HCP-MEPPO
Publishers of MEPPO and MODERN MEDICINE

SALMETAROL

GlaxoSmithKline

TITLE

Salmeterol-Fluticasone Propionate (Salmeterol-FP).

SCOPE

Trade Name(s)

SERETIDE™ ACCUHALER™/DISKUS™,
ADVAIR™ ACCUHALER™/DISKUS™,
VIANI™ ACCUHALER™/DISKUS™,
ATMADISC™ ACCUHALER™/DISKUS™,
ALIFLUS™ ACCUHALER™/DISKUS™,
VERASPIR™ ACCUHALER™/DISKUS™
SERETIDE™ EVOHALER™,
ADVAIR™ EVOHALER™,
VIANI™ EVOHALER™,
ALIFLUS™ EVOHALER™,
VERASPIR™ EVOHALER™

Formulation, Strength and Device* (*if appropriate)

Accuhaler/Diskus:

Inhalation powder.

Moulded plastic device containing a foil strip with 28 or 60 regularly placed blisters each containing 50 micrograms of salmeterol as salmeterol xinafoate and 100, 250 or 500 micrograms of fluticasone propionate.

Evohaler:

Inhalation aerosol.

Salmeterol-FP Evohaler has been formulated in three strengths and one pack size, delivering 120 actuations per inhaler.

Each single actuation of salmeterol-FP provides salmeterol xinafoate equivalent to 25 micrograms of salmeterol and 50, 125 or 250 micrograms of fluticasone propionate.

Excipients

Accuhaler/Diskus:

Lactose (which contains milk protein).

Evohaler:

Hydrofluoralkane 134a propellant (HFA 134a)

Indications

REVERSIBLE OBSTRUCTIVE AIRWAYS DISEASE (ROAD)

Salmeterol-FP is indicated in the regular treatment of reversible obstructive airways disease (ROAD), including asthma in children and adults, where use of a combination (bronchodilator and inhaled corticosteroid) is appropriate. This may include:

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

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Salmeterol-FP is indicated for the maintenance treatment of COPD including chronic bronchitis and emphysema and has been shown to reduce all-cause mortality.

Dosage and Administration

Salmeterol-FP Accuhaler/Diskus or Evohaler is for inhalation only.

Patients should be made aware that salmeterol-FP Accuhaler/Diskus or Evohaler must be used regularly for optimum benefit, even when asymptomatic.

Patients should be regularly reassessed by a doctor, so that the strength of salmeterol-FP they are receiving remains optimal and is only changed on medical advice.

REVERSIBLE OBSTRUCTIVE AIRWAYS DISEASE (ROAD)

The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. Where the control of symptoms is maintained with twice daily salmeterol-FP, titration to the lowest effective dose could include salmeterol-FP given once daily.

Patients should be given the strength of salmeterol-FP containing the appropriate fluticasone propionate dosage for the severity of their disease.

If a patient is inadequately controlled on inhaled corticosteroid therapy alone, substitution with salmeterol-FP at a therapeutically equivalent corticosteroid dose may result in an improvement in asthma control. For patients whose asthma control is acceptable on inhaled corticosteroid therapy alone, substitution with salmeterol-FP may permit a reduction in corticosteroid dose while maintaining asthma control. For further information, please refer to the 'Clinical Studies' section.

Populations

Accuhaler/Diskus:

• Adults and adolescents 12 years and older

One inhalation (50 micrograms salmeterol and 100 micrograms fluticasone propionate) twice daily.

or

One inhalation (50 micrograms salmeterol and 250 micrograms fluticasone propionate) twice daily.

or

One inhalation (50 micrograms salmeterol and 500 micrograms fluticasone propionate) twice daily.

• Adults 18 years and older

Doubling the dose of all strengths of salmeterol-FP in adults for up to 14 days has comparable safety and tolerability to regular twice daily dosing and may be considered when patients require additional short term (up to 14 days) inhaled corticosteroid therapy as outlined in asthma treatment guidelines.

• Children 4 years and older

One inhalation (50 micrograms salmeterol and 100 micrograms fluticasone propionate) twice daily.

There are no data available for use of salmeterol-FP in children aged under 4 years.

Evohaler:

• Adults and adolescents 12 years and older

Two inhalations of 25 micrograms salmeterol and 50 micrograms fluticasone propionate twice daily.

or

Two inhalations of 25 micrograms salmeterol and 125 micrograms fluticasone propionate twice daily.

or

Two inhalations of 25 micrograms salmeterol and 250 micrograms fluticasone propionate twice daily.

• Adults 18 years and older

Doubling the dose of all strengths of salmeterol-FP in adults for up to 14 days has comparable safety and tolerability to regular twice daily dosing and may be considered when patients require additional short term (up to 14 days) inhaled corticosteroid therapy as outlined in asthma treatment guidelines.

• Children 4 years and older

Two inhalations of 25 micrograms salmeterol and 50 micrograms fluticasone propionate twice daily.

There are no data available for use of salmeterol-FP in children aged under 4 years.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Populations

Accuhaler/Diskus:

• Adults

For adult patients the maximum recommended dose is one inhalation (50 micrograms salmeterol and 500 micrograms fluticasone propionate) twice daily. At this dose, salmeterol-FP has been shown to reduce all-cause mortality (see Clinical Studies).

Evohaler:

• Adults

For adult patients the maximum recommended dose is two inhalations (25 micrograms salmeterol and 250 micrograms fluticasone propionate) twice daily.

Accuhaler/Diskus & Evohaler:

• Special patient groups

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

Contraindications

- Salmeterol-FP is contraindicated in patients with a history of hypersensitivity to any of the ingredients (see Excipients). [1]

Warnings and Precautions

The management of ROAD should normally follow a stepwise programme and patient response should be monitored clinically and by lung function tests.

