The European Agency for the Evaluation of Medicinal Products
Post-authorisation Evaluation of Medicines for Human Use

7 July 2003
CPMP/1327/03

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)
OPINION FOLLOWING AN ARTICLE 7(5) REFERRAL

SALMETEROL AND FLUTICASONE PROPIONATE

International Non-Proprietary Name (INN): **Salmeterol and fluticasone**

BACKGROUND INFORMATION*

The fixed combination medicinal product formulated as inhalation powder, pre-dispensed consisting of salmeterol (50µg), a long-acting beta-2-adrenoceptor agonist, and fluticasone propionate (FP 100µg, 250µg, or 500µg), a corticosteroid, was first authorised in Sweden for the regular treatment of asthma where use of a combination (long-acting beta agonist and inhaled corticosteroid) is appropriate. It was subsequently licensed via a Mutual Recognition Procedure (MRP) in December 1998 with Sweden as Reference Member State (RMS); the Concerned Member States were Austria, Belgium, Germany, Denmark, Greece, Spain, Finland, France, Ireland, Italy, Luxembourg, Portugal, the Netherlands and United Kingdom.

In September 2001, the Marketing Authorisation Holders (MAHs) applied for a Type II variation through MRP to include chronic obstructive pulmonary disease (COPD) as a therapeutic indication for the fixed-dose combination of salmeterol/FP 50/500 µg twice daily. The RMS reached a negative view on use in COPD even after the proposed treatment population was restricted to patients with moderate to severe COPD as indicated by an FEV_1 of 50% or less of predicted normal.

The separate components of the salmeterol/FP combination are not approved for use in the treatment of chronic obstructive pulmonary disease (COPD) in all EU Member States.

On 19 April 2002, Ireland via the Irish Medicines Board (IMB) triggered a referral to the EMEA under Article 7(5) of Commission Regulation (EC) No 541/95. The IMB believed that having both components as a fixed dose combination could represent a convenience and compliance advantage to patients suffering from this common condition (i.e. COPD), as is recognised in the CPMP Note for Guidance for Fixed Combination Medicinal Products (section 1.2.b – a simplification of therapy). Moreover, the IMB considered that this aspect has not been sufficiently taken into consideration when the RMS, reached its opinion that the clinical benefit of the combination was marginal and that the efficacy advantage of the combination had not been convincingly demonstrated with respect to that of the separate components. The IMB therefore requested the CPMP to give an opinion on the scope of this variation application, i.e. the indication of treatment of COPD.

The referral procedure started on 26 April 2002. The Rapporteur and Co-Rapporteur appointed were: Dr. D. Lyons and Dr. P. Arlett, respectively. Written explanations were provided by the MAHs on 13 August 2002. Supplementary information was provided by the MAHs on 16 December 2002. Oral explanations were given by MAHs on 21 January 2003.

Based on re-evaluation of the currently available information on the above-concerned medicinal products, the CPMP considered that overall the balance of risks and benefits of the above-concerned medicinal product is favourable for the new restricted indication, and therefore adopted by majority an opinion on 23 January 2003 recommending the granting of the variation of the Marketing Authorisations for the fixed combination medicinal products containing salmeterol and fluticasone propionate for the indication of "the symptomatic treatment of patients with severe COPD (FEV_1 <50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy" and the amendment of the summary of product characteristics

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The list of product names concerned is given in the Annex I. The scientific conclusions are provided in the Annex II together with the amended Summary of Product Characteristics in the Annex III.

The final opinion was converted into a Decision by the European Commission on 21 May 2003.

* **Notes**: The information given in this document and Annexes reflect only the CPMP Opinion dated 23 January 2003. The Member States competent authorities will continue to keep the product under regular review.

