ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES

Member State	Marketing Authorisation Holder	Product Name	Strength	Pharmaceutical Form	Route of administration
Austria	Glaxo SmithKline Pharma GmbH, Albert-Schweitzer-Gasse 6 A-1140 Wien Austria	Seretide Diskus forte	50/500	Inhalation powder, predispensed	Inhalation use
Austria	Glaxo SmithKline Pharma GmbH, Albert-Schweitzer-Gasse 6 A-1140 Wien Austria	Seretide Diskus standard	50/250	Inhalation powder, predispensed	Inhalation use
Austria	Glaxo SmithKline Pharma GmbH, Albert-Schweitzer-Gasse 6 A-1140 Wien Austria	Seretide Diskus junior	50/100	Inhalation powder, predispensed	Inhalation use
Belgium	GlaxoSmithKline s.a./n.v., Rue du Tilleul 13, B-1332 Genval Belgium	Seretide 50/100 Diskus	50/100	Inhalation powder, predispensed	Inhalation use
Belgium	GlaxoSmithKline s.a./n.v., Rue du Tilleul 13 B-1332 Genval Belgium	Seretide 50/250 Diskus	50/250	Inhalation powder, predispensed	Inhalation use
Belgium	GlaxoSmithKline s.a./n.v., Rue du Tilleul 13 B-1332 Genval Belgium	Seretide 50/500 Diskus	50/500	Inhalation powder, predispensed	Inhalation use
Denmark	GlaxoSmithKline Pharma A/S, Nykær 68 DK-2605 Brøndby Denmark	Seretide	50/100	Inhalation powder, predispensed	Inhalation use
Denmark	GlaxoSmithKline Pharma A/S, Nykær 68 DK-2605 Brøndby Denmark	Seretide	50/250	Inhalation powder, predispensed	Inhalation use

Denmark	GlaxoSmithKline Pharma A/S, Nykær 68 DK-2605 Brøndby Denmark	Seretide	50/500	Inhalation powder, predispensed	Inhalation use
Finland	GlaxoSmithKline Oy Piispansilta 9A, P.O. Box 24 FIN-02231 Espoo Finland	Seretide Diskus	50/100	Inhalation powder, predispensed	Inhalation use
Finland	GlaxoSmithKline Oy Piispansilta 9A, P.O. Box 24 FIN-02231 Espoo Finland	Seretide Diskus	50/250	Inhalation powder, predispensed	Inhalation use
Finland	GlaxoSmithKline Oy Piispansilta 9A, P.O. Box 24 FIN-02231 Espoo Finland	Seretide Diskus	50/500	Inhalation powder, predispensed	Inhalation use
France	Laboratoire GlaxoSmithKline 100 route de Versailles 78163 Marly-le-roi Cedex, France	Seretide Diskus	50/100	Inhalation powder, predispensed	Inhalation use
France	Laboratoire GlaxoSmithKline 100 route de Versailles 78163 Marly-le-roi Cedex France	Seretide Diskus	50/250	Inhalation powder, predispensed	Inhalation use
France	Laboratoire GlaxoSmithKline 100 route de Versailles 78163 Marly-le-roi Cedex France	Seretide Diskus	50/500	Inhalation powder, predispensed	Inhalation use
Germany	Schwarz Pharma Deutschland GmbH Alfred-Nobel-Str. 10 D-40789 Monheim Germany	atmadisc mite 50µg/100µg Diskus	50/100	Inhalation powder, predispensed	Inhalation use

Germany	Schwarz Pharma Deutschland GmbH Alfred-Nobel-Str. 10 D-40789 Monheim Germany	atmadisc 50µg/250µg Diskus	50/250	Inhalation powder, predispensed	Inhalation use
Germany	Schwarz Pharma Deutschland GmbH Alfred-Nobel-Str. 10 D-40789 Monheim Germany	atmadisc forte 50µg/500µg Diskus	50/500	Inhalation powder, predispensed	Inhalation use
Greece	GlaxoSmithKline A.E.B.E Leof. Kifisias 266 15232 Halandri, Athens, Greece	Seretide Diskus	50/100	Inhalation powder, predispensed	Inhalation use
Greece	GlaxoSmithKline A.E.B.E Leof. Kifisias 266 15232 Halandri, Athens Greece	Seretide Diskus	50/250	Inhalation powder, predispensed	Inhalation use
Greece	GlaxoSmithKline A.E.B.E Leof. Kifisias 266 15232 Halandri, Athens Greece	Seretide Diskus	50/500	Inhalation powder, predispensed	Inhalation use
Ireland	GlaxoSmithKline (Ireland) Limited Stonemasons Way, Rathfarnham, Dublin 16 Ireland	Seretide Diskus 100	50/100	Inhalation powder, predispensed.	Inhalation use
Ireland	GlaxoSmithKline (Ireland) Limited Stonemasons Way, Rathfarnham, Dublin 16 Ireland	Seretide Diskus 250	50/250	Inhalation powder, predispensed.	Inhalation use
Ireland	GlaxoSmithKline (Ireland) Limited (trading as: Allen & Hanbury) Stonemasons Way, Rathfarnham, Dublin 16 Ireland	Seretide Diskus 500	50/500	Inhalation powder, predispensed.	Inhalation use

Italy	GlaxoSmithKline S.p.A. Via A. Fleming, 2 37135 Verona Italy	Seretide Diskus	50/100	Inhalation powder, predispensed	Inhalation use
Italy	GlaxoSmithKline S.p.A. Via A. Fleming, 2 37135 Verona Italy	Seretide Diskus	50/250	Inhalation powder, predispensed	Inhalation use
Italy	GlaxoSmithKline S.p.A. Via A. Fleming, 2 37135 Verona Italy	Seretide Diskus	50/500	Inhalation powder, predispensed	Inhalation use
Luxembourg	GlaxoSmithKline s.a./n.v., Rue du Tilleul 13 B-1332 Genval Belgium	Seretide 50/100 Diskus	50/100	Inhalation powder, predispensed	Inhalation use
Luxembourg	GlaxoSmithKline s.a./n.v., Rue du Tilleul 13 B-1332 Genval Belgium	Seretide 50/250 Diskus	50/250	Inhalation powder, predispensed	Inhalation use
Luxembourg	GlaxoSmithKline s.a./n.v., Rue du Tilleul 13 B-1332 Genval Belgium	Seretide 50/500 Diskus	50/500	Inhalation powder, predispensed	Inhalation use
Portugal	Glaxo Wellcome Farmacêutica, Lda. Rua Dr. António Loureiro Borges, 3, Arquiparque , Miraflores 1495-131 Algés Portugal	Seretaide Diskus	50/100	Inhalation powder, predispensed	Inhalation use

Portugal	Glaxo Wellcome Farmacêutica, Lda. Rua Dr. António Loureiro Borges, 3, Arquiparque , Miraflores 1495-131 Algés Portugal	Seretaide Diskus	50/250	Inhalation powder, predispensed	Inhalation use
Portugal	Glaxo Wellcome Farmacêutica, Lda. Rua Dr. António Loureiro Borges, 3, Arquiparque , Miraflores 1495-131 Algés Portugal	Seretaide Diskus	50/500	Inhalation powder, predispensed	Inhalation use
Spain	GlaxoSmithKline SA Parque Tecnologico de Madrid, Calle Severo Ochoa 2, 28760, Tres Cantos, Madrid Spain	Seretide Accuhaler	50/100	Inhalation powder, predispensed	Inhalation use
Spain	GlaxoSmithKline SA Parque Tecnologico de Madrid, Calle Severo Ochoa 2, 28760, Tres Cantos, Madrid Spain	Seretide Accuhaler	50/250	Inhalation powder, predispensed	Inhalation use
Spain	GlaxoSmithKline SA Parque Tecnologico de Madrid, Calle Severo Ochoa 2, 28760, Tres Cantos, Madrid Spain	Seretide Accuhaler	50/500	inhalation powder, predispensed	Inhalation use
Sweden	GlaxoSmithKline AB Box 516 SE-169 29 Solna Sweden	Seretide Diskus mite	50/100	Inhalation powder, predispensed	Inhalation use
Sweden	GlaxoSmithKline AB Box 516, SE-169 29 Solna Sweden	Seretide Diskus	50/250	Inhalation powder, predispensed	Inhalation use

Sweden	GlaxoSmithKline AB Box 516 SE-169 29 Solna Sweden	Seretide Diskus forte	50/500	inhalation powder, predispensed	Inhalation use
The Netherlands	GlaxoSmithKline B.V. Huis ter Heideweg 62, 3705 LZ Zeist The Netherlands	Seretide 50/100 Diskus	50/100	Inhalation powder, predispensed	Inhalation use
The Netherlands	GlaxoSmithKline B.V. Huis ter Heideweg 62, 3705 LZ Zeist The Netherlands	Seretide 50/250 Diskus	50/250	Inhalation powder, predispensed	Inhalation use
The Netherlands	GlaxoSmithKline B.V. Huis ter Heideweg 62, 3705 LZ Zeist The Netherlands	Seretide 50/500 Diskus	50/500	Inhalation powder, predispensed	Inhalation use
United Kingdom	Glaxo Wellcome UK Limited, Stockley Park West, Uxbridge, Middlesex UB11 1BT United Kingdom	Seretide 100 Accuhaler	50/100	Inhalation powder, predispensed	Inhalation use
United Kingdom	Glaxo Wellcome UK Limited, Stockley Park West, Uxbridge, Middlesex UB11 1BT United Kingdom	Seretide 250 Accuhaler	50/250	Inhalation powder, predispensed	Iinhalation use
United Kingdom	Glaxo Wellcome UK Limited, Stockley Park West, Uxbridge, Middlesex UB11 1BT United Kingdom	Seretide 500 Accuhaler	50/500	Inhalation powder, predispensed	Inhalation use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF SERETIDE DISKUS AND ASSOCIATED NAMES (SEE ANNEX I)

Seretide Diskus and associated names (see Annex I of Opinion) contain salmeterol and fluticasone propionate, a fixed dose combination of the long acting β-agonist (LABA) salmeterol and the inhaled corticosteroid (ICS) fluticasone propionate (FP) indicated in the regular treatment of asthma where use of a combination product (long-acting beta-2-agonist and inhaled corticosteroid) is appropriate: - patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting beta-2-agonist or - patients already adequately controlled on both inhaled corticosteroid and long-acting beta-2-agonist.

In several EU Member States Seretide Diskus and associated names (see Annex I) are approved through the Mutual Recognition Procedure (MRP). In the MRP Sweden is the Reference Member State and Austria, Belgium, Denmark, Finland, France, Greece, Germany, Italy, Ireland, Luxembourg, The Netherlands, Portugal, Spain and the UK are Concerned Member States.

The MAHs applied for a type II variation subject to MRP to extend the current approved indications to include initial maintenance therapy (IMT) with the fixed dose combination in patients with chronic persistent asthma. The Reference and Concerned Member States rejected the variation to extend the indication on 3 August 2005. The main objection relating to the identification of the patient population especially those patients who would respond to inhaled corticosteroids alone had not been adequately identified.

The MAHs were of the opinion that the issues identified during the MRP were issues of clinical management and as such cannot be addressed by conducting further clinical trials. On 12 August 2005, the MAHs presented to the EMEA a referral under Article 6(13) of Commission Regulation (EC) No 1084/2003.
The issue to be considered by CHMP was whether it is appropriate to introduce initial maintenance therapy with the fixed dose combination of salmeterol and fluticasone propionate in all patients with chronic persistent asthma.

The CHMP performed a re-evaluation of the type II variation application data. A discussion on the appropriateness of initial maintenance therapy with the fixed dose combination took place in CHMP based on the Rapporteur's and Co-Rapporteur's Assessment Reports and the data presented by the Marketing Authorisation Holders (MAHs).

EFFICACY

The MAHs have demonstrated in a series of substantial and well conducted clinical studies that in patients with moderate chronic persistent asthma poorly controlled on a short acting β-agonist alone the introduction of combination therapy with salmeterol and fluticasone is more effective in improving disease control than the introduction of salmeterol or fluticasone alone.