Salmeterol-FP Accuhaler/Diskus or Evohaler is not for relief of acute symptoms for which a fast and short-acting 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 salmeterol-FP has failed to give adequate control of ROAD, 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 with salmeterol-FP 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.

#There was an increased reporting of pneumonia in studies of patients with COPD receiving salmeterol-FP (see Adverse Reactions). Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbation frequently overlap. [19]

As with all inhaled medication containing corticosteroids, salmeterol-FP should be administered with caution in patients with active or quiescent pulmonary tuberculosis.

Salmeterol-FP should be administered with caution in patients with thyrotoxicosis.

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, salmeterol-FP should be used with caution in patients with pre-existing cardiovascular disease. [12]

A transient decrease in serum potassium may occur with all sympathomimetic drugs at higher therapeutic doses. Therefore, salmeterol-FP should be used with caution in patients predisposed to low levels of serum potassium. [13]

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods; these effects are much less likely to occur than with oral corticosteroids (see Overdosage). Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. It is important, therefore for ROAD patients, that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control is maintained. [2]

The possibility of impaired adrenal response should always be borne in mind in emergency and elective situations likely to produce stress and appropriate corticosteroid treatment considered (see Overdosage). [3]

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroid is regularly monitored.

Certain individuals can show greater susceptibility to the effects of inhaled corticosteroid than do most patients.

Because of the possibility of impaired adrenal response, patients transferring from oral steroid therapy to inhaled fluticasone propionate therapy should be treated with special care, and adrenocortical function regularly monitored.

Following introduction of inhaled fluticasone propionate, withdrawal of systemic therapy should be gradual and patients encouraged to carry a steroid warning card indicating the possible need for additional therapy in times of stress.

There have been very rare reports of increases in blood glucose levels (see Adverse Reactions) and this should be considered when prescribing to patients with a history of diabetes mellitus.[11]

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 (see Interactions). [4, 5]

Data from a large US study (SMART) comparing the safety of salmeterol (a component of salmeterol-FP) 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. (see Clinical Studies) [20]

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. Caution should be exercised when strong CYP3A4 inhibitors (e.g. ketoconazole) are co-administered with salmeterol. (see Interactions, and Pharmacokinetics). [22]

[# For markets with the COPD indication registered this statement must also be included in local labelling]

Interactions

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. [4, 5]

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. [4, 5]

Co-administration of ketoconazole and salmeterol resulted in a significant increase in plasma salmeterol exposure (1.4-fold Cmax and 15-fold AUC) and this may cause a prolongation of the QTc interval. (see Warnings and Precautions, and Pharmacokinetics). [22]

Pregnancy and Lactation

Administration of drugs during pregnancy and lactation should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus or child.

There is insufficient experience of the use of salmeterol xinafoate and fluticasone propionate in human pregnancy and lactation.

Fertility
No Text.

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 beta2-adrenoreceptor agonist and glucocorticosteroid.

Extensive clinical experience with drugs in these classes has revealed no evidence that the effects are relevant at therapeutic doses. Neither salmeterol xinafoate or fluticasone propionate have shown any potential for genetic toxicity.

Lactation
Salmeterol and fluticasone propionate concentrations in plasma after inhaled therapeutic doses are very low and therefore concentrations in human breast milk are likely to be correspondingly low. This is supported by studies in lactating animals, in which low drug concentrations were measured in milk. There are no data available for human breast milk.

Ability to perform tasks that require judgement, motor or cognitive skills
There have been no specific studies of the effect of salmeterol-FP on the above activities, but the pharmacology of both drugs does not indicate any effect.

Adverse Reactions
As the combination product contains salmeterol and fluticasone propionate, the type and severity of adverse reactions associated with each of the components may be expected. There are no additional adverse reactions above those seen with the individual components following concurrent administration of salmeterol and fluticasone propionate.

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 and short-acting inhaled bronchodilator. Salmeterol-FP Accuhaler/Diskus or Evohaler should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

Clinical Trial Data
Salmeterol-FP

There have been uncommon reports of contusions. [23]

The following undesirable effects were commonly reported:

Hoarseness/dysphonia, throat irritation, headache, candidiasis of mouth and throat and palpitations. # Pneumonia (in COPD patients). [19]

[# For markets with the COPD indication registered this statement must also be included in local labelling]

Postmarketing Data
Salmeterol-FP

There have been uncommon reports of cutaneous hypersensitivity reactions. There have also been rare reports of hypersensitivity reactions manifesting as angioedema (mainly facial and oropharyngeal oedema), respiratory symptoms (dyspnoea and/or bronchospasm) and very rarely, anaphylactic reactions. [6]

There have been very rare reports of anxiety, sleep disorders and behavioural changes, including hyperactivity and irritability (predominantly in children). [7]

There have also been very rare reports of hyperglycaemia. [11]

Salmeterol
The pharmacological side effects of beta2-agonist treatment, such as tremor, subjective palpitations and headache, have been reported, but tend to be transient and reduce with regular therapy.

Cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia and extrasystoles) may occur, usually in susceptible patients.

There have been very rare reports of arthralgia. [14]

Hypersensitivity reactions, including anaphylactic reactions such as oedema and angioedema, bronchospasm and anaphylactic shock have been reported very rarely.

There have also been uncommon reports of rash. [15]

There have been reports of oropharyngeal irritation. [8]

There have been common reports of muscle cramps. [14]

There have been very rare reports of hyperglycaemia. [11]

Fluticasone propionate

Hoarseness and candidiasis (thrush) of the mouth and throat can occur in some patients. Both hoarseness and incidence of candidiasis may be relieved by gargling with water after use of salmeterol-FP Accuhaler/Diskus or Evohaler. Symptomatic candidiasis can be treated with topical anti-fungal therapy whilst still continuing with salmeterol-FP Accuhaler/Diskus or Evohaler.

There have been uncommon reports of cutaneous hypersensitivity reactions. There have also been rare reports of hypersensitivity reactions manifesting as angioedema (mainly facial and oropharyngeal oedema), respiratory symptoms (dyspnoea and/or bronchospasm) and very rarely, anaphylactic reactions. [6]

Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma (see Warnings and Precautions). There have been very rare reports of hyperglycaemia. [2, 11]

There have been very rare reports of anxiety, sleep disorders and behavioural changes, including hyperactivity and irritability (predominantly in children). [7]

Overdosage

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

It is not recommended that patients receive higher than approved doses of salmeterol-FP. It is important to review therapy regularly and titrate down to the lowest approved 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–adrenergic stimulation, including tremor, headache, tachycardia, increases in systolic blood pressure and hypokalaemia. 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. [12, 13]

If higher than approved doses of salmeterol-FP 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); observed features have included hypoglycaemia associated with decreased consciousness and/or convulsions.

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. [3]

Treatment

The preferred antidotes for salmeterol overdosage are cardioselective beta-blocking agents, which should be used with caution in patients with a history of bronchospasm.

If salmeterol-FP therapy has to be withdrawn due to overdose of the beta agonist component of the drug, provision of appropriate replacement corticosteroid therapy should be considered.

Clinical Pharmacology

Pharmacodynamics

ATC Code

No Text.

Mechanism of Action

Salmeterol and fluticasone propionate have differing modes of action. Salmeterol protects against symptoms, fluticasone propionate improves lung function and prevents exacerbations of the condition. Salmeterol-FP can offer a more convenient regime for patients on concurrent beta-agonist and inhaled corticosteroid therapy.

The respective mechanisms of action of both drugs are discussed below:

Salmeterol

Salmeterol is a selective long-acting (12 h) beta2-adrenoceptor agonist with a long side chain which binds to the exo-site of the receptor.

These pharmacological properties of salmeterol offer more effective protection against histamine-induced bronchoconstriction and produce a longer duration of bronchodilation, lasting for at least 12 h, than recommended doses of conventional short-acting beta2-agonists.

Fluticasone propionate

Fluticasone propionate given by inhalation at recommended doses has a potent glucocorticoid anti-inflammatory action within the lungs, resulting in reduced symptoms and exacerbations of asthma, without the adverse effects observed when corticosteroids are administered systemically.

Pharmacodynamic Effects

Salmeterol

In vitro tests have shown salmeterol is a potent and long-lasting inhibitor of the release, from human lung, of mast cell mediators such as histamine, leukotrienes and prostaglandin D2.

In man salmeterol inhibits the early and late phase response to inhaled allergen; the latter persisting for over 30 h after a single dose when the bronchodilator effect is no longer evident. Single dosing with salmeterol attenuates bronchial hyper-responsiveness. These properties indicate that salmeterol has additional non-bronchodilator activity but the full clinical significance is not yet clear. This mechanism is different from the anti-inflammatory effect of corticosteroids.

Fluticasone propionate

Daily output of adrenocortical hormones usually remain within the normal range during chronic treatment with inhaled fluticasone propionate, even at the highest recommended doses in children and adults. After transfer from other inhaled steroids, the daily output gradually improves despite past and present intermittent use of oral steroids, thus demonstrating return of normal adrenal function on inhaled fluticasone propionate. The adrenal reserve also remains normal during chronic treatment, as measured by a normal increment on a stimulation test. However, any residual impairment of adrenal reserve from previous treatment may persist for a considerable time and should be borne in mind (see Warnings and Precautions).

Pharmacokinetics

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

In a placebo-controlled, crossover drug interaction study in 15 healthy subjects, co-administration of salmeterol (50 mcg 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 Cmax 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. In the remaining 12 subjects, co-administration of salmeterol and ketoconazole did not result in a clinically significant effect on heart rate, blood potassium or QTc duration. (see Warnings and Precautions, and Interactions). [22]

Absorption

Salmeterol

Salmeterol acts locally in the lung therefore plasma levels are not an indication of therapeutic effects. In addition there are only limited data available on the pharmacokinetics of salmeterol because of the technical difficulty of assaying the drug in plasma due to the low plasma concentrations at therapeutic doses (approximately 200 picograms/ml or less) achieved after inhaled dosing. After regular dosing with salmeterol xinafoate, hydroxynaphthoic acid can be detected in the systemic circulation, reaching steady state concentrations of approximately 100

nanograms/ml. These concentrations are up to 1000 fold lower than steady state levels observed in toxicity studies. No detrimental effects have been seen following long-term regular dosing (more than 12 months) in patients with airway obstruction.

Fluticasone propionate

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. In healthy adult subjects the absolute bioavailability has been estimated for fluticasone propionate Accuhaler/Diskus (7.8%), fluticasone propionate Diskhaler (9.0%), fluticasone propionate Evohaler (10.9%), salmeterol-fluticasone propionate Evohaler (5.3%) and salmeterol- fluticasone propionate Accuhaler/Diskus (5.5%) respectively. In patients with asthma or COPD a lesser degree of systemic exposure to inhaled fluticasone propionate has been observed. Systemic absorption occurs mainly through the lungs and is initially rapid then prolonged. The remainder of the inhaled dose may be swallowed but contributes minimally to systemic exposure due to the low aqueous solubility and pre-systemic metabolism, resulting in oral availability of less than 1%. There is a linear increase in systemic exposure with increasing inhaled dose. [9, 10, 21, 24]

Distribution

Salmeterol

No Text.

Fluticasone propionate

Fluticasone propionate has a large volume of distribution at steady-state (approximately 300 l). Plasma protein binding is moderately high (91%).

Metabolism

Salmeterol

An in vitro study showed that salmeterol is extensively metabolised to α-hydroxysalmeterol (aliphatic oxidation) by cytochrome P450 3A4 (CYP3A4). A repeat dose study with salmeterol and erythromycin in healthy volunteers showed no clinically significant changes in pharmacodynamic effects at 500 mg three times daily doses of erythromycin. However, a salmeterol-ketoconazole interaction study resulted in a significant increase in plasma salmeterol exposure. (see Warnings and Precautions, and Interactions) [16]

Fluticasone propionate

Fluticasone propionate is cleared very rapidly from the systemic circulation, principally by metabolism to an inactive carboxylic acid metabolite, by the cytochrome P450 enzyme CYP3A4. Care should be taken when co-administering known CYP3A4 inhibitors, as there is potential for increased systemic exposure to fluticasone propionate.

Elimination

Salmeterol

No Text.

Fluticasone propionate

The disposition of fluticasone propionate is characterised by high plasma clearance (1150 ml/min) and a terminal half-life of approximately 8 h. The renal clearance of fluticasone propionate is negligible (less than 0.2%) and less than 5% as the metabolite.

Special Patient Populations

Salmeterol-FP

Accuhaler/Diskus:

Population pharmacokinetic analysis was performed utilising data for asthmatic subjects (nine clinical studies for FP and five studies for salmeterol) and showed the following:

- Higher FP exposure seen following administration of salmeterol-FP (50/100 micrograms) compared to FP alone (100 micrograms) in adolescents and adults (ratio 1.52 [90% CI 1.08, 2.13]) and children (ratio 1.20 [90% CI 1.06, 1.37]).
- Higher FP exposure observed in children taking salmeterol-FP (50/100 micrograms) compared to adolescents and adults (ratio 1.63 [90% CI 1.35, 1.96]).
- The clinical relevance of these findings are not known, however, no differences in HPA axis effects were observed in clinical studies of up to 12 weeks

duration comparing Salmeterol-FP (50/100 micrograms) and FP (100 micrograms) in both adolescents and adults and in children.

- FP exposure was similar at the higher salmeterol-FP 50/500 microgram dose compared to the equivalent FP dose alone.
- Higher salmeterol exposure was observed in children taking Salmeterol-FP (50/100 micrograms) compared to adolescents and adults (ratio 1.23 [90% CI 1.10, 1.38]).
- The clinical relevance of these findings are not known, however there were no differences observed in cardiovascular effects or reports of tremor between adults, adolescents and children in clinical studies of up to 12 weeks duration. [17]

Clinical Studies

Salmeterol clinical trials

Asthma

The Salmeterol Multi-center Asthma Research Trial (SMART) was a large US study that compared the safety of salmeterol or placebo added to usual therapy. There were no significant differences in the primary endpoint of the combined number of respiratory-related deaths and respiratory-related life-threatening experiences. The study showed a significant increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo). The study was not designed to assess the impact of concurrent inhaled corticosteroid use. However, post-hoc analyses showed there was no significant difference between treatment groups for asthma-related deaths for those patients using inhaled steroids at baseline (4/6127 on salmeterol versus 3/6138 on placebo). The numbers of asthma-related deaths in the groups not using inhaled steroids were 9/7049 on salmeterol versus 0/7041 on placebo. Further, a meta-analysis of 42 clinical studies involving 8,030 patients on salmeterol-FP and 7,925 patients on fluticasone propionate did not show a statistical difference between salmeterol-FP and fluticasone propionate for serious respiratory-related events or asthma-related hospitalisations. [20]

Salmeterol-FP clinical trials

Asthma

A large twelve-month study (Gaining Optimal Asthma ControL, GOAL) in 3416 asthma patients compared the efficacy and safety of salmeterol-FP versus inhaled corticosteroid alone in achieving pre-defined levels of asthma control. Treatment was stepped-up every 12 weeks until ##'Total control' was achieved or the highest dose of study drug was reached. Control needed to be sustained for at least 7 out of the last 8 weeks of treatment. The study showed that:

- 71% of patients treated with salmeterol-FP achieved #'Well-controlled' asthma compared with 59% of patients treated with inhaled corticosteroid alone.
- 41% of patients treated with salmeterol-FP achieved ##'Total control' of asthma compared with 28% of patients treated with inhaled corticosteroid alone.

These effects were observed earlier with salmeterol-FP compared with inhaled corticosteroid alone and at a lower inhaled corticosteroid dose.

The GOAL study also showed that:

- The rate of exacerbations was 29% lower with salmeterol-FP compared to inhaled corticosteroid treatment alone.
- Attaining 'Well controlled' and 'Totally controlled' asthma improved Quality of Life (QoL). 61% of patients reported minimal or no impairment on QoL, as measured by an asthma specific quality of life questionnaire, after treatment with salmeterol-FP compared to 8% at baseline.

Well controlled asthma; occasional symptoms or SABA use or less than 80% predicted lung function plus no night-time awakenings, no exacerbations and no side effects enforcing a change in therapy.

Total control of asthma; no symptoms, no SABA use greater than or equal to 80% predicted lung function, no night-time awakenings, no exacerbations and no side effects enforcing a change in therapy.

Two further studies have shown improvements in lung function, percentage of symptom free days and reduction in rescue medication use, at 60% lower inhaled corticosteroid dose with salmeterol-FP compared to treatment with inhaled corticosteroid alone, whilst the control of the underlying airway inflammation, measured by bronchial biopsy and bronchoalveolar lavage, was maintained.

Additional studies have shown that treatment with salmeterol-FP significantly improves asthma symptoms, lung function and reduces the use of rescue medication compared to treatment with the individual components alone and placebo. Results from GOAL show that the improvements seen with salmeterol-FP, in these endpoints, are maintained over at least 12 months.

COPD

Symptomatic COPD patients who demonstrated less than 10% reversibility to a short acting beta2-agonist:

Placebo-controlled clinical trials, over six and 12 months, have shown that regular use of salmeterol-FP 50/500 micrograms rapidly and significantly improves lung function, significantly reduced breathlessness and the use of relief medication. Over a 12-month period the risk of COPD exacerbations and the need for additional courses of oral corticosteroids was significantly reduced. There were also significant

improvements in health status.

Salmeterol-FP 50/500 micrograms was effective in improving lung function, health status and reducing the risk of COPD exacerbations, in both current and ex-smokers.

Symptomatic COPD patients without restriction to 10% reversibility to a short acting beta2-agonist:

Placebo-controlled clinical trials, over six months, have shown that regular use of both Salmeterol-FP 50/250 and 50/500 micrograms rapidly and significantly improves lung function, significantly reduced breathlessness and the use of relief medication.

There were also significant improvements in health status.

TORCH study (TOwards a Revolution in COPD Health):

TORCH was a 3-year study to assess the effect of treatment with salmeterol-FP Accuhaler/Diskus 50/500 micrograms twice daily, salmeterol Accuhaler/Diskus 50 micrograms twice daily, FP Accuhaler/Diskus 500 micrograms twice daily or placebo on all-cause mortality in patients with COPD. Patients with moderate to severe COPD with a baseline (pre bronchodilator) FEV1 <60% of predicted normal were randomised to double-blind medication. During the study, patients were permitted usual COPD therapy with the exception of other inhaled corticosteroids, long acting bronchodilators, and long-term systemic corticosteroids. Survival status at 3 years was determined for all patients regardless of withdrawal from study medication. The primary endpoint was reduction in all-cause mortality at 3 years for salmeterol-FP vs placebo.

	Placebo N = 1524	Salmeterol 50 N = 1521	FP 500 N = 1534	Salmeterol-FP 50/500 N = 1533
All cause mortality at 3 years				
Number of deaths (%)	231 (15.2%)	205 (13.5%)	246 (16.0%)	193 (12.6%)
Hazard Ratio vs Placebo (CIs) p value	N/A	0.879 (0.73, 1.06) 0.180	1.060 (0.89, 1.27) 0.525	0.825 (0.68, 1.00) 0.052[1]
Hazard Ratio Salmeterol-FP 50/500 vs components (CIs) p value	N/A	0.932 (0.77, 1.13) 0.481	0.774 (0.64, 0.93) 0.007	N/A

[1]. P value adjusted for 2 interim analyses on the primary efficacy comparison from a log-rank analysis stratified by smoking status

Salmeterol-FP reduced the risk of dying at any time during the 3 years by 17.5% compared to placebo (Hazard Ratio 0.825 (95% CI 0.68, 1.00, p=0.052); all adjusted for interim analyses). There was a 12% reduction in the risk of dying at any time within 3 years from any cause for salmeterol compared with placebo (p=0.180) and a 6% increase for FP compared with placebo (p=0.525).

A supporting analysis using Cox's Proportional Hazards model gave a hazard ratio of 0.811 (95% CI 0.670, 0.982, p=0.031) for salmeterol-FP vs placebo which represented a 19% reduction in the risk of dying at any time within 3 years. The model adjusted for important factors (smoking status, age, sex, region, baseline FEV1 and Body Mass Index).

There was no evidence that treatment effects varied for these factors.

The percentage of patients who died within 3 years due to COPD-related causes was 6.0% for placebo, 6.1% for salmeterol, 6.9% for FP and 4.7% for salmeterol-FP.

Salmeterol-FP reduced the rate of moderate to severe exacerbations by 25% (95% CI: 19% to 31%; p<0.001) compared with placebo. Salmeterol-FP reduced the exacerbation rate by 12% compared with salmeterol (95% CI: 5% to 19%, p=0.002) and 9% compared with FP (95% CI: 1% to 16%, p=0.024). Salmeterol and FP significantly reduced exacerbation rates compared with placebo by 15% (95% CI: 7% to 22%; p<0.001) and 18% (95% CI: 11% to 24%; p<0.001) respectively.

Health Related Quality of Life, as measured by the St George's Respiratory Questionnaire (SGRQ) was improved by all active treatments in comparison with placebo. The average improvement over three years for salmeterol-FP compared with placebo was -3.1 units (95% CI: -4.1 to -2.1; p<0.001), compared with salmeterol was -2.2 units (p<0.001) and compared with FP was 1.2 units (p=0.017).

Over the 3 year treatment period, FEV1 values were higher in subjects treated with salmeterol-FP than for those treated with placebo (average difference over 3 years 92 mL, 95% CI: 75 to 108 ml; p<0.001). Salmeterol-FP was also more effective than salmeterol or FP in improving FEV1 (average difference 50 ml, p<0.001 for salmeterol and 44 mL, p<0.001 for FP).

The estimated 3 year probability of having pneumonia reported as an adverse event was 12.3% for placebo, 13.3% for salmeterol, 18.3% for FP and 19.6% for salmeterol-FP (Hazard ratio for salmeterol-FP vs placebo: 1.64, 95% CI: 1.33 to 2.01, p<0.001). There was no increase in pneumonia related deaths; deaths while on treatment that were adjudicated as primarily due to pneumonia were 7 for placebo, 9 for salmeterol, 13 for FP and 8 for salmeterol-FP. There was no significant difference in probability of bone fracture (5.1% placebo, 5.1% salmeterol, 5.4% FP and 6.3% salmeterol-FP; Hazard ratio for salmeterol-FP vs placebo: 1.22, 95% CI: 0.87 to 1.72, p=0.248). The incidence of adverse events of eye disorders, bone disorders, and HPA axis disorders was low and there was no difference observed between treatments.

There was no evidence of an increase in cardiac adverse events in the treatment groups receiving salmeterol.

NON-CLINICAL INFORMATION

Salmeterol xinafoate and fluticasone propionate 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 beta2- adrenoreceptor agonist and glucocorticosteroid.

In long term studies, salmeterol xinafoate induced benign tumours of smooth muscle in the mesovarium of rats and the uterus of mice.

Rodents are sensitive to the formation of these pharmacologically-induced tumours.

Salmeterol is not considered to represent a significant oncogenic hazard to man.

Co-administration of salmeterol and fluticasone propionate resulted in some cardiovascular interactions at high doses. In rats, mild atrial myocarditis and focal coronary arteritis were transient effects that resolved with regular dosing. In dogs, heart rate increases were greater after co-administration than after salmeterol alone.

No clinically relevant serious adverse cardiac effects have been observed in studies in man.

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

Evohaler:

The non-CFC propellant, 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.

PHARMACEUTICAL INFORMATION

Chemical Structure

No Text.

Shelf-Life
Accuhaler/Diskus:
18 months.

Evohaler:
2 years.

Storage
Accuhaler/Diskus:
Do not store above 30oC.
Store in a dry place.

Evohaler:
Replace the mouthpiece cover firmly and snap it into position [18].
Do not store above 30oC.
Protect from frost and direct sunlight.
As with most inhaled medications in pressurised canisters, the therapeutic effect of this medication may decrease when the canister is cold.
The canister should not be punctured, broken or burnt even when apparently empty.

Nature and Contents of Container
Accuhaler/Diskus:
As registered locally.

Evohaler:
Salmeterol-FP Evohaler comprises a suspension of salmeterol and fluticasone propionate in the non-CFC propellant HFA 134a. The suspension is contained in an aluminium alloy can sealed with a metering valve. The canisters are fitted into plastic actuators incorporating an atomising orifice and fitted with dustcaps.

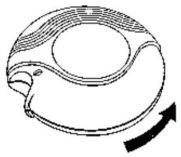
Evohaler with Counter:
The canister has a counter attached to it, which shows how many actuations of medicine are left. The number will show through a window in the back of the plastic actuator.

Incompatibilities
No Text.

Use and Handling
Accuhaler/Diskus:
The Accuhaler/Diskus releases a powder which is inhaled into the lungs.
A dose indicator on the Accuhaler/Diskus indicates the number of doses left.

Instructions for use of your salmeterol-FP Accuhaler/Diskus

CLOSED
When you take your Accuhaler/Diskus out of its box, it will be in the closed position.



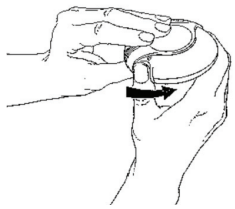
OPENED
A new Accuhaler/Diskus contains 28 or 60 doses of your medicine. The dose indicator tells you how many doses are left.
This Accuhaler/Diskus contains 28 or 60 individually protected doses of your medicine, in powder form.
Each dose is accurately measured and hygienically protected. It requires no maintenance - and no refilling.
The dose indicator on top of your Accuhaler/Diskus tells you how many doses are left. Numbers 5 to 0 will appear in RED, to warn you when there are only a few doses left.
The Accuhaler/Diskus is easy to use. When you need a dose, just follow the four simple steps illustrated
1. Open.
2. Slide.
3. Inhale.
4. Close.

How your Accuhaler/Diskus works
Sliding the lever of your Accuhaler/Diskus opens a small hole in the mouthpiece and unwraps a dose, ready for you to inhale it. When you close the

Accuhaler/Diskus, the lever automatically moves back to its original position, ready for your next dose when you need it. The outer case protects your Accuhaler/Diskus when it is not in use.

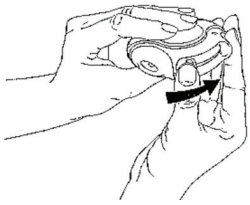
1. Open - How to use the Accuhaler/Diskus.

To open your Accuhaler/Diskus, hold the outer case in one hand and put the thumb of your other hand on the thumbgrip. Push your thumb away from you as far as it will go.



2. Slide.

Hold your Accuhaler/Diskus with the mouthpiece towards you. Slide the lever away from you, as far as it will go - until it clicks. Your Accuhaler/Diskus is now ready to use. Every time the lever is pushed back, a dose is made available for inhaling. This is shown by the dose counter. Do not play with the lever as this releases doses which will be wasted.



3. Inhale.

Before you start to inhale the dose, read through this section carefully.

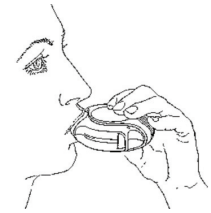
Hold the Accuhaler/Diskus away from your mouth. Breathe out as far as is comfortable. Remember - never breathe into your Accuhaler/Diskus.

Put the mouthpiece to your lips. Breathe in steadily and deeply - through the Accuhaler/Diskus, not through your nose.

Remove the Accuhaler/Diskus from your mouth.

Hold your breath for about 10 seconds, or for as long as is comfortable.

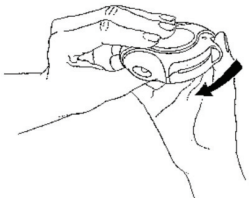
Breathe out slowly.



4. Close

To close your Accuhaler/Diskus, put your thumb in the thumbgrip, and slide the thumbgrip back towards you, as far as it will go.

When you close the Accuhaler/Diskus, it clicks shut. The lever automatically returns to its original position and is reset. Your Accuhaler/Diskus is now ready for you to use again.



If you have been instructed to take two inhalations you must close the Accuhaler/Diskus and repeat stages 1 to 4.

REMEMBER

Keep your Accuhaler/Diskus dry.

Keep it closed when not in use.

Never breathe into your Accuhaler/Diskus.

Only slide the lever when you are ready to take a dose.

Do not exceed the stated dose. Keep out of reach of children.

Evohaler with Counter:

Instructions for use of your salmeterol-FP Evohaler with Counter:

Testing your inhaler

Before using for the first time, remove the mouthpiece cover by gently squeezing the sides of the

cover, shake the inhaler well, hold the inhaler between fingers and thumb with your thumb at the base, below the mouthpiece and release puffs into the air until the counter reads 120 to make sure that it works. The inhaler should be shaken immediately before releasing each puff. If your inhaler has not been used for a week or more remove the mouthpiece cover, shake the inhaler well and release one puff into the air. Each time the inhaler is activated the number on the counter will count down by one.

In certain circumstances dropping the inhaler may cause the counter to count on.

Using your inhaler

1. Remove the mouthpiece cover by gently squeezing the sides of the cover.
2. Check inside and outside of the inhaler including the mouthpiece for the presence of loose objects.
3. Shake the inhaler well to ensure that any loose objects are removed and that the contents of the inhaler are evenly mixed.
4. Hold the inhaler upright between fingers and thumb with your thumb on the base, below the mouthpiece.
5. Breathe out as far as is comfortable and then place the mouthpiece in your mouth between your teeth and close your lips around it, but do not bite it.
6. Just after starting to breathe in through your mouth, press firmly down on the top of the inhaler to release salmeterol and fluticasone propionate, while still breathing in steadily and deeply.
7. While holding your breath, take the inhaler from your mouth and take your finger from the top of the inhaler. Continue holding your breath for as long as is comfortable.
8. To take a second inhalation keep the inhaler upright and wait about half a minute before repeating steps 3 to 7.
9. Immediately replace the mouthpiece cover in the correct position. The cap when correctly fitted will click into position. If it does not click into place, turn the cap the other way round and try again. Do not use excessive force [18].

IMPORTANT

Do not rush stages 5, 6 and 7. It is important that you start to breathe in as slowly as possible just before operating your inhaler. Practise in front of a mirror for the first few times. If you see “mist” coming from the top of your inhaler or the sides of your mouth you should start again from stage

2. You should consider getting a replacement when the counter shows the number 020.

When the counter reads 000 you must replace it. Any puffs left in the device may not be enough to give you a full dose.

Never try to alter the numbers on the counter or detach the counter from the metal canister. The counter cannot be reset and is permanently attached to the canister.

If your doctor has given you different instructions for using your inhaler, please follow them carefully. Tell your doctor if you have any difficulties.

Children

Young children may need help and an adult may need to operate the inhaler for them.

Encourage the child to breathe out and operate the inhaler just after the child starts to breathe in. Practice the technique together. Older children or people with weak hands should hold the inhaler with both hands. Put the two forefingers on top of the inhaler and both thumbs on the base below the mouthpiece.

Cleaning

Your inhaler should be cleaned at least once a week.

1. Remove the mouth piece cover.
2. Do not remove the canister from the plastic casing.
3. Wipe the inside and outside of the mouthpiece and the plastic casing with a dry cloth or tissue.
4. Replace the mouthpiece cover in the correct position. The cap when correctly fitted will click into position. If it does not click into place, turn the cap the other way round and try again. Do not use excessive force.

DO NOT PUT THE METAL CANISTER INTO WATER.

Evohaler without Counter:

Instructions for use of your salmeterol-FP Evohaler without Counter:

Testing your inhaler

Before using for the first time or if your inhaler has not been used for a week or more remove the mouthpiece cover by gently squeezing the sides of the cover, shake the inhaler well, and release one puff into the air to make sure that it works.

Using your inhaler

1. Remove the mouthpiece cover by gently squeezing the sides of the cover.
2. Check inside and outside of the inhaler including the mouthpiece for the presence of loose objects.
3. Shake the inhaler well to ensure that any loose objects are removed and that the contents of the inhaler are evenly mixed.
4. Hold the inhaler upright between fingers and thumb with your thumb on the base, below the mouthpiece.
5. Breathe out as far as is comfortable and then place the mouthpiece in your mouth between your teeth and close your lips around it, but do not bite it.
6. Just after starting to breathe in through your mouth, press firmly down on the top of the inhaler to release salmeterol and fluticasone propionate, while still breathing in steadily and deeply.
7. While holding your breath, take the inhaler from your mouth and take your finger from the top of the inhaler. Continue holding your breath for as long as is comfortable.
8. To take the second inhalation, keep the inhaler upright and wait about half a minute before repeating steps 3to 7.
9. Replace the mouthpiece cover by firmly pushing and snapping the cap into position [18].

IMPORTANT

Do not rush stages 5, 6 and 7. It is important that you start to breathe in as slowly as possible just before operating your inhaler. Practise in front of a mirror for the first few times. If you see “mist” coming from the top of your inhaler or the sides of your mouth you should start again from stage 2.

If your doctor has given you different instructions for using your inhaler, please follow them carefully. Tell your doctor if you have any difficulties.

Children

Young children may need help and an adult may need to operate the inhaler for them.

Encourage the child to breathe out and operate the inhaler just after the child starts to breathe in. Practice the technique together. Older children or people with weak hands should hold the inhaler with both hands. Put the two forefingers on top of the inhaler and both thumbs on the base below the mouthpiece.

Cleaning

Your inhaler should be cleaned at least once a week.

1. Remove the mouth piece cover.
2. Do not remove the canister from the plastic casing.
3. Wipe the inside and outside of the mouthpiece and the plastic casing with a dry cloth, tissue or cottonbud.
4. Replace the mouthpiece cover.

DO NOT PUT THE METAL CANISTER INTO WATER.

REFERENCES

[1] Yogendran, L. Milk Protein Content of Dry Powder Inhalers. GlaxoSmithKline Internal Document RSD/02/038.

[2] Taylor I Fluticasone Propionate + Salmeterol Xinafoate, Inhaled Fluticasone Propionate, and Inhaled Beclomethasone Dipropionate: Cushing’s Syndrome. GlaxoSmithKline Internal Document GM2004/00019/00

[3] Yogendran, L. Fluticasone Propionate / Salmeterol xinafoate: Acute Adrenal Crisis. GlaxoSmithKline Internal Document GM2003/00079/00.

[4] An open, three-period, balanced, incomplete block crossover study in healthy subjects to investigate the effect of 7 days co-administration of fluticasone propionate aqueous nasal spray (FPANS) with ritonavir, ketoconazole, or erythromycin on serum cortisol levels. GlaxoSmithKline Document Number GM2002/00378/00 Study ID FNM10004.

[5] Lulic-Burns, Z. Inhaled/Intranasal Fluticasone Propionate & Fluticasone Propionate/Salmeterol Xinafoate: Amendment of Prescribing Information Relating to Possible Drug Interactions with Ritonavir & Other Cytochrome P450 3A4 Inhibitors. GlaxoSmithKline Internal Document GM2003/00261/00.

[6] Taylor, I. Seretide and Anaphylaxis. GlaxoSmithKline Internal Document RSD/02/036

[7] Taylor I Inhaled Fluticasone Propionate, Salmeterol + Fluticasone Propionate, and Inhaled Beclomethasone Dipropionate: Amendment of Prescribing Information Relating to Neuropsychiatric Events. GlaxoSmithKline Internal Document GM2003/00636/04
[8] Salmeterol: Oropharyngeal Irritation. RSD/00/047.
[9] Brutsche M.H., Brutsche I.C, Munavvar M., Langley S.J., Masterson C.M., Daley- Yates P.T et al. Comparison of pharmacokinetics and systemic effects of inhaled flutctasone propionate in patients with asthma and healthy volunteers: A randomised crossover study. Lancet 2000; 356: 556-561
[10] Daley-Yates P.T., Tournant J. and Kunka R.L. Comparison of the systemic availability of fluticasone propionate in healthy volunteers and patients with asthma. Clin. Pharmacokinet 2000; 39 Suppl 1: 39-45
[11] Salmeterol + Fluticasone Propionate, Inhaled Fluticasone Propionate and Salmeterol xinafoate: Hyperglycaemia RSD GM2004/00404/00.
[12] Salmeterol + Fluticasone propionate. Regulatory supporting documentation for the addition of hypertension. GlaxoSmithKline Internal Document (Confidential) GM2005/00364/00.
[13] Salmeterol + Fluticasone propionate. Regulatory supporting documentation for the addition of hypokalaemia. GlaxoSmithKline Internal Document (Confidential) GM2005/00365/00.
[14] Salmeterol Xinafoate (Serevent Metered Dose Inhaler, Rotadisk, and Accuhaler/Diskus formulations): Restructure of the Undesirable Effects section of the Global Core Texts according to MedDRA System Organ Class Headings and adverse event frequencies. GlaxoSmithKline Internal Document (Confidential) GM2003/00241/00.
[15] Salmeterol Xinafoate: Amendment of prescribing information relating to anaphylactic reaction/shock. GlaxoSmithKline Internal Document (Confidential) GM2004/00579/00.
[16] Salmeterol-FP Accuhaler/Diskus and Evohaler. Regulatory Supporting documentation for update to the metabolism statement. GlaxoSmithKline Internal Document (Confidential) D2006–3195.
[17] Salmeterol-FP Accuhaler/Diskus and Evohaler. Regulatory Supporting documentation for Pop PK update. GlaxoSmithKline Internal Document (Confidential) D2006–3196.
[18] Amendment to prescribing information for Metered Dose Inhalers: Foreign body aspiration. GlaxoSmithKline Internal Document (Confidential) GM2006/00425/00.
[19] Clinical Expert Statement. Update to Seretide/Viani (Salmeterol xinafoate and fluticasone propionate) prescribing information for pneumonia. GlaxoSmithKline Internal Document (Confidential) GM2006/00531/00.
[20] Update to the Prescribing Information following the findings of a planned interim analysis of SMART (Multi-centre Asthma Research Trial). GlaxoSmithKline Internal Document (Confidential).
[21] S. D. Singh, C. Whale, N. Houghton, P.T. Daley-Yates, S. M. Kirby, A. A. Woodcock. Pharmacokinetics and systemic effects of inhaled fluticasone propionate in chronic obstructive pulmonary disease. Br. J. Clin. Pharmacol. 2003, 55: 375-381.
[22] Lamb Y. Amendment to Prescribing Information Salmeterol Xinofoate-Fluticasone propionate. GlaxoSmithKline YM2007/00032/00 RSD
[23] Salmeterol FP + Fluticasone propionate. Regulatory supporting documentation for the addition of Contusions. GlaxoSmithKline Internal Document (Confidential). YM2008-00015-00.
[24] Amendment to Prescribing Information for Fluticasone Propionate and Salmeterol-FP relating to FP Bioavailability. D2007-6605.