ANNEX I

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

SALMETEROL AND FLUTICASONE FIXED COMBINATION MEDICINAL PRODUCTS WITH MARKETING AUTHORISATION IN THE MEMBER STATES

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package size
Austria	GlaxoSmithKline Pharma GmbH, Albert-Schweitzer-Gasse 6, A-1140 Wien	Seretide Diskus forte	50/500	Inhalation powder, pre-dispensed	Inhalation	Blister. Double foil 28 or 60 dose	1x28, 1x60, 2x60, 3x60, 10x60 doses
Austria	GlaxoSmithKline Pharma GmbH, Albert-Schweitzer-Gasse 6, A-1140 Wien	Seretide Diskus junior	50/100	Inhalation powder, pre-dispensed	Inhalation	Blister. Double foil 28 or 60 dose	1x28, 1x60, 2x60, 3x60, 10x60
Austria	GlaxoSmithKline Pharma GmbH, Albert-Schweitzer-Gasse 6, A-1140 Wien	Seretide Diskus standard	50/250	Inhalation powder, pre-dispensed	Inhalation	Blister. Double foil 28 or 60 dose	1x28, 1x60, 2x60, 3x60, 10x60 doses
Belgium	GlaxoSmithKline s.a./n.v. Rue du Tilleul,13 B-1332 GENVAL	SERETIDE DISKUS 50/100	50/100	Inhalation powder, pre-dispensed	Inhalation	Blister. Double foil 28 or 60 dose	1x28, 1x60, 2x60, 3x60, 10x60 doses
Belgium	GlaxoSmithKline s.a./n.v. Rue du Tilleul,13 B-1332 GENVAL	SERETIDE DISKUS 50/250	50/250	Inhalation powder, pre-dispensed	Inhalation	Blister. Double foil 28 or 60 dose	1x28, 1x60, 2x60, 3x60, 10x60 doses
Belgium	GlaxoSmithKline s.a./n.v. Rue du Tilleul,13 B-1332 GENVAL	SERETIDE DISKUS 50/500	50/500	Inhalation powder, pre-dispensed	Inhalation	Blister. Double foil 28 or 60 dose	1x28, 1x60, 2x60, 3x60, 10x60 doses
Denmark	GlazoSmithKline Pharma A/S, Nykær 68, DK-2605 Brøndby, Denmark	Seretide (Diskos)	50/100, 50/250 and 50/500	Inhalation powder, pre-dispensed	Inhalation	Blister. Double foil 28 or 60 dose	1x28, 1x60, 2x60, 3x60, 10x60 doses
Finland	GlaxoSmithKline Oy, Kurjenkellontie 5, 02271 Espoo	Seretide Diskus	50/100	Inhalation powder, pre-dispensed	Inhalation	Blister. Double foil 28 or 60 dose	1x28, 1x60, 2x60, 3x60, 10x60 doses
Finland	GlaxoSmithKline Oy, Kurjenkellontie 5, 02271 Espoo	Seretide Diskus	50/250	Inhalation powder, pre-dispensed	Inhalation	Blister. Double foil 28 or 60 dose	1x28, 1x60, 2x60, 3x60, 10x60 doses

Finland	GlaxoSmithKline Oy, Kurjenkellontie 5, 02271 Espoo	Seretide Diskus	50/100	Inhalation powder, pre-dispensed	Inhalation	Blister. Double foil 28 or 60 dose	1x28, 1x60, 2x60, 3x60, 10x60 doses
France	Laboratoire GlaxoSmithkline 100 route de Versailles 78163 Marly le Roi Cedex	SERETIDE DISKUS	50/100	Inhalation powder, pre-dispensed	Inhalation	Blister. Double foil 28 or 60 dose	1x28, 1x60, 2x60, 3x60, 10x60 doses
France	Laboratoire GlaxoSmithkline 100 route de Versailles 78163 Marly-le-Roi Cedex	SERETIDE DISKUS	50/250	Inhalation powder, pre-dispensed	Inhalation	Blister. Double foil 28 or 60 dose	1x28, 1x60, 2x60, 3x60, 10x60 doses
France	Laboratoire GlaxoSmithkline 100 route de Versailles 78163 Marly-le-Roi Cedex	SERETIDE DISKUS	50/500	Inhalation powder, pre-dispensed	Inhalation	Blister. Double foil 28 or 60 dose	1x28, 1x60, 2x60, 3x60, 10x60 doses
Germany	Schwarz Pharma Deutschland GmbH, Alfred-Nobel-Str. 10 D-40789 Monheim	Atmadisc mite Diskus	50/100	Inhalation Powder, predispensed	Inhalation	Blister. Double foil 28 or 60 dose	1x28, 1x60, 2x60, 3x60, 10x60 doses
Germany	Schwarz Pharma Deutschland GmbH, Alfred-Nobel-Str. 10 D-40789 Monheim	Atmadisc Diskus	50/250	Inhalation Powder, predispensed	Inhalation	Blister. Double foil 28 or 60 dose	1x28, 1x60, 2x60, 3x60, 10x60 doses
Germany	Schwarz Pharma Deutschland GmbH, Alfred-Nobel-Str. 10 D-40789 Monheim	Atmadisc forte Diskus	50/500	Inhalation Powder, predispensed	Inhalation	Blister. Double foil 28 or 60 dose	1x28, 1x60, 2x60, 3x60, 10x60 doses
Greece	Allen Pharmaceuticals S.A Filellinon 34 152 32 Halandri Athens	Seretide diskus	50/100	Inhalation powder, pre-dispensed	Inhalation	Blister. Double foil 28 or 60 dose	1x28, 1x60, 2x60, 3x60, 10x60 doses
Greece	Allen Pharmaceuticals S.A Filellinon 34 152 32 Halandri Athens	Seretide diskus	50/250	Inhalation powder, pre-dispensed	Inhalation	Blister. Double foil 28 or 60 dose	1x28, 1x60, 3x60, 2x60, 10x60
Greece	Allen Pharmaceuticals S.A Filellinon 34 152 32 Halandri Athens	Seretide diskus	50/500	Inhalation powder, pre-dispensed	Inhalation	Blister. Double foil 28 or 60 dose	1x28, 1x60, 2x60, 3x60, 10x60 doses
Ireland	Allen & Hansburys Limited, Stockley Park West, Uxbridge, Middlesex, UB11 1BT, England.	Seretide Diskus	50/100, 50/250 and 50/500	Inhalation powder, pre-dispensed	Inhalation	Blister. Double foil 28 or 60 dose	1x28, 1x60, 2x60, 3x60, 10x60 doses

