

It is not recommended that patients receive higher than approved doses of fluticasone propionate/salmeterol. It is important to review therapy regularly and titrate down to the lowest dose at which effective control of disease is maintained (see **DOSAGE AND ADMINISTRATION**).

Symptoms and signs

The expected symptoms and signs of salmeterol overdosage are those typical of excessive beta-2-adrenergic stimulation, including tremor, headache, tachycardia, increases in systolic blood pressure, hypokalaemia and raised blood glucose levels.

Acute inhalation of fluticasone propionate doses in excess of those approved may lead to temporary suppression of the hypothalamic-pituitary-adrenal axis. This does not usually require emergency action as normal adrenal function typically recovers within a few days.

If higher than approved doses of fluticasone propionate/salmeterol are continued over prolonged periods, significant adrenocortical suppression is possible. There have been very rare reports of acute adrenal crisis, mainly occurring in children exposed to higher than approved doses over prolonged periods (several months or years). Presenting symptoms are typically vague and may include anorexia, abdominal pain, weight loss, tiredness, headache, nausea, vomiting, decreased levels of consciousness, hypoglycaemia and seizures. Situations which could potentially trigger acute adrenal crisis include exposure to trauma, surgery, infection or any rapid reduction in the dosage of the inhaled fluticasone propionate component. Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

Treatment

There is no specific treatment for an overdose of fluticasone propionate and salmeterol. If overdose occurs, the patient should be treated supportively with appropriate monitoring necessary.

PRESENTATION AND STORAGE CONDITIONS

Fluticasone + Salmeterol Cipla 125/25 delivers 125 micrograms of fluticasone propionate and 25 micrograms of salmeterol (as xinafoate) per inhalation. Packs of 120 metered doses.

Fluticasone + Salmeterol Cipla 125/25 are a rigid, aluminium, container fitted with a metered dose valve, containing a white homogeneous suspension, fitted to a plastic actuator with a white coloured body and pink coloured cap, with a dose indicator.

Fluticasone + Salmeterol Cipla 250/25 delivers 250 micrograms of fluticasone propionate and 25 micrograms of salmeterol (as xinafoate) per inhalation. Packs of 120 metered doses.

Fluticasone + Salmeterol Cipla 250/25 are a rigid, aluminium, container fitted with a metered dose valve, containing a white homogeneous suspension, fitted to a plastic actuator with a white coloured body and rubin red coloured cap, with a dose indicator.

Fluticasone + Salmeterol Cipla is available with a dose indicator (see **DOSAGE AND ADMINISTRATION**).

Fluticasone + Salmeterol Cipla should be stored below 25^0C. Protect from frost and direct sunlight.

Do not store inhaler in a cold place as it may not work as well.

Replace the mouthpiece cover firmly and snap it into position.

As with most inhaled medications in pressurised canisters, the therapeutic effect of this fluticasone propionate/salmeterol MDI may decrease when the canister is cold. The canister should not be punctured, broken or burnt even when apparently empty.

NAME AND ADDRESS OF THE SPONSOR

Cipla Australia Pty Ltd
Level 1, 132-136 Albert Road
South Melbourne, VIC 3205.

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

Date of First Inclusion in the Australian Register of Therapeutic Goods (ARTG)

15.12.2016

Date of Most Recent Amendment