A subpopulation from the GOAL study (Gaining Optimal Asthma ControL study) i.e. stratum 1, addendum, step 1 (patients without ICS at entry who fulfilled the criteria for moderate persistent asthma and who are randomised to Seretide 50/100 or FP 100 mcg), can be considered as an adequate target population to assess the adequacy of Seretide as IMT. Patients with mild persistent asthma are not considered to be candidates for a combination therapy as IMT and patients with a more severe disease would deserve more intensive therapeutic approaches.

The primary endpoint in the GOAL study was the proportion of patients reaching asthma control (well-control of asthma). The CHMP considered the use of "Control of Asthma" as the primary efficacy variable a reliable parameter of the patient clinical status and, as such, clinically meaningful.

The CHMP had a concern that a general recommendation i.e. the therapeutic indication in the Summary of Product Characteristics (SPC), will result in over treatment particularly in patients who would have responded to inhaled corticosteroids alone. The MAH's proposed therapeutic indication to include "*patients with persistent asthma not adequately controlled on "as needed" inhaled short-acting beta-2-agonists alone who exhibit a combination of at least two of the following clinical features of asthma: airflow limitation, daily use of rescue medication, daily symptoms (day-time and/or night-time*)" was not considered acceptable as it does not effectively identify a population in need of combination therapy.

Nevertheless the CHMP acknowledged that current clinical guidelines (e.g. the Global Initiative for Asthma (GINA) guidelines) describe circumstances which could lead to the initiation of maintenance therapy with the combination. Therefore the CHMP considered it acceptable to give guidance to physicians as to the most appropriate dose strategy for initiating maintenance therapy with the fixed dose combination. A recommendation in section 4.2 "Posology and method of administration" was considered acceptable.

The recommendation included in section 4.2 allows a short term trial of Seretide Diskus in adults and adolescents with moderate persistent asthma for whom rapid control of asthma is essential. The initial starting dose is 1 inhalation of 50 mcg salmeterol/100 mcg FP twice daily. The wording also indicates the importance for stepping down to inhaled corticosteroids alone once asthma control is attained. It is also highlighted that Seretide is not appropriate as IMT in patients with mild and severe asthma and that in general inhaled corticosteroids remain the first line treatment for most patients.

In addition to the update in section 4.2 of the SPC, some factual data from the GOAL study in particular the timing of reaching more rapidly control with Seretide than with ICS alone have been included in section 5.1 "Pharmacodynamic properties" of the SPC. The information currently in section 5.1 of the SPC have also been amended in line with the recommendation in section 4.2.

SAFETY

Data from six pivotal studies and two supporting studies have been presented to confirm the safety profile of salmeterol/FP when initiated as maintenance treatment. Although the safety profile of salmeterol/fluticasone propionate is well known, the CHMP considered it not justified to expose the whole intended target population to an increased incidence of beta-agonists related adverse events. In line with above arguments, the CHMP was not in agreement with a general recommendation for IMT of the fixed dose combination in section 4.1. but considered it acceptable to include guidance for a short term trial of initial maintenance therapy with Seretide in section 4.2.

GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Whereas

- the CHMP considered the referral made under Article 6(13) of Commission Regulation (EC) N 1084/2003 for Seretide Diskus and associated names (see Annex I)

- the CHMP considered that an initial maintenance therapy indication with the fixed dose combination of salmeterol and fluticasone propionate in patients with moderate persistent asthma in section 4.1 of the SPC is not acceptable as it could result in overtreatment particularly in patients who would have responded to inhaled corticosteroids alone. CHMP considered it not acceptable to expose the whole target population to beta-agonists related adverse events.

- the CHMP agreed, however, that a recommendation for a short term trial with the fixed dose combination of salmeterol and fluticasone propionate as initial maintenance therapy in adults

and adolescents with moderate persistent asthma for whom rapid control of asthma is essential, in section 4.2 of the SPC is acceptable.

- the CHMP agreed that factual data from the GOAL study in particular the timing of reaching more rapidly control with Seretide than with ICS alone should be included in section 5.1 of the SPC and that some amendments in this section were necessary in line with the agreed recommendation in section 4.2.

The CHMP has recommended the granting of the variation of the Marketing Authorisations for which the Summary of Product Characteristics, labelling and package leaflet are set out in Annex III.

ANNEX III

Note: This Annex III (Summary of Product Characteristics, Labelling and Package Leaflet) is the one that was Annexed to the Commission Decision on this Article 6(13) referral for Seretide Diskus and associated names. The text was valid at that time.

After the Commission Decision, the Member State competent authorities will update Annex III as required. Therefore, Annex III may not necessarily represent the current text.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Seretide Diskus and associated names (see Annex I) 50/100 microgram/dose inhalation powder, pre-dispensed.

Seretide Diskus and associated names (see Annex I) 50/250 microgram/dose inhalation powder, pre-dispensed.

Seretide Diskus and associated names (see Annex I) 50/500 microgram/dose inhalation powder, pre-dispensed.

[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single dose of Seretide provides:
50 micrograms of salmeterol (as salmeterol xinafoate) and 100, 250 or 500 micrograms of fluticasone propionate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation powder, pre-dispensed.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Asthma

Seretide is indicated in the regular treatment of asthma where use of a combination product (long-acting beta-2-agonist and inhaled corticosteroid) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting beta-2-agonist

  or

- patients already adequately controlled on both inhaled corticosteroid and long-acting beta-2-agonist.

Note: Seretide 50/100 microgram strength is not appropriate in adults and children with severe asthma.

Chronic Obstructive Pulmonary Disease (COPD)

Seretide is indicated for the symptomatic treatment of patients with severe COPD (FEV1 <50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy.

4.2 Posology and method of administration

Seretide Diskus is for inhalation use only.

Patients should be made aware that Seretide Diskus must be used daily for optimum benefit, even when asymptomatic.

Patients should be regularly reassessed by a doctor, so that the strength of Seretide 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. Where the control of symptoms is maintained with the lowest strength of the combination given twice daily then the next step could include a test of inhaled corticosteroid alone.** As an alternative, patients requiring a long acting beta-2-agonist could be titrated to Seretide given once daily if, in the opinion of the prescriber, it would be adequate to maintain disease control. In the event of once daily dosing when the patient has a history of nocturnal symptoms the dose should be given at night and when the patient has a history of mainly day-time symptoms the dose should be given in the morning.

Patients should be given the strength of Seretide containing the appropriate fluticasone propionate dosage for the severity of their disease. Prescribers should be aware that, in patients with asthma, fluticasone propionate is as effective as other inhaled steroids at approximately half the microgram daily dose. For example, 100mcg of fluticasone propionate is approximately equivalent to 200mcg of beclomethasone dipropionate (CFC containing) or budesonide. If an individual patient should require dosages outside the recommended regimen, appropriate doses of beta-agonist and/or corticosteroid should be prescribed.

Recommended Doses:

Asthma

Adults and adolescents 12 years and older:

One inhalation of 50 micrograms salmeterol and 100 micrograms fluticasone propionate twice daily.
or
One inhalation of 50 micrograms salmeterol and 250 micrograms fluticasone propionate twice daily.
or
One inhalation of 50 micrograms salmeterol and 500 micrograms fluticasone propionate twice daily.

A short term trial of Seretide may be considered as initial maintenance therapy in adults or adolescents with moderate persistent asthma (defined as patients with daily symptoms, daily rescue use and moderate to severe airflow limitation) for whom rapid control of asthma is essential. In these cases, the recommended initial dose is one inhalation of 50 micrograms salmeterol and 100 micrograms fluticasone propionate twice daily. Once control of asthma is attained treatment should be reviewed and consideration given as to whether patients should be stepped down to an inhaled corticosteroid alone.

A clear benefit has not been shown as compared to inhaled fluticasone propionate alone used as initial maintenance therapy when one or two of the criteria of severity are missing. In general inhaled corticosteroids remain the first line treatment for most patients. Seretide is not intended for the initial management of mild asthma. Seretide 50/100 micrograms strength is not appropriate in adults and children with severe asthma; it is recommended to establish the appropriate dosage of inhaled corticosteroid before any fixed combination can be used in patients with severe asthma.

Children 4 years and older:

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

The maximum licensed dose of fluticasone propionate delivered by Seretide Diskus in children is 100mcg twice daily.

There are no data available for use of Seretide in children aged under 4 years.

COPD

Adults:

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

Special patient groups:

There is no need to adjust the dose in elderly patients or in those with renal impairment. There are no data available for use of Seretide in patients with hepatic impairment.

Using the Diskus:

The device is opened and primed by sliding the lever. The mouthpiece is then placed in the mouth and the lips closed round it. The dose can then be inhaled and the device closed.

4.3 Contraindications

Seretide is contraindicated in patients with hypersensitivity (allergy) to any of the active substances or to the excipient (see 6.1 List of Excipients).

4.4 Special warnings and precautions for use

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

Seretide Diskus should not be used to treat acute asthma symptoms for which a fast and short acting bronchodilator is required. Patients should be advised to have their medicinal product to be used for relief in an acute asthma attack 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 undergo urgent medical assessment. Consideration should be given to increasing corticosteroid therapy. The patient should also be medically reviewed where the current dosage of Seretide has failed to give adequate control of asthma. For patients with asthma or COPD, consideration should be given to additional corticosteroid therapies.

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

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

Seretide should be administered with caution in patients with severe cardiovascular disorders, including heart rhythm abnormalities, diabetes mellitus, untreated hypokalaemia or thyrotoxicosis.

There have been very rare reports of increases in blood glucose levels (see 4.8 Undesirable Effects) and this should be considered when prescribing to patients with a history of diabetes mellitus.

Potentially serious hypokalaemia may result from systemic beta-2-agonist therapy but following inhalation at therapeutic doses plasma levels of salmeterol are very low.

As with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. Seretide Diskus should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

Seretide contains lactose up to 12.5 milligram /dose. This amount does not normally cause problems in lactose intolerant people.

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

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. **It is important, therefore, that the patient is reviewed regularly and the dose of inhaled corticosteroid is reduced to the lowest dose at which effective control of asthma is maintained.**

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

Prolonged treatment of patients with high doses of inhaled corticosteroids may result in adrenal suppression and acute adrenal crisis. Children and adolescents <16years taking high doses of fluticasone propionate (typically ≥ 1000mcg/day) may be at particular risk. Very rare cases of adrenal suppression and acute adrenal crisis have also been described with doses of fluticasone propionate between 500 and less than 1000mcg. Situations, which could potentially trigger acute adrenal crisis include trauma, surgery, infection or any rapid reduction in dosage. Presenting symptoms are typically vague and may include anorexia, abdominal pain, weight loss, tiredness, headache, nausea, vomiting, hypotension, decreased level of consciousness, hypoglycaemia, and seizures. Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

The benefits of inhaled fluticasone propionate therapy should minimise the need for oral steroids, but patients transferring from oral steroids may remain at risk of impaired adrenal reserve for a considerable time. Patients who have required high dose emergency corticosteroid therapy in the past may also be at risk. This possibility of residual impairment should always be borne in mind in emergency and elective situations likely to produce stress, and appropriate corticosteroid treatment must be considered. The extent of the adrenal impairment may require specialist advice before elective procedures.

Ritonavir can greatly increase the concentration of fluticasone propionate in plasma. Therefore, concomitant use should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side-effects. There is also an increased risk of systemic side effects when combining fluticasone propionate with other potent CYP3A inhibitors (see 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction).

4.5 Interaction with other medicinal products and other forms of interaction

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

Concomitant use of other beta-adrenergic containing drugs can have a potentially additive effect. 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.

In an interaction study in healthy subjects with intranasal fluticasone propionate, ritonavir (a highly potent cytochrome P450 3A4 inhibitor) 100 mg b.i.d. increased the fluticasone propionate plasma concentrations several hundred fold, resulting in markedly reduced serum cortisol concentrations. Information about this interaction is lacking for inhaled fluticasone propionate, but a marked increase in fluticasone propionate plasma levels is expected. Cases of Cushing's syndrome and adrenal suppression have been reported. The combination should be avoided unless the benefit outweighs the increased risk of systemic glucocorticoid side-effects.

In a small study in healthy volunteers, the slightly less potent CYP3A inhibitor ketoconazole increased the exposure of fluticasone propionate after a single inhalation by 150%. This resulted in a greater reduction of plasma cortisol as compared with fluticasone propionate alone. Co-treatment with other potent CYP3A inhibitors, such as itraconazole, is also expected to increase the systemic fluticasone propionate exposure and the risk of systemic side-effects. Caution is recommended and long-term treatment with such drugs should if possible be avoided.

4.6 Pregnancy and lactation

There are insufficient data on the use of salmeterol and fluticasone propionate during pregnancy and lactation in man to assess the possible harmful effects. In animal studies foetal abnormalities occur after administration of beta-2-adrenoreceptor agonists and glucocorticosteroids (see 5.3 Preclinical Safety Data).

Administration of Seretide to pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

The lowest effective dose of fluticasone propionate needed to maintain adequate asthma control should be used in the treatment of pregnant women.

There are no data available for human breast milk. Both salmeterol and fluticasone propionate are excreted into breast milk in rats. Administration of Seretide 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.

4.7 Effects on ability to drive and use machines

No studies of the effect on the ability to drive and use machines have been performed.

4.8 Undesirable effects

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

Adverse events which have been associated with salmeterol fluticasone propionate are given below, listed by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), and very rare (<1/10,000) including isolated reports. Very common, common and uncommon events were derived from clinical trial data. The incidence in placebo was not taken into account. Very rare events were derived from post-marketing spontaneous data.

System Organ Class	Adverse Event	Frequency
Infections & Infestations	Candidiasis of the mouth and throat	Common
Immune System Disorders	Hypersensitivity reactions with the following manifestations: Cutaneous hypersensitivity reactions Angioedema (mainly facial and oropharyngeal oedema), Respiratory symptoms (dyspnoea and/or bronchospasm), Anaphylactic reactions	 Uncommon Very Rare
Endocrine Disorders	Cushing's syndrome, Cushingoid features, Adrenal suppression, Growth retardation in children and adolescents, Decreased bone mineral density, Cataract, Glaucoma	Very Rare
Metabolism & Nutrition Disorders	Hyperglycaemia	Very Rare
Psychiatric Disorders	Anxiety, sleep disorders and behavioural changes, including hyperactivity and irritability (predominantly in children)	Very Rare
Nervous System Disorders	Headache Tremor	*Very Common Common
Cardiac Disorders	Palpitations Tachycardia Cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia and extrasystoles).	Common Uncommon Very Rare
Respiratory, Thoracic & Mediastinal Disorders	Throat irritation Hoarseness/dysphonia Paradoxical bronchospasm	Common Common Very Rare
Musculoskeletal & Connective Tissue Disorders	Muscle cramps Arthralgia Myalgia	Common Very Rare Very Rare

*Reported commonly in placebo

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

Due to the fluticasone propionate component, 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 using the product. Symptomatic candidiasis can be treated with topical anti-fungal therapy whilst still continuing with the Seretide Diskus.

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 4.4 Special Warnings and Precautions For Use).

There have been very rare reports of hyperglycaemia (see 4.4 Special Warnings and Precautions for Use).

As with other inhalation therapy, paradoxical bronchospasm may occur (see 4.4 Special Warnings and Precautions for Use).

4.9 Overdose

There are no data available from clinical trials on overdose with Seretide, however data on overdose with both drugs are given below:

The signs and symptoms of salmeterol overdose are tremor, headache and tachycardia. The preferred antidotes are cardioselective beta-blocking agents, which should be used with caution in patients with a history of bronchospasm. If Seretide therapy has to be withdrawn due to overdose of the beta agonist component of the drug, provision of appropriate replacement steroid therapy should be considered. Additionally, hypokalaemia can occur and potassium replacement should be considered.

Acute: 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 as adrenal function is recovered in a few days, as verified by plasma cortisol measurements.

Chronic overdose of inhaled fluticasone propionate: Refer to section 4.4: risk of adrenal suppression: Monitoring of adrenal reserve may be necessary. In cases of fluticasone propionate overdose Seretide therapy may still be continued at a suitable dosage for symptom control.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Adrenergics and other anti-asthmatics.

ATC Code: R03AK06

Seretide Asthma clinical trials

A twelve month study (Gaining Optimal Asthma ControL, GOAL), in 3416 adult and adolescent patients with persistent asthma, compared the safety and efficacy of Seretide versus inhaled corticosteroid (Fluticasone Propionate) alone to determine whether the goals of asthma management were achievable. Treatment was stepped up every 12 weeks until **Total control was achieved or the highest dose of study drug was reached. GOAL showed more patients treated with Seretide achieved asthma control than patients treated with ICS alone and this control was attained at a lower corticosteroid dose.

Well Controlled asthma was achieved more rapidly with Seretide than with ICS alone. The time on treatment for 50% of subjects to achieve a first individual Well Controlled week was 16 days for Seretide compared to 37 days for the ICS group. In the subset of steroid naive asthmatics the time to an individual Well Controlled week was 16 days in the Seretide treatment compared to 23 days following treatment with ICS.

The overall study results showed:

Percentage of Patients Attaining *Well Controlled (WC) and **Totally Controlled (TC) Asthma over 12 months				
	Salmeterol/FP		FP	
Pre-Study Treatment	**WC**	**TC**	**WC**	**TC**
No ICS (SABA alone)	78%	50%	70%	40%
Low dose ICS (≤500mcg BDP or equivalent/day)	75%	44%	60%	28%
Medium dose ICS (>500-1000mcg BDP or equivalent/day)	62%	29%	47%	16%
Pooled results across the 3 treatment levels	71%	41%	59%	28%

*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

The results of this study suggest that Seretide 50/100mcg bd may be considered as initial maintenance therapy in patients with moderate persistent asthma for whom rapid control of asthma is deemed essential (see section 4.2).

Seretide COPD clinical trials

Placebo-controlled clinical trials, over 6 and 12 months, have shown that regular use of Seretide 50/500 micrograms improves lung function and reduces breathlessness and the use of relief medication. Over a 12 month period the risk of COPD exacerbations was reduced from 1.42 per year to 0.99 per year compared with placebo and the risk of exacerbations requiring oral corticosteroids was significantly reduced from 0.81 to 0.47 per year compared with placebo.

Mechanism of action:

Seretide contains salmeterol and fluticasone propionate which have differing modes of action. The respective mechanisms of action of both drugs are discussed below:

Salmeterol:

Salmeterol is a selective long-acting (12 hour) beta-2-adrenoceptor agonist with a long side chain which binds to the exo-site of the receptor.

Salmeterol produces a longer duration of bronchodilation, lasting for at least 12 hours, than recommended doses of conventional short-acting beta-2-agonists.

Fluticasone propionate:

Fluticasone propionate given by inhalation at recommended doses has a 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.

5.2 Pharmacokinetic properties

When salmeterol and fluticasone propionate were administered in combination by the inhaled route, the pharmacokinetics of each component were similar to those observed when the drugs were administered separately. For pharmacokinetic purposes therefore each component can be considered separately.

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 picogram /ml or less) achieved after inhaled dosing.

Fluticasone propionate:

The absolute bioavailability of inhaled fluticasone propionate in healthy subjects varies between approximately 10-30% of the nominal dose depending on the inhalation device used. 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.

The disposition of fluticasone propionate is characterised by high plasma clearance (1150ml/min), a large volume of distribution at steady-state (approximately 300l) and a terminal half-life of approximately 8 hours.

Plasma protein binding is 91%.

Fluticasone propionate is cleared very rapidly from the systemic circulation. The main pathway is metabolism to an inactive carboxylic acid metabolite, by the cytochrome P450 enzyme CYP3A4. Other unidentified metabolites are also found in the faeces.

The renal clearance of fluticasone propionate is negligible. Less than 5% of the dose is excreted in urine, mainly as metabolites. The main part of the dose is excreted in faeces as metabolites and unchanged drug.

5.3 Preclinical safety data

The only safety concerns for human use derived from animal studies of salmeterol xinafoate and fluticasone propionate given separately were effects associated with exaggerated pharmacological actions.

In animal reproduction studies, glucocorticosteroids have been shown to induce malformations (cleft palate, skeletal malformations). However, these animal experimental results do not seem to be relevant for man given recommended doses. Animal studies with salmeterol xinafoate have shown embryofoetal toxicity only at high exposure levels. Following co-administration, increased incidences of transposed umbilical artery and incomplete ossification of occipital bone were found in rats at doses associated with known glucocorticoid-induced abnormalities.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate (which contains milk proteins).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

The inhalation powder is contained in blisters held on a formed PVC coated base, with a peelable foil laminate lid. The strip is contained in a moulded plastic device.

The plastic devices are available in cardboard containers, which hold

1 x 28 dose Diskus
or 1 x 60 dose Diskus
or 2 x 60 dose Diskus
or 3 x 60 dose Diskus
or 10 x 60 dose Diskus

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The Diskus releases a powder which is inhaled into the lungs.

A dose indicator on the Diskus indicates the number of doses left.

For detailed instructions for use see the Patient Information Leaflet.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

LABELLING AND PACKAGE LEAFLET

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Seretide Diskus and associated names (see Annex I) 50/100 microgram/dose inhalation powder, pre-dispensed
[See Annex I – To be completed nationally]

Salmeterol xinafoate and fluticasone propionate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

50 micrograms of salmeterol (as xinafoate) and 100 micrograms of fluticasone propionate per actuation

3. LIST OF EXCIPIENTS

Lactose monohydrate

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, pre-dispensed

1 x 28 inhalations

1 x 60 inhalations

2 x 60 inhalations

3 x 60 inhalations

10 x 60 inhalations

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use

Inhalation use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

DISKUS LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Seretide Diskus and associated names (see Annex I) 50/100 microgram/dose inhalation powder, pre-dispensed
[See Annex I – To be completed nationally]

Salmeterol xinafoate and fluticasone propionate

Inhalation use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

28 doses
60 doses

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Seretide Diskus and associated names (see Annex I) 50/250 microgram/dose inhalation powder, pre-dispensed
[See Annex I – To be completed nationally]

Salmeterol xinafoate and fluticasone propionate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

50 micrograms of salmeterol (as xinafoate) and 250 micrograms of fluticasone propionate per actuation

3. LIST OF EXCIPIENTS

Lactose monohydrate

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, pre-dispensed

1 x 28 inhalations

1 x 60 inhalations

2 x 60 inhalations

3 x 60 inhalations

10 x 60 inhalations

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use

Inhalation use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

DISKUS LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Seretide Diskus and associated names (see Annex I) 50/250 microgram/dose inhalation powder, pre-dispensed
[See Annex I – To be completed nationally]

Salmeterol xinafoate and fluticasone propionate

Inhalation use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

28 doses
60 doses

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Seretide Diskus and associated names (see Annex I) 50/500 microgram/dose inhalation powder, pre-dispensed
[See Annex I – To be completed nationally]

Salmeterol xinafoate and fluticasone propionate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

50 micrograms of salmeterol (as xinafoate) and 500 micrograms of fluticasone propionate per actuation

3. LIST OF EXCIPIENTS

Lactose monohydrate

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, pre-dispensed

1 x 28 inhalations

1 x 60 inhalations

2 x 60 inhalations

3 x 60 inhalations

10 x 60 inhalations

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use

Inhalation use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

DISKUS LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Seretide Diskus and associated names (see Annex I) 50/500 microgram/dose inhalation powder, pre-dispensed
[See Annex I – To be completed nationally]

Salmeterol xinafoate and fluticasone propionate

Inhalation use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

28 doses
60 doses

6. OTHER

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Seretide Diskus and associated names (see Annex I) 50/100 microgram/dose inhalation powder, pre-dispensed
Seretide Diskus and associated names (see Annex I) 50/250 microgram/dose inhalation powder, pre-dispensed
Seretide Diskus and associated names (see Annex I) 50/500 microgram/dose inhalation powder, pre-dispensed
[See Annex I – To be completed nationally]

Salmeterol xinafoate and fluticasone propionate

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT SERETIDE IS AND WHAT IT IS USED FOR

Seretide is supplied to you in an inhaler device which contains a foil strip. The foil protects the powder for inhalation from the effects of the atmosphere. Each dose contains 50 micrograms of salmeterol (as xinafoate) together with either 100, 250 or 500 micrograms of fluticasone propionate.

Salmeterol is one of a group of medicines called long-acting bronchodilators (effect lasting for at least 12 hours). It helps the airways in the lung to stay open making it easier for air to get in and out. Fluticasone propionate is one of a group of medicines called corticosteroids which reduces swelling and irritation in the lungs. This combination of salmeterol and fluticasone propionate when used regularly prevents asthma attacks occurring. Seretide does not work in controlling sudden attacks of breathlessness and wheezing where you would need to use your fast acting 'rescue' medication. Seretide Diskus is also used for the regular treatment of the symptoms of severe Chronic Obstructive Pulmonary Disease (COPD). To work properly in controlling asthma and treating COPD symptoms, Seretide must be taken every day as directed by your doctor.

2. BEFORE YOU TAKE SERETIDE

Do not take Seretide
If you are allergic (hypersensitive) to salmeterol xinafoate, fluticasone propionate or to the other ingredient lactose monohydrate.

Take special care with Seretide
Your doctor will supervise your treatment more closely if you have medical conditions such as heart disease including an irregular or fast heart beat, overactive thyroid gland, high blood pressure, diabetes mellitus (Seretide may increase your blood sugar), low potassium in your blood or if you are being, or have been treated for tuberculosis (TB).

Seretide Diskus contains up to 12.5 milligrams of lactose in each dose. However, the amount of lactose in this medicine does not normally cause problems in lactose intolerant people.

If you are using high doses of Seretide for a long time, one of the active ingredients, fluticasone propionate, may stop the natural production of steroid hormones by the adrenal gland. This may cause thinning of the bones, cataract, glaucoma, weight gain, rounded (moon shaped) face, high blood pressure and slowing of growth in children and adolescents. Your doctor will check you regularly for any of these side effects and to make sure you are taking the lowest dose of Seretide to control your asthma.

Very rarely side effects may occur if you have taken high doses of Seretide for a long time and you stop or reduce your dose suddenly. Side effects may also occur if you get an infection or at times of extreme stress (such as after a serious accident or if you have surgery). These effects include stomach pain, tiredness, loss of appetite, sickness, diarrhoea, weight loss, headache or drowsiness, low levels of potassium in your blood, low blood pressure and seizures. To prevent these symptoms occurring, your doctor may prescribe extra corticosteroids during this time.

Taking other medicines
Please tell your doctor if you are taking or have recently taken any other medicines, including those for asthma or any medicines obtained without a prescription. In some cases, Seretide may not be suitable to be taken with other medicines.

Your doctor will need to know if you have recently been treated with corticosteroids (orally or by injection). This is to reduce the risk of affecting the function of your adrenal gland.

Seretide should not be taken with medicines called β-blockers (such as atenolol, propranolol, sotalol), unless your doctor tells you to do so. Some types of antiviral and antifungal medication (such as ritonavir, ketoconazole and itraconazole) may increase the amount of fluticasone propionate in your body and therefore increase your risk of having side effects. Only take these medicines whilst on Seretide, if told to do so by your doctor.

Pregnancy and breast-feeding
You should ask your doctor for advice before taking Seretide whilst you are pregnant or breastfeeding. The doctor will assess whether you can take Seretide during this time.

Driving and using machines
The possible side effects associated with Seretide are unlikely to affect your ability to drive or use machines.

3. HOW TO TAKE SERETIDE

Dosage
It is very important that you take your Seretide every day as directed, until you are advised to stop by your doctor.

Seretide Diskus is for inhalation by mouth only.

Asthma

Adults and adolescents 12 years and over

Seretide 50/100 Diskus	One inhalation twice a day
Seretide 50/250 Diskus	One inhalation twice a day
Seretide 50/500 Diskus	One inhalation twice a day

Children 4 to 12 years of age

Seretide 50/100 Diskus	One inhalation twice a day

This medicine if not recommended for use in children below 4 years of age.

COPD

Adults

Seretide 50/500 Diskus	One inhalation twice a day

The doctor will prescribe the lowest strength of Seretide Diskus that will best control your symptoms. If your symptoms are well controlled using Seretide Diskus twice daily, your doctor may decide to reduce your dose to once daily. This may be either once at night if you have night-time symptoms or once in the morning if you have daytime symptoms. It is very important to follow your doctor's instructions as to how many inhalations to take and how often to take your medicine.

If you find it difficult to breathe or your wheezing gets worse after taking Seretide, stop using it immediately and tell your doctor straightaway so they can assess your treatment.

If your asthma gets worse or is not well controlled (you will feel wheezy and need more of your fast acting 'rescue' medicine), do not increase the number of inhalations of Seretide you take. See your doctor immediately so they can review your condition and assess the medication you need to take.

Do not use Seretide to treat a sudden attack of breathlessness or wheezing as it will not help you immediately. You must use your fast acting 'rescue' medicine (such as salbutamol) for this purpose which you should carry with you at all times. Be careful not to confuse your Seretide inhaler with your 'rescue' inhaler.

Instructions for proper use
Your doctor, nurse or pharmacist should instruct you in the proper use of your inhaler.

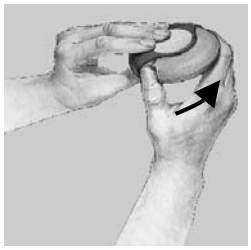
When you first take Seretide Diskus out of the box, it will be in the closed position.

The Diskus device holds blisters containing Seretide in powder form. There is a counter on top of the Diskus which tells you how many doses are left. It counts down to 0 and numbers 5 to 0 will appear in red to warn you when there are only a few doses left. Once the counter shows 0, your inhaler is empty.

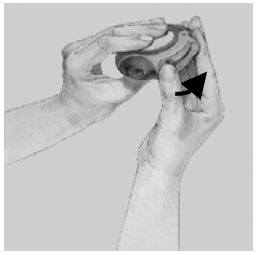
Use of the inhaler

Sliding the lever of the Diskus opens a small hole in the mouthpiece and opens a blister in a foil strip, ready for you to inhale the powder. When you close the Diskus, the lever automatically moves back to the original position, with the outer casing protecting the Diskus when not in use. When you need to use it, follow these steps:

1. OPEN: to open your 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 and you hear a click.



2. SLIDE: Hold your Diskus with the mouthpiece towards you. You can hold it in either your right or left hand. Slide the lever away from you as far as it will go until it clicks. Your Diskus is now ready for you to use. Every time the lever is pulled back a blister is opened and the powder made ready for you to inhale. Do not play with the lever as this opens the blisters and wastes medicine.



3. INHALE: Read this section carefully before taking your medicine.

    - Hold the Diskus away from your mouth, breathe out as far as is comfortable. Do not breathe into your Diskus inhaler.

    - Put the mouthpiece to your lips; breathe in steadily and deeply through the Diskus, not through your nose.

    - Remove the Diskus from your mouth.

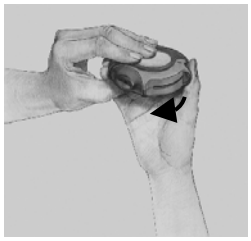
    - Hold your breath for about 10 seconds or for as long as is comfortable.

    - Breathe out slowly.

    - Rinse your mouth with water and spit it out as this may help prevent the occurrence of thrush and hoarseness.

4. CLOSE:
    - To close the Diskus, slide the thumbgrip back towards you, as far as it will go.

    - When you close the Diskus, it clicks shut. The lever will return to its original position and is reset. Your Diskus is now ready for you to use again.



Cleaning your inhaler

Wipe the mouthpiece of the Diskus with a dry tissue to clean it.

If you take more Seretide than you should
It is important to take Seretide as your doctor recommended. If you accidentally take a larger dose, you may develop side effects such as your heart beating faster than usual, feeling shaky, headache, muscle weakness, aching joints and also a reduction of steroid hormones produced by the adrenal gland. These effects usually wear off with continued treatment, however, if you have used larger doses for a long period of time, you should contact your doctor or pharmacist for advice.

If you forget to take Seretide
If you forget to take your medicine, take your next dose when it is due. Do not take a double dose to make up for a forgotten dose.

If you stop taking Seretide
It is very important that you take your Seretide every day as directed, until you are advised to stop by your doctor. Do not stop taking Seretide suddenly as this could make your symptoms worse and could cause problems with the body's hormones.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Seretide can cause side effects, although not everybody gets them. To help prevent side effects occurring, your doctor will make sure you are on the lowest dose of Seretide that will control your asthma. These are the side effects reported by people taking Seretide.

Very Common effects: this means that more than 1 in 10 people taking the medicine are affected.
- Headache, although this side effect usually lessens as treatment continues.

Common effects: means that between 1 in 10 and 1 in 100 people taking the medicine are affected.
- Thrush (sore, creamy-yellow, raised patches) in the mouth and throat. Soreness of the tongue, throat and hoarseness of the voice. Rinsing the mouth out with water and spitting it out immediately after taking each puff may help. Your doctor may prescribe additional anti fungal medication to treat the thrush.

- Feeling shaky and fast or irregular heartbeat (palpitations). These side effects are usually harmless and lessen as treatment continues.

- Muscle cramps.

Uncommon effects: means that between 1 in 100 and 1 in 1000 people taking the medicine are affected.
- Rash

- Very fast heart rate (tachycardia).

Very rare: means that fewer than 1 in 10,000 people taking the medicine are affected.
- Signs of allergy, such as itching, swelling (usually of the face, lips, tongue or throat), difficulty in breathing, wheezing or coughing (bronchospasm). If you notice these symptoms or they appear suddenly after taking Seretide, tell your doctor immediately as you could be allergic to Seretide.

- Seretide may affect the normal production of steroid hormones in the body, particularly if you have taken high doses for long periods of time. The effects are slowing of growth in children and adolescents, thinning of the bones, cataract, glaucoma, weight gain, high blood pressure and rounded (moon shaped) face (Cushing's Syndrome).

- Uneven heartbeat or heart gives an extra beat (arrhythmias). Tell your doctor, but do not stop taking Seretide unless they tell you to do so.

- Increases in the amount of sugar (glucose) in your blood (hyperglycaemia). If you have diabetes, more frequent blood sugar monitoring and possibly adjustment of your usual diabetic treatment may be required.

- Feeling anxious, disturbed sleep and behavioural changes, such as being unusually active and irritable (mainly in children).

- Breathing difficulties or wheezing (bronchospasm) worsens immediately after taking Seretide.

- Aching, swollen joints and muscle pain.

If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE SERETIDE

Keep out of the reach and sight of children.

Do not store above 30°C.

Do not use Seretide after the expiry date which is stated on the label and carton.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Seretide contains

- The active substance(s) are 50 micrograms salmeterol (as xinafoate) and 100, 250 or 500 micrograms fluticasone propionate.
- The other ingredient is lactose monohydrate (which contains milk proteins).

What Seretide looks like and contents of the pack

Inhalation powder, pre-dispensed.

The devices are packed in cartons which hold:

1 x Diskus 28 inhalations

or 1, 2, 3 or 10 x Diskus each containing 60 inhalations

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
[See Annex I - To be completed nationally]

Manufacturer:
Glaxo Operations UK Ltd (trading as Glaxo Wellcome Operations),
Priory Street, Ware, Hertfordshire SG12 ODJ, United Kingdom.
Tel: +44 (0)1920 463993
Fax: +44 (0)1920 864000

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria	Seretide Diskus
Belgium	Seretide Diskus
Denmark	Seretide
Finland	Seretide Diskus
France	Seretide Diskus
Germany	atmadisc Diskus
Greece	Seretide Diskus
Ireland	Seretide Diskus
Italy	Seretide Diskus
Luxembourg	Seretide Diskus
The Netherlands	Seretide Diskus
Portugal	Seretaide Diskus
Spain	Seretide Accuhaler
Sweden	Seretide Diskus
United Kingdom	Seretide Accuhaler

This leaflet was last approved in {MM/YYYY}.

[To be completed nationally]

<Detailed information on this medicine is available on the web site of {MA/Agency}>