Italy	GlaxoSmithKline S.p.A. Via A. Fleming, 2 37135 Verona	Seretide Diskus	50/100, 50/250, 50/500	Inhalation powder, pre-dispensed	Inhalation	Blister. Double foil 28 or 60 dose	1x28, 1x60, 2x60, 3x60, 10x60 doses
Luxembourg	GlaxoSmithKline s.a./n.v. 13 rue du Tilleul B-1332 GENVAL, Belgium	Seretide Diskus	50/100	Inhalation powder, pre-dispensed	Inhalation	Blister. Double foil 28 or 60 dose	1x28, 1x60, 2x60, 3x60, 10x60 doses
Luxembourg	GlaxoSmithKline s.a./n.v. 13 rue du Tilleul B-1332 GENVAL, Belgium	Seretide Diskus	50/250	Inhalation powder, pre-dispensed	Inhalation	Blister. Double foil 28 or 60 dose	1x28, 1x60, 2x60, 3x60, 10x60 doses
Luxembourg	GlaxoSmithKline s.a./n.v. 13 rue du Tilleul B-1332 GENVAL, Belgium	Seretide Diskus	50/500	Inhalation powder, pre-dispensed	Inhalation	Blister. Double foil 28 or 60 dose	1x28, 1x60, 2x60, 3x60, 10x60 doses
Netherlands	GlaxoSmithKline B.V. Huis ter Heideweg 62 3705 LZ Zeist	Seretide 50/100 Diskus	50/100	Inhalation powder, pre-dispensed	Inhalation	Blister. Double foil 28 or 60 dose	1x28, 1x60, 2x60, 3x60, 10x60 doses
Netherlands	GlaxoSmithKline B.V. Huis ter Heideweg 62 3705 LZ Zeist	Seretide 50/250 Diskus	50/250	Inhalation powder, pre-dispensed	Inhalation	Blister. Double foil 28 or 60 dose	1x28, 1x60, 2x60, 3x60, 10x60 doses
Netherlands	GlaxoSmithKline B.V. Huis ter Heideweg 62 3705 LZ Zeist	Seretide 50/500 Diskus	50/500	Inhalation powder, pre-dispensed	Inhalation	Blister. Double foil 28 or 60 dose	1x28, 1x60, 2x60, 3x60, 10x60 doses
Portugal	Glaxo Wellcome Farmacêutica, Lda. Rua Dr. António Loureiro Borges, 3, Arquiparque , Miraflores 1495-131 Algés	Seretaide Diskus	50/500	Inhalation powder, pre-dispensed	Inhalation	Blister. Double foil 28 or 60 dose	1x28, 1x60, 2x60, 3x60, 10x60 doses
Portugal	Glaxo Wellcome Farmacêutica, Lda. Rua Dr. António Loureiro Borges, 3, Arquiparque , Miraflores 1495-131 Algés	Seretaide Diskus	50/250	Inhalation powder, pre-dispensed	Inhalation	Blister. Double foil 28 or 60 dose	1x28, 1x60, 2x60, 3x60, 10x60 doses
Portugal	Glaxo Wellcome Farmacêutica, Lda. Rua Dr. António Loureiro Borges, 3, Arquiparque , Miraflores 1495-131 Algés	Seretaide Diskus	50/100	Inhalation powder, pre-dispensed	Inhalation	Blister. Double foil 28 or 60 dose	1x28, 1x60, 2x60, 3x60, 10x60 doses

SPAIN	Glaxo Wellcome S.A. Parque Tecnologico de Madrid, Calle Severo Ochoa 2, 28760, Tres Cantos, Madrid	Seretide 50/500 Accuhaler	50/500	Inhalation powder, pre-dispensed	Inhalation	Blister. Double foil 28 or 60 dose	1x28, 1x60, 2x60, 3x60, 10x60 doses
SPAIN	Glaxo Wellcome S.A. Parque Tecnologico de Madrid, Calle Severo Ochoa 2, 28760, Tres Cantos, Madrid	Seretