Attachment 1: Product information for AusPAR Flutiform Mundipharma Pty Ltd PM-2010-03251-3-5 Final 13 June 2013. This Product Information was approved at the time this AusPAR was published.

PRODUCT INFORMATION

FLUTIFORM® pressurised inhalation 50 micrograms/5 micrograms, 125 micrograms/5 micrograms and 250 micrograms/10 micrograms

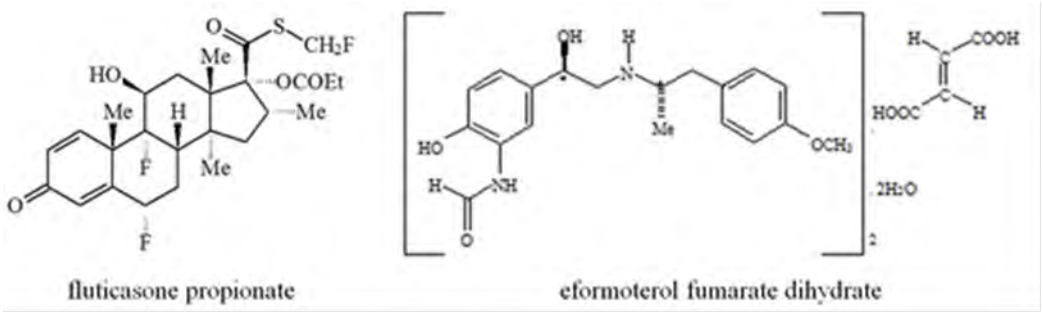
NAME OF THE MEDICINE

fluticasone propionate and eformoterol fumarate dihydrate

DESCRIPTION

Fluticasone propionate: It is a white to almost white powder, practically insoluble in water, slightly soluble in alcohol and sparingly soluble in dichloromethane. The chemical name is S-fluoromethyl 6α, 9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyl-oxy-androsta-1, 4-diene-17β-carbothioate (CAS No: 80474-14-2). The molecular formula is $C_{25}H_{31}F_3O_5S$. The structural formula is below.

Eformoterol fumarate dihydrate: It is a white to almost white or yellowish powder. It is slightly soluble in water, sparingly soluble in isopropyl alcohol, soluble in methanol and practically insoluble in acetonitrile. The chemical name is (±)-2'-hydroxy-5'-[(RS)]-1-hydroxy-2-[[(RS)-p-methoxy-α-methylphenethyl]amino]ethyl] formanilide fumarate dihydrate (CAS No: 43229-80-7). The molecular formula is $(C_{19}H_{24}N_2O_4)_2.C_4H_4O_4.2H_2O$. The structural formula is:



FLUTIFORM® inhaler: FLUTIFORM® pressurised inhalation ("inhaler") is a white to off-white liquid suspension inside a pressurised metal canister. The inactive ingredients are sodium cromoglycate, absolute ethanol and apaflurane (HFA 227). The active ingredients delivered by each metered dose from the canister valve are given in the table below:

Strengths (micrograms)	Active ingredient per actuation
Flutiform 50/5	50 micrograms of fluticasone propionate and 5 micrograms of eformoterol fumarate dihydrate (equivalent to an ex-actuator delivered dose of approximately 46 micrograms of fluticasone propionate and 4.5 micrograms of eformoterol fumarate dihydrate).
Flutiform 125/5	125 micrograms of fluticasone propionate and 5 micrograms of eformoterol fumarate dihydrate (equivalent to an ex-actuator

	delivered dose of approximately 115 micrograms of fluticasone propionate and 4.5 micrograms of eformoterol fumarate dihydrate).
Flutiform 250/10	250 micrograms of fluticasone propionate and 10 micrograms of eformoterol fumarate dihydrate (equivalent to an ex-actuator delivered dose of approximately 230 micrograms of fluticasone propionate and 9 micrograms of eformoterol fumarate).

PHARMACOLOGY

Actions

Fluticasone propionate is a synthetic trifluorinated glucocorticoid with potent anti-inflammatory activity in the lungs when administered by inhalation. Fluticasone propionate reduces the symptoms, improves lung function and prevents exacerbations of asthma, with fewer adverse effects than when corticosteroids are administered systemically. The use of an inhaled steroid improves symptomatic control of asthma, should reduce the need for short-acting bronchodilators and may limit the reduction in lung function over time.

Eformoterol fumarate is a potent long-acting, selective β_2-adrenergic receptor agonist. Inhaled eformoterol fumarate acts locally in the lungs as a bronchodilator, which provides symptomatic relief. After a single dose, onset of bronchodilation occurs rapidly within 1-3 minutes, with a duration of effect of at least 12 hours.

FLUTIFORM® inhaler belongs to the pharmacotherapeutic group 'adrenergics and other drugs for obstructive airway diseases' (ATC code: R03AK07). As with other combinations of inhaled corticosteroids and long-acting β2-adrenergic agonists, the additive effect produces a reduction in the exacerbation of asthma.

PHARMACOKINETICS

Fluticasone propionate: Pharmacokinetic data are available for the inhalation and intravenous administration routes.

Absorption

Following inhalation, systemic absorption of fluticasone propionate occurs mainly through the lungs. Absorption is initially rapid then prolonged. Published studies using oral dosing of labelled and unlabelled drug have demonstrated that the absolute oral systemic bioavailability of fluticasone propionate is negligible (<1%), due to a combination of incomplete absorption from the gastrointestinal 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, 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 approximately 91%. Fluticasone propionate is weakly and reversibly bound to erythrocytes.

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 an 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 (CYP 3A4) pathway. This metabolite has only very weak affinity for the glucocorticoid receptor of human lung cytosol *in vitro*.

Elimination
87-100% of an oral dose is excreted in the faeces, 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 faeces as parent drug and metabolites.

Eformoterol fumarate: Pharmacokinetic data are available for inhalation of therapeutic dosages in COPD patients, for inhalation of higher than recommended dosages in healthy volunteers, and for oral administration in healthy volunteers.

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

In studies investigating the cumulative urinary excretion of eformoterol and/or its (RR) and (SS)-enantiomers, absorption increased linearly with the dose after inhalation of 12-96 micrograms of dry powder or aerosol formulations. After 12 weeks' administration of 12 or 24 micrograms eformoterol powder twice daily, the urinary excretion of unchanged eformoterol increased by 63-73% in adult patients with asthma, by 19-38% in adult patients with COPD and by 18-84% in children. These results suggested a modest and self-limiting accumulation of eformoterol in plasma after repeated dosing.

As reported for other inhaled drugs, it is likely that about 90% of eformoterol administered from an inhaler will be swallowed and then absorbed from the gastrointestinal tract. This means that the pharmacokinetic characteristics of the oral formulation largely apply to the inhalation powder. When 80 micrograms of ^{3}H-labelled eformoterol fumarate was orally administered to two healthy volunteers, at least 65% of the drug was absorbed.

Distribution
The plasma protein binding of eformoterol 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 eformoterol used to assess the plasma protein binding were higher than those achieved in plasma following inhalation of a single 120 micrograms dose.

Metabolism

Eformoterol 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 sulphate conjugation of eformoterol and deformylation followed by sulphate conjugation. Multiple isozymes catalyse the glucuronidation (UGT1A1, 1A3, 1A6, 1A7, 1A8, 1A9, 1A10, 2B7 and 2B15) and O-demethylation (CYP 2D6, 2C19, 2C9 and 2A6) of eformoterol, and consequently the potential for metabolic drug-drug interaction is low. Eformoterol did not inhibit cytochrome P450 isozymes at therapeutically relevant concentrations. The kinetics of eformoterol 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 micrograms eformoterol fumarate twice daily approximately 10% and 7% of the dose, respectively, were recovered in the urine as unchanged eformoterol. In asthmatic children, approximately 6% of the dose was recovered in the urine as unchanged eformoterol after multiple dosing of 12 and 24 micrograms. The (R, R) and (S, S)-enantiomers accounted for 40% and 60% respectively of urinary recovery of unchanged eformoterol, after single doses (12 to 120 micrograms) in healthy volunteers, and after single and repeated doses in asthma patients. After a single oral dose of 3H-eformoterol, 59-62% of the dose was recovered in the urine and 32-34% in the faeces. Renal clearance of eformoterol is 150 mL/min.

After inhalation, plasma eformoterol 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 within 1.5 hours. Approximately 6.4-8% of the dose was recovered in the urine as unchanged eformoterol, with the (R, R) and (S, S)-enantiomers contributing 40% and 60%, respectively.

Fluticasone propionate/eformoterol fumarate in combination: A number of studies have examined the pharmacokinetic characteristics of fluticasone propionate and eformoterol fumarate in FLUTIFORM® inhaler compared with the individual components, administered 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 eformoterol to be less with FLUTIFORM® inhaler than with the individual components administered together.

Absorption

FLUTIFORM® inhaler (fluticasone propionate): Following inhalation of a single 250 micrograms dose of fluticasone propionate from 2 actuations of FLUTIFORM® inhaler 125 micrograms/5 micrograms by healthy volunteers, fluticasone propionate was rapidly absorbed into the plasma, reaching a mean maximum plasma fluticasone concentration of 32.8 picograms/mL within 45 minutes of inhalation. In asthma patients who received single doses of fluticasone propionate from FLUTIFORM® inhaler, mean maximum plasma concentrations of

15.4 picograms/mL and 27.4 picograms/mL were achieved within 20 minutes and 30 minutes for 100 micrograms/10 micrograms (2 actuations of FLUTIFORM® inhaler 50 micrograms/5 micrograms) and 250 micrograms/10 micrograms (2 actuations of FLUTIFORM® inhaler 125 micrograms/5 micrograms) doses, respectively.

In multiple dose studies in healthy volunteers, FLUTIFORM® inhaler doses of 100 micrograms/10 micrograms, 250 micrograms/10 micrograms and 500 micrograms/ 20 micrograms resulted in mean maximum plasma fluticasone concentrations of 21.4, 25.9 to 34.2 and 178 picograms/mL, respectively. The data for the 100 micrograms/10 micrograms and 250 micrograms/10 micrograms doses were generated by the use of a device without a spacer, and the data for the 500 micrograms/20 micrograms dose were generated by the use of a device with a spacer. Although there are no data directly comparing the exposure of fluticasone from a device with or without a spacer, spacers are known to increase the systemic exposure of fluticasone, and this may account for some of the difference in the levels achieved between the different doses.

FLUTIFORM® inhaler (eformoterol fumarate): Following a single dose of FLUTIFORM® inhaler in healthy volunteers, a dose of 20 micrograms of eformoterol fumarate from 2 actuations of FLUTIFORM® inhaler 250 micrograms/10 micrograms resulted in a mean maximum plasma eformoterol concentration of 9.92 picograms/mL within 6 minutes of inhalation. Following multiple doses, 20 micrograms of eformoterol fumarate from 2 actuations of FLUTIFORM® inhaler 250 micrograms/10 micrograms resulted in a mean maximum plasma eformoterol concentration of 34.4 picograms/mL.

Elimination
Following the inhalation of fluticasone propionate from 2 actuations of FLUTIFORM® inhaler 250 microgram/10 microgram, fluticasone propionate has a terminal elimination half-life of approximately 14.2 hours.

Following the inhalation of eformoterol fumarate from 2 actuations of FLUTIFORM® inhaler 250 microgram/10 microgram, eformoterol fumarate has a terminal elimination half-life of approximately 6.5 hours. Less than 2% of a single dose of eformoterol fumarate from FLUTIFORM® inhaler is excreted in the urine.

CLINICAL TRIALS

Summary of clinical trials
Studies to compare FLUTIFORM® inhaler with combination treatments (i.e. fluticasone plus eformoterol, or Seretide® inhaler consisting of fluticasone plus salmeterol), or with its individual components administered separately, or administered with and without a spacer were conducted. Four of these studies were pivotal, randomised, double-blind, parallel-group, stratified and active comparator controlled studies, two of which included a placebo control. A dose response relationship was not demonstrated for FLUTIFORM® inhaler for subjects with moderate to severe asthma.

Phase 3 studies

1. FLUTIFORM® inhaler vs concurrent therapy (combination fluticasone and eformoterol)

In study FLT3503, two strengths of FLUTIFORM® inhalers, 2 x 50/5 and 2 x 250/10 micrograms, were compared with combination therapy fluticasone 2 x 250 micrograms + eformoterol 2 x 12 micrograms, and with fluticasone 2 x 250 micrograms. Each treatment was taken twice daily. This randomised, double-blind, parallel-group, active-controlled study was 8 weeks in duration, and enrolled 620 patients: 155 on FLUTIFORM® inhaler lower dose, 154 on FLUTIFORM® inhaler higher dose, 156 on fluticasone + eformoterol and 155 on fluticasone alone. The primary objective was to show non-inferiority in the efficacy of FLUTIFORM® inhaler *versus* fluticasone and eformoterol administered concurrently in adult patients with moderate to severe, persistent asthma ($FEV_1 \geq 40\%$ to $\leq 80\%$ for predicted normal values). Two secondary objectives were to show superiority in the efficacy of FLUTIFORM® inhaler high dose *versus* fluticasone alone, and to show superiority in the efficacy of FLUTIFORM® inhaler high dose *versus* FLUTIFORM® inhaler low dose.

The primary efficacy endpoint was the mean change in pre-morning dose FEV_1 from baseline to the end of treatment. The co-primary endpoint was the mean change in FEV_1 from pre-morning dose at baseline to 2-hour post-morning dose at the end of treatment.

The LS mean change in pre-morning dose FEV_1 from baseline to end of treatment was 0.345 L in the FLUTIFORM® inhaler high-dose group and 0.284 L in the fluticasone + eformoterol group. The treatment difference was 0.060 L (95% CI: -0.059 to 0.180). The LS mean change in FEV_1 from pre-morning dose at baseline to 2-hour post-morning dose at the end of treatment was 0.518 L in the FLUTIFORM® inhaler high-dose group and 0.500 L in the fluticasone + eformoterol group. The treatment difference was 0.018 L (95% CI: -0.098 to 0.135). Non-inferiority of FLUTIFORM® inhaler high dose to fluticasone + eformoterol was demonstrated for both co-primary endpoints, as the lower limit of the 95% CI for the treatment difference exceeded the non-inferiority acceptance limit of -0.2 L ($p<0.001$). All secondary spirometric and symptom-based endpoints demonstrated no statistically significant or clinically relevant differences between FLUTIFORM® inhaler high-dose and fluticasone + eformoterol. This study was not designed to assess the relative efficacy of high and low dose FLUTIFORM® inhaler, however differences in mean change from baseline FEV_1 at the end of treatment in subjects taking low dose FLUTIFORM® inhaler were similar to those achieved in subjects taking high dose FLUTIFORM® inhaler.

2. FLUTIFORM® inhaler vs. fluticasone or eformoterol alone

Three pivotal randomised, double-blind, active-controlled, parallel-group, studies, two of which were also placebo-controlled, were conducted to compare FLUTIFORM® inhaler with its individual components administered separately. The primary objective of each study was to demonstrate the efficacy of FLUTIFORM® inhaler compared with fluticasone and eformoterol alone and placebo when administered over 12 weeks.

FLUTIFORM® inhaler 2 x 50/5 micrograms was compared with fluticasone 2 x 50 micrograms, eformoterol 2 x 5 micrograms and placebo. All treatments were taken twice daily. The study enrolled a total of 475 adolescents and adult subjects with mild to moderate asthma (the number

of subjects randomised to each group was 118, 119, 120 and 118, respectively). The three co-primary endpoints were: mean change in FEV_1 from morning predose at baseline to predose at Week 12 (to determine efficacy vs. fluticasone alone), the mean change in FEV_1 from predose at baseline to 2 hours postdose at Week 12 (to determine efficacy vs. eformoterol alone) and discontinuations due to lack of efficacy (to determine efficacy vs, placebo). FLUTIFORM® inhaler was superior to each of its comparators for each if the co-primary endpoints. The least squares mean difference in mean change in FEV_1 from morning predose at baseline to predose at Week 12 was 0.101 L (95%CI: 0.002 to 0.199; p = 0.045). The least squares mean difference in mean change in FEV_1 from morning predose at baseline to 2 hours postdose at Week 12 was 0.200 L (95%CI: 0.109 to 0.292, p< 0.001). 7 (6.1%) subjects given FLUTIFORM® inhaler, 9 (7.7%) given fluticasone, 13 (11.2%) given eformoterol and 18 (16.2%) given placebo discontinued prematurely due to lack of efficacy.

FLUTIFORM® inhaler 2 x 50/5 micrograms was compared with fluticasone 2 x 50 micrograms and eformoterol 2 x 5 micrograms. All treatments were taken twice daily. The study enrolled a total of 357 adolescents and adult subjects with mild to moderate asthma. The number of subjects randomised to each group was 119, 119 and 119, respectively. The two co-primary endpoints were: mean change in FEV_1 from morning predose at baseline to predose at Week 12 (to determine efficacy vs. fluticasone alone), the mean change in FEV_1 from predose at baseline to 2 hours postdose at Week 12 (to determine efficacy vs. eformoterol alone) and discontinuations due to lack of efficacy (to determine efficacy vs, placebo). FLUTIFORM was superior to each of its comparators for each of the co-primary endpoints.The least squares mean difference in mean change in FEV_1 from morning predose at baseline to predose at Week 12 was 0.118 L (95%CI: 0.034 to 0.201; p = 0.006). The least squares mean difference in mean change in FEV_1 from predose at baseline to 2 hours postdose at Week 12 The least squares mean difference in mean change in FEV_1 from predose at baseline to 2 hours postdose at Week 12 was 0.122 L (95%CI: 0.040 to 0.204, p = 0.004).

FLUTIFORM® inhaler 2 x 50/5 and 2 x 125/5 micrograms were compared with fluticasone 2 x 125 micrograms, eformoterol 2 x 5 micrograms and placebo. All treatments were taken twice daily. The study enrolled a total of 557 adolescents and adult subjects with mild to moderate asthma. The number of subjects randomised to each group was 110, 114, 113, 111 and 109, respectively.

The three co-primary endpoints were for the comparison of the 250/10 dose to its components and to placebo. These endpoints were: mean change in FEV_1 from morning predose at baseline to predose at Week 12 (to determine efficacy vs. fluticasone alone), the mean change in FEV_1 from predose at baseline to 2 hours postdose at Week 12 (to determine efficacy vs. eformoterol alone) and discontinuations due to lack of efficacy (to determine efficacy vs, placebo). FLUTIFORM® inhaler 250/10 was superior to each of its components and to placebo for each of the co-primary endpoints. The least squares mean difference in mean change in FEV_1 from morning predose at baseline to predose at Week 12 was 0.189 L ((p<0.001). The least squares mean difference in mean change in FEV_1 from predose at baseline to 2 hours postdose at Week 12 was 0.146 L, (p= 0.006). 7 (6.1%) subjects given FLUTIFORM, 9 (7.7%) given fluticasone, 13 (11.2%) given eformoterol and 18 (16.2%) given placeo discontinued prematurely due to lack

of efficacy. The number of subjects who discontinued prematurely due to lack of efficacy was 11 (10.2%) for FLUTIFORM® 250/10 inhaler, 14 (12.8%) for fluticasone, 23 (20.9%) for eformoterol and 41 (39.0%) for placebo groups.

This study was not designed to assess the relative efficacy of the two FLUTIFORM® inhaler doses (250/10 and 100/10 micrograms), however FLUTIFORM® inhaler 100/10 appeared to show similar results to the 250/10 dose.

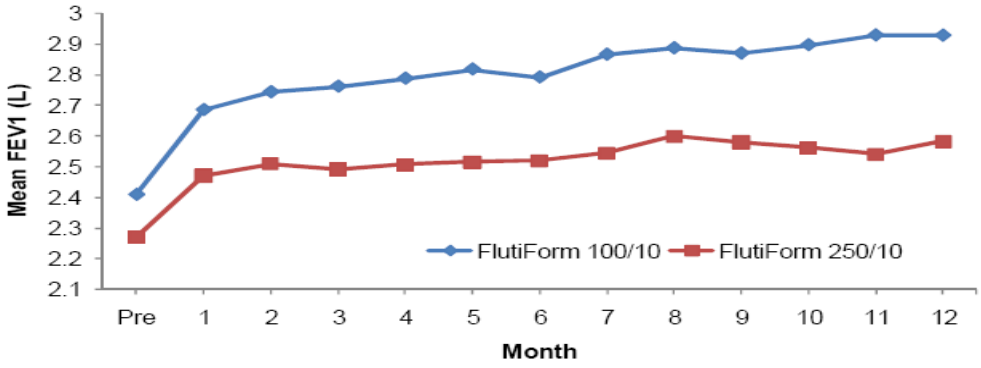
3 Long-term efficacy

Efficacy was assessed as a secondary objective in a long-term, open-label safety study (SKY2028-3-003). Subjects were assigned to a 6- or 12-month treatment duration subset. The change from baseline to each visit in pre-dose and post-dose FEV_1, FEV_1% predicted, FVC and PEFR was summarised for the two subsets, and changes within each dose group were analysed using the paired t-test.

Clinically important improvements at the $\alpha = 0.001$ level were observed for all the efficacy assessments for FLUTIFORM® inhaler treatment overall and for each dose group (100/10 and 250/10 micrograms) at every assessment time point. These included: (i) the mean changes from baseline to pre-dose assessment at Week 2, at Week 4, monthly thereafter and at the Final Visit; (ii) the mean changes from baseline to the 1-hour post-dose assessment at Week 2, Week 4, Month 2 and Month 3; and (iii) the improved mean pre-dose FEV_1 values for both FLUTIFORM® inhaler doses, that were sustained throughout the 12-month treatment period.

The data presented in Figure 1 below represents that from 175 patients who had data available at Month 1 and Month 12. These data demonstrates that pre-dose FEV_1 improved over the first 4 weeks and was then sustained over the entire 12 months treatment period.

Figure 1: Pre-dose FEV_1 values from Day 1 to Month 12 for patients that reached Month 12.



INDICATIONS

FLUTIFORM® inhaler is indicated for the regular maintenance treatment of asthma where the use of a combination product (an inhaled corticosteroid and a long-acting β2 agonist) is appropriate. It is appropriate both for patients not adequately controlled with inhaled corticosteroids and inhaled short-acting β2 agonist on an "as required" basis, and for patients already adequately controlled on both an inhaled corticosteroid and a long-acting β2 agonist.

CONTRAINDICATIONS

FLUTIFORM® inhaler is contraindicated in patients with hypersensitivity to any of the active substances or to the excipients.

PRECAUTIONS

Treatment guidelines

FLUTIFORM® inhaler should not be used as the first treatment for asthma. It is indicated for adolescents over 12 years and adults over 18 years. The management of asthma should normally follow a stepwise programme and patients' responses should be monitored clinically and with lung function tests.

FLUTIFORM® inhaler should not be used to treat acute asthma symptoms, for which a fast and short-acting bronchodilator is required. FLUTIFORM® inhaler should not be used to transfer patients from oral to inhaled corticosteroids. Patients should be advised to have their medicine available at all times for relief during an acute asthma attack.

Patients should not be initiated on 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 FLUTIFORM® inhaler. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on FLUTIFORM® inhaler.

Increasing use of short-acting bronchodilators to relieve asthma symptoms indicates a deterioration of asthma control, and these patients should be reviewed by a physician. Sudden and progressive deterioration in the control of asthma is potentially life-threatening and these patients require urgent medical assessment. Patients should be medically reviewed when their current dosage of FLUTIFORM® fails to give adequate control of asthma. Consideration should be given to either increasing, or to additional corticosteroid therapies. The lowest effective dose of FLUTIFORM® inhaler should be used. Treatment with FLUTIFORM® should not be stopped abruptly in patients with asthma, due to risk of exacerbation. Therapy should be down-titrated under the supervision of a physician.

To avoid overtreatment and unnecessary adverse events:

Initiate therapy with sufficient medication to achieve best lung function promptly, and after about 3 months of good control (which is characterised by few symptoms, minimal use of short-acting beta2-agonists and no exercise limitation), reduce inhaled corticosteroids to the minimum dose needed to maintain adequate asthma control ('stepping down').

Precautions for use

FLUTIFORM® inhaler should not be used more often than recommended, at higher doses than recommended or in combination with other medications containing long-acting beta2-agonists.

As with all inhaled medication containing corticosteroids, FLUTIFORM® inhaler should be administered with caution in patients with pulmonary tuberculosis.

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, FLUTIFORM® inhaler should be used with caution in patients with pre-existing cardiovascular disease.

A transient increase in serum potassium may be seen with all sympathomimetic drugs at higher therapeutic doses.

FLUTIFORM® inhaler should be used with caution in patients with a history of diabetes mellitus, thyrotoxicosis, uncorrected hypokalaemia or patients predisposed to low levels of serum potassium.

Care should be taken when transferring patients to 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 after dosing. FLUTIFORM® inhaler should be discontinued immediately, the patient assessed and alternative therapy instituted if required.

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

Inhaled corticosteroids are designed to direct glucocorticoid delivery to the lungs in order to reduce the overall systemic glucorticoid 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 the normal range on inhaled fluticasone propionate therapy.

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 corticosteroids and/or intermittent treatment with oral steroids, remain at risk of impaired adrenal reserve for a considerable time. The extent of adrenal impairment may require specialist advice before elective procedures. The possibility of residual impaired adrenal response should always be born in mind in emergency and elective situations likely to produce stress, and appropriate corticosteroid treatment must be considered.

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.

Additional systemic corticosteroid treatment should be considered during periods of stress or elective surgery.

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 at the 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. The breath should be held 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 the initial use of the spacer and at least monthly thereafter.

Driving and operating dangerous machinery

FLUTIFORM® inhaler is unlikely to have an effect on the ability to drive and operate machines.

Effects on fertility

No animal studies have been conducted with fluticasone propionate and eformoterol fumarate in combination to evaluate effects on fertility. Studies in rats with the individual active components showed no evidence of impairment of fertility with fluticasone propionate at subcutaneous doses up to 50 micrograms/kg/day (approximately half the maximum recommended human dose [MRHD] on a micrograms/m^2 body surface area basis), nor with eformoterol fumarate at oral doses up to 60 mg/kg/day.

Use in pregnancy

Australian Pregnancy Categorisation B3. There are no adequate and well-controlled studies with FLUTIFORM® inhaler in pregnant or breastfeeding women. . In pregnant rabbits, treatment with fluticasone propionate and eformoterol fumarate in combination by inhalation during the period of organogenesis (doses of 2/0.2 to 40/4 micrograms/kg/day fluticasone propionate/eformoterol fumarate) caused serious adverse effects on embryofetal development including increased post-implantation loss and malformations (cleft palate). These occurred in the absence of maternotoxicity and at doses yielding exposure to the two drugs (plasma and AUC) less than that expected in patients at MRHD. Decreased fetal weight and increased incidences of fetal skeletal variations and retarded ossification were observed in a corresponding study in rats in which treatment (doses up to 160/16 micrograms/kg/day fluticasone propionate/eformoterol fumarate) yielded drug exposure up to four times (fluticasone propionate) or six times (eformoterol fumarate) the clinical AUC at the MRHD. These findings are compatible with those of previous studies conducted with the individual drugs. Corticosteroids are known to induce fetotoxicity and teratogenicity in animals, but these results may not be relevant to human therapy. Administration of FLUTIFORM® 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. Because of the potential for beta-agonist interference with uterine contractility, use of FLUTIFORM® inhaler for management of asthma during labour should be restricted to those patients in whom the benefit outweighs the risks.

Use in lactation

It is not known whether fluticasone propionate or eformoterol fumarate, or their metabolites, are excreted in human breast milk. Such excretion has been demonstrated for both drugs in lactating rats. In addition, growth and survival of pups were found to be decreased when lactating rats were given eformoterol fumarate at oral doses greater than 1 mg/kg/day. Therefore, the administration of FLUTIFORM® to women who are breastfeeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

Use in children

Only limited data are available for FLUTIFORM® inhaler in children under 12 years of age. Therefore, FLUTIFORM® inhaler is not recommended for children under 12 years until further data become available.

Use in the elderly

There is no need to adjust the dose in elderly patients. No data are available on the use of FLUTIFORM® inhaler in patients with hepatic or renal impairment.

Genotoxicity

The potential genotoxicity of fluticasone propionate and eformoterol fumarate in combination has not been studied. Individually, the two agents exhibited no mutagenic or clastogenic effects in a battery of *in vitro* and *in vivo* tests.

Carcinogenicity
No carcinogenic studies with fluticasone propionate and eformoterol fumarate in combination have been conducted. Long-term rodent studies have been performed with the individual active components.

Fluticasone propionate: No evidence of tumourigenic activity was observed with fluticasone propionate in an 18-month study in mice treated at oral doses up to 1,000 micrograms/kg (approximately 5 times the MRHD in adults and children, on a micrograms/m^2 basis) or in a 2-year study in rats given doses up to 57 micrograms/kg (less than the MRHD in adults and children, on a micrograms/m^2 basis).

Eformoterol fumarate: In 2-year studies in mice and rats, treatment with eformoterol fumarate, given *via* the diet or drinking water at very high doses, was associated with increases in several tumour types. In mice, these included hepatocellular adenoma and carcinomas (≥2 mg/kg/day), leiomyomas and leiomyosarcomas in the female reproductive tract (≥2 mg/kg/day) and adrenal subcapsular cell tumours (≥66 mg/kg/day). In rats, treatment was associated with benign granulosa/theca cell tumours in the ovaries (≥0.5 mg/kg/day), mesovarian leiomyomas (≥18 mg/kg/day), mammary adenocarcinomas (≥36 mg/kg/day) and thyroid C-cell neoplasms (46 mg/kg/day. A mesovarian leiomyoma was also observed in a female rat dosed by inhalation at 130 micrograms/kg/day for two years (approximately 30-47 times the MRHD in adults and children on a micrograms/m^2 basis). Mammary adenocarcinomas, smooth muscle tumours in the female reproductive tract and effects on the ovary have been reported in rats and mice treated with other β_2- adrenoreceptor agonists and are likely to be secondary to prolonged stimulation of β_2-adrenoreceptors in these tissues.

INTERACTIONS WITH OTHER MEDICINES
No formal drug interaction studies have been performed with FLUTIFORM® inhaler.

CYP34A inhibitors
There is an increased risk of systemic side-effects when combining fluticasone propionate with potent CYP3A4 inhibitors. Fluticasone propionate, an individual component of FLUTIFORM® inhaler, is a substrate of CYP 3A4. Co-medication of strong CYP3A4 inhibitors (e.g. ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, saquinavir, ketaconazole) together with FLUTIFORM® inhaler should be avoided unless the benefit outweighs the increased risks. Information about this interaction is lacking for inhaled fluticasone propionate, but a marked increase in fluticasone propionate plasma levels would be expected. Cases of Cushing's syndrome and adrenal suppression have been reported.

Non-potassium sparing diuretics
The ECG changes and/or hypokalaemia 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
Xanthine derivatives and glucocorticosteroids may add to the possible hypokalaemic effect of β-agonists discussed above.

Drugs known to prolong QTc interval
Eformoterol fumarate, as with other β_2-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants (or within two weeks of their discontinuation), or drugs known to prolong the electrocardiographic QTc interval such as quinidine, disopyramide, procainamide, phenothiazines and antihistamines. Drugs that are known to prolong the QTc interval increase the risk of ventricular arrhythmias.

Adrenergic drugs
If additional adrenergic drugs are to be administered by any route, they should be used with caution, because the pharmacologically predictable sympathetic effects of eformoterol may be potentiated.

β-blockers
Beta-adrenergic receptor antagonists (β-blockers) and eformoterol fumarate may inhibit the effect of each other when administered concurrently. β-blockers may also produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with β-blockers. 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.

Sodium cromoglycate
FLUTIFORM® inhaler contains sodium cromoglycate at non-pharmacological levels. Patients should not discontinue any cromoglycate-containing medication.

ADVERSE EFFECTS
Adverse effects with fluticasone propionate and eformoterol in FLUTIFORM® inhaler are listed by system organ class (SOC), in order of decreasing seriousness within each SOC in Table 1.

Table 1: Adverse effects which have been associated with FLUTIFORM® inhaler

System Organ Class	Adverse Effect	Frequency
Infections and infestations	Oral candidiasis Acute sinusitis	Rare
Metabolism and nutrition disorders	Hyperglycaemia	Uncommon
Psychiatric disorders	Abnormal dreams Agitation Insomnia	Rare
	Psychomotor hyperactivity, anxiety, depression, aggression, behavioural changes (predominantly in children)	Not known
Nervous system disorders	Headache Tremor Ddizziness	Uncommon

	Dysgeusia	
Ear and labyrinth disorders	Vertigo	Rare
Cardiac disorders	Palpitations Ventricular extrasystoles	Uncommon
	Angina pectoris Tachycardia	Rare
Vascular disorders	Hypertension	Rare
Respiratory, thoracic and mediastinal disorders	Exacerbation of asthma Dysphonia Throat irritation	Uncommon
	Dyspnoea Cough	Rare
Gastrointestinal disorders	Dry mouth	Uncommon
	Diarrhoea Dyspepsia	Rare
Skin and subcutaneous tissue disorders	Rash	Rare
Musculoskeletal connective tissue disorders	Muscle spasms	Rare
General and administration site disorders	Peripheral oedema	Uncommon
	Asthenia	Rare

Frequency: 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 including isolated reports); not known (cannot be estimated from the available data).

As with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid-acting inhaled bronchodilator and should be treated immediately. Inhalation therapy should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

The common adverse events reported for ≥ 1.0% of subjects in any treatment group in the pooled safety analysis are presented in Table 2 below. The adverse event profile was generally comparable amongst all the treatment groups, but the longer exposure time in the FLUTIFORM® inhaler group compared with other comparator groups could be expected to influence the rates.

Table 2: Pooled safety data (8 Phase 3 studies) adverse events for ≥1.0% of subjects in any treatment group

System Organ Class Preferred Term	**FLT** **N = 1746** n (%)	**FP + FF** **N = 345** n (%)	**SER** **N = 100** n (%)	**FP** **N = 995** n (%)	**FF** **N = 349** n (%)	**PBO** **N = 223** n (%)
Subjects with any adverse reaction	545 (31.2)	88 (25.5)	24 (24.0)	351 (35.3)	144 (41.3)	98 (43.9)
Infections and infestations	**322 (18.4)**	**41 (11.9)**	**13 (13.0)**	**185 (18.6)**	**65 (18.6)**	**34 (15.2)**
Bronchitis	35 (2.0)	1 (0.3)	1 (1.0)	15 (1.5)	3 (0.9)	3 (1.3)
Ear infection	1 (0.1)	0 (0.0)	1 (1.0)	3 (0.3)	0 (0.00	0 (0.0)
Gastroenteritis viral	4 (0.2)	0 (0.0)	0 (0.0)	3 (0.3)	5 (1.4)	0 (0.0)
Influenza	11 (0.6)	2 (0.6)	0 (0.0)	12 (1.2)	2 (0.6)	0 (0.0)
Laryngitis	2 (0.1)	3 (0.9)	1 (1.0)	3 (0.3)	2 (0.6)	0 (0.0)
Nasopharyngitis	95 (5.4)	6 (1.7)	4 (4.0)	45 (4.5)	10 (2.9)	6 (2.7)
Pharyngitis	30 (1.7)	7 (2.0)	1 (1.0)	15 (1.5)	1 (0.3)	2 (0.9)
Pneumonia pneumococcal	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)

Respiratory tract infection	15 (0.9)	2 (0.6)	1 (1.0)	4 (0.4)	1 (0.3)	1 (0.4)
Rhinitis	13 (0.7)	1 (0.3)	0 (0.0)	10 (1.0)	0 (0.0)	0 (0.0)
Sinusitis	17 (1.0)	2 (0.6)	0 (0.0)	12 (1.2)	3 (0.9)	5 (2.2)
Tonsilitis	1 (0.1)	1 (0.3)	1 (1.0)	0 (0.0)	0 (0.0)	2 (0.9)
Upper respiratory tract infection	34 (1.9)	1 (0.3)	1 (1.0)	26 (2.6)	18 (5.2)	7 (3.1)
Urinary tract infection	19 (1.1)	0 (0.0)	0 (0.0)	12 (1.2)	9 (2.6)	1 (0.4)
Viral infection	8 (0.5)	5 (1.4)	1 (1.0)	4 (0.4)	3 (0.9)	0 (0.0)
Respiratory thoracic and mediastinal disorders	145 (8.3)	16 (4.6)	4 (4.0)	70 (7.0)	57 (16.3)	45 (20.2)
Asthma	45 (2.6)	3 (0.9)	2 (2.0)	25 (2.5)	36 (10.3)	39 (17.5)
Cough	29 (1.7)	5 (1.4)	1 (1.0)	10 (1.0)	6 (1.7)	2 (0.9)
Dyspnoea	24 (1.4)	0 (0.0)	1 (1.0)	2 (0.2)	0 (0.0)	1 (0.4)
Dysphonia	15 (0.9)	6 (1.7)	0 (0.0)	5 (0.5)	0 (0.0)	0 (0.0)
Rhinitis allergic	17 (1.0)	1 (0.3)	0 (0.0)	14 (1.4)	3 (0.9)	3 (1.3)
Rhinitis seasonal	2 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	5 (1.4)	0 (0.0)
Nervous system disorders	61 (3.5)	10 (2.9)	0 (0.0)	45 (4.5)	17 (4.9)	16 (7.2)
Headache	32 (2.0)	4 (1.2)	0 (0.0)	23 (3.3)	9 (2.6)	12 (5.4)
Psychiatric disorders	12 (0.7)	2 (0.6)	1 (1.0)	11 (1.1)	2 (0.6)	1 (0.4)
Depression	3 (0.2)	2 (0.6)	1 (1.0)	1 (0.1)	0 (0.0)	0 (0.0)
Renal and urinary disorders	5 (0.3)	0 (0.0)	1 (1.0)	2 (0.2)	0 (0.0)	1 (0.4)
Dysuria	0 (0.0)	0 (0.0)	(1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Reproductive and breast disorders	4 (0.2)	0 (0.0)	1 (1.0)	6 (0.6)	0 (0.0)	1 (0.4
Adenomyosis	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	51 (2.9)	5 (1.4)	1 (1.0)	41 (4.1)	9 (2.6)	8 (3.6)
Abdominal pain upper	2 (0.1)	1 (0.3)	1 (0.0)	3 (0.3)	1 (0.3)	0 (0.0)
Diarrhoea	10 (0.6)	2 (0.6)	0 (0.0)	4 (0.4)	2 (0.6)	4 (1.8)
Vomiting	5 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.3)	3 (1.3)
Musculoskeletal and connective tissue disorder	53 (3.0)	7 (2.0)	1 (1.0)	21 (2.1)	14 (4.0)	4 (1.8)
Arthralgia	9 (0.5)	0 (0.0)	1 (0.1)	4 (0.4)	1 (0.3)	0 (0.0)
Back pain	13 (0.8)	1 (0.3)	0 (0.0)	6 (0.6)	8 (2.3)	2 (0.9)
Myalgia	4 (0.2)	0 (0.0)	1 (0.1)	4 (0.4)	1 (0.3)	0 (0.0)
Pain in extremity	8 (0.5)	0 (0.0)	1 (1.0)	3 (0.3)	0 (0.0)	1 (0.4)
Injury, poisoning and procedural complications	30 (1.7)	2 (0.6)	2 (2.0)	21 (2.1)	6 (1.7)	8 (3.6)
Fall	2	0 (0.0)	1 (1.0)	1 (0.1)	0 (0.0)	0 (0.0)
Neck injury	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	5 (0.3)	3 (0.9)	2 (2.0)	4 (0.4)	1 (0.3)	1 (0.4)
Hypercholesterolaemia	0 (0.0)	2 (0.6)	1 (1.0)	1 (0.1)	0 (0.0)	0 (0.0)
Hyperlipidaemia	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders	9 (0.5)	6 (1.7)	0 (0.0)	3 (0.3)	3 (0.9)	0 (0.0)
Hypertension	5 (0.3)	4 (1.2)	0 (0.0)	3 (0.3)	2 (0.6)	0 (0.0)
Neoplasms benign, malignant and unspecified (including cysts &polyps)	1 (0.1)	0 (0.0)	3 (3.0)	0 (0.0)	1 (0.3)	0 (0.0)
Melanocytic naevus	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Prostatic adenoma	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)

Skin papilloma	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Surgical and medical procedures	3 (0.2)	1 (0.3)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dental prosthesis placement	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)

FLT = FLUTIFORM, FP+FF = fluticasone + eformoterol, SER = Serotide, FP = fluticasone, FF = eformoterol, PBO = placebo
N = no. of subjects in treatment group, n = no. of subjects with events in specified category, % = percentage based on N

Patient exposure

A total of 1,746 adult and adolescent patients with mild to severe asthma have been treated with FLUTIFORM® inhaler in clinical phase 3 studies. A pooled analysis of safety was conducted and the results from eight pooled phase 3 trials are presented in Tables 1 and 2, above. The studies were all 12 weeks in duration, apart from one study which was up to 52 weeks and one which was 8 weeks. Additionally, a total of 337 subjects were treated with FLUTIFORM® inhaler in four Phase 1 and Phase 2 single-dose studies, making a total of over 2,000 patients who have received at least one dose of FLUTIFORM® inhaler. No long-term studies beyond 12 weeks were conducted at the highest FLUTIFORM® dose (500/20 microgram).

Since FLUTIFORM® inhaler contains both fluticasone propionate and eformoterol fumarate, the same pattern of undesirable effects as reported for these substances may occur, as indicated below, although these have not been seen during the clinical development of FLUTIFORM® inhaler:

Fluticasone propionate: Hypersensitivity reactions including urticaria, pruritus, angioedema (mainly facial and oropharyngeal), anaphylactic reactions. Systemic effects of inhaled corticosteroids may occur, particularly at high dosages prescribed for prolonged periods. These may include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma, sleep disorders, contusion, skin atrophy and susceptibility to infections. The ability to adapt to stress may be impaired. The systemic effects described, however, are much less likely to occur with inhaled corticosteroids than with oral corticosteroids. Prolonged treatment with high doses of inhaled corticosteroids may result in clinically significant adrenal suppression and acute adrenal crisis. Additional systemic corticosteroid cover may be required during periods of stress (trauma, surgery, infection).

Eformoterol fumarate: Hypersenstivity reactions (including hypotension, angioneurotic oedema, pruiritus, exanthema), QTc interval prolongation, hypokalaemia, nausea, myalgia, increased blood lactate levels. Treatment with β_2-agonists such as eformoterol may result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies.

Hypersensitivity reactions have been reported in patients using inhaled sodium cromoglycate as an active ingredient. Whilst FLUTIFORM® inhaler contains only a low concentration of sodium cromoglycate as an excipient, it is unknown if hypersensitivity reactions are dose dependent.

In the unlikely event of a hypersensitivity reaction to FLUTIFORM® inhaler treatment should be initiated in accordance with standard treatment for any other hypersensitivity reaction, which may include the use of antihistamines and other treatment as required. FLUTIFORM® inhaler may be discontinued immediately and an alternative asthma therapy may be initiated if necessary.

Dysphonia and candidiasis may be relieved by gargling or rinsing the mouth with water or brushing the teeth after using the product. Symptomatic candidiasis may be treated with tropical anti-fungal therapy while continuing the treatment with FLUTIFORM® inhaler.

DOSAGE AND ADMINISTRATION

FLUTIFORM® inhaler is for administration by the inhaled route in patients with asthma from the age of 12 years and older. FLUTIFORM® inhaler is delivered by a press-and-breathe pressurised metered dose inhaler (pMDI) which also contains an integrated dose indicator. Each inhaler will provide at least 120 actuations (60 doses).

Patients will need to be trained on the use of the inhaler and should be regularly reassessed by a doctor, so that the strength of 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. Patients should be regularly assessed by a doctor so the dose of FLUTIFORM® inhaler they are receiving remains optimal. The strength of the dose should only be increased or decreased on medical advice (see PAEDIATRIC USE).

Patients should be given the strength of FLUTIFORM® inhaler containing the appropriate fluticasone propionate dosage for the severity of their disease. Note: FLUTIFORM® inhaler

50 micrograms/5 micrograms strength is not appropriate in adults and adolescents with severe asthma. If an individual patient should require dosages outside the recommended regimen, appropriate doses of beta-agonist and/or corticosteroid in single inhalers should be prescribed.

The long-term efficacy of the highest dose of 500/20 micrograms (2 actuations of 250/10 micrograms) twice daily has not been evaluated. The efficacy and safety data for the highest dose are only available from the 8-week Phase 3 study FLT3503 (see **CLINICAL TRIALS**).

Recommended dose for adults and children aged 12 years and above
Two inhalations of FLUTIFORM® inhaler 50/5 micrograms or FLUTIFORM® inhaler125/5 micrograms twice daily. If the patient's asthma remains poorly controlled on FLUTIFORM® inhaler 50/5 micrograms, the total daily dose of the inhaled corticosteroid can be increased by administering the next highest strength combination product, i.e. FLUTIFORM® inhaler 125/5 micrograms, two puffs twice daily.

Recommended dose for adults only
Two inhalations of FLUTIFORM® inhaler 250/10 micrograms twice daily. If the patient's asthma remains poorly controlled on FLUTIFORM® inhaler 125/5 micrograms, the total daily

dose can be increased by administering the next highest strength combination product, i.e. FLUTIFORM® inhaler 250/10 micrograms, two puffs twice daily.

Children Under 12 Years
FLUTIFORM® inhaler is not recommended for children under 12 years (see **Use in children**).

Patients currently receiving medium to high doses of inhaled corticosteroids
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 twice daily of FLUTIFORM® inhaler 125/5 micrograms.

Special patient groups
There is no need to adjust the dose in elderly patients.

There is no data available for use of FLUTIFORM® inhaler in patients with hepatic or renal impairment.

General Information
Patients should be made aware that FLUTIFORM® inhaler must be used daily for optimum benefit, even when asymptomatic. Patients using FLUTIFORM® inhaler should not use additional long-acting β2-agonists for any reason. If asthma symptoms arise in the period between doses, an inhaled, short-acting β2-agonist should be taken for immediate relief.

Each dose of FLUTIFORM® inhaler is administered as two inhalations twice daily (normally taken in the morning and the evening). Rinsing the mouth, gargling with water or brushing the teeth after every dose and swallowing is advised to minimise the risk of oropharyngeal candida infection. The use of only one actuation twice daily of FLUTIFORM inhaler has not been investigated in clinical trials.

Use of a spacer device with FLUTIFORM® inhaler is recommended in patients who find it difficult to synchronise aerosol actuation with inspiration of breath. The Aero Chamber Plus® spacer device can be used.

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.

Instruction for Use
To ensure proper administration of the drug, the patient should be shown how to use the inhaler correctly by a physician or other healthcare professionals. The correct use of the pressurised metered dose inhaler (pMDI) is essential for successful treatment. The patient should be advised to read the Consumer Medicine Information leaflet carefully and follow the instructions for use in the leaflet.

Priming the Inhaler
Before using the inhaler for the first time or if the inhaler has not been used for 3 days or more, the inhaler should be primed before use:

- Remove the mouthpiece cover and shake the inhaler well.
- Spray (away from the face). This step should 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 the inhaler is exposed to freezing conditions, then the patient must be advised to allow the product to warm up at room temperature for 30 minutes, and then re-prime the inhaler using two actuations.

Steps to follow for use of inhaler

1. Remove the cap from the mouthpiece and check that the mouthpiece is clean, and free from dust and dirt. The inhaler should be shaken immediately before releasing each puff.
2. Breathe out as slowly and deeply as possible.
3. Hold the canister vertically with its body upwards and put the lips around the mouthpiece. Do not bite the mouthpiece.
4. At the same time, breathe in slowly and deeply through the mouth. After starting to breathe in, press down on the top of the inhaler to release one puff.
5. Hold the breath for as long as possible and, finally, remove the inhaler from the 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, shake the inhaler, and repeat steps 2 to 5.
7. After use, replace the protective cap over the mouthpiece.

Important information
Do not perform steps 2 to 5 too quickly.

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 rinse their mouth, gargle with water or brush the teeth after inhaling.

Cleaning
Patients should be advised to read the Consumer Medicine Information leaflet carefully for cleaning instructions, and to clean their inhalers 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 in the correct orientation.

Disposal
The container should not be punctured, broken or burnt, even when apparently empty, as the canister contains a pressurised liquid. Apart from this, there are no special requirements for the disposal of FLUTIFORM® inhaler.

OVERDOSAGE
There are no data available from clinical trials on overdose with FLUTIFORM® inhaler. Information on overdose by the single active components is provided below:

Fluticasone propionate
Symptoms: Acute inhalation of fluticasone propionate doses in excess of those recommended may lead to temporary suppression of adrenal function. This does not need emergency action because plasma cortisol measurements have verified that adrenal function is recovered in a few days.

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

Chronic use of inhaled fluticasone propionate carries a risk of adrenal suppression (see also **PRECAUTIONS**, Precautions for use). Monitoring of adrenal reserve may be necessary.

Treatment: In cases of fluticasone propionate overdose the dose of FLUTIFORM® inhaler should be tapered. Therapy with FLUTIFORM® inhaler may still be continued at a suitable dosage for symptom control.

Eformoterol fumarate
Symptoms: An overdose of eformoterol 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, hypokalaemia, hyperglycaemia, nausea and vomiting.

Treatment: Treatment of eformoterol over-dosage consists of discontinuation of the medication together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective β-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial in cases of eformoterol overdose. Cardiac monitoring is recommended in cases of overdosage.

If FLUTIFORM® inhaler therapy has to be withdrawn due to overdose of the beta agonist component, provision of appropriate replacement steroid therapy should be considered. Additionally, hypokalaemia can occur and potassium replacement should be considered.

Please phone the Poisons Information Centre on 131126 for advice on managing overdose.

PRESENTATION AND STORAGE CONDITIONS

FLUTIFORM® pressurised inhalation is contained in an aluminium pressurised canister crimped with a standard metering valve. The canister is inserted into a press-and-breathe actuator fitted with a dust cap, and an integrated dose indicator which indicates the number of doses remaining. The assembled inhaler is pouched in an aluminium foil laminate, and then packed in a cardboard carton.

The strengths of FLUTIFORM® pressurised inhalation are:

- 50 micrograms fluticasone propionate/5 micrograms eformoterol fumarate
- 125 micrograms fluticasone propionate/5 micrograms eformoterol fumarate
- 250 micrograms fluticasone propionate/10 micrograms eformoterol fumarate.

Each container for the three strengths delivers 120 actuations.

Store below 25ºC. Do not refrigerate or freeze.

The in-use shelf-life is 3 months after the inhaler is removed from the foil pouch, or after the dose indicator reads ‘0’ (whichever comes first).

NAME AND ADDRESS OF THE SPONSOR

Mundipharma Pty Limited
ABN 87 081 322 509
50 Bridge Street
SYDNEY NSW 2000

POISONS SCHEDULE OF THE MEDICINE

S4

DATE OF FIRST INCLUSION IN AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

DATE OF MOST RECENT AMENDMENT

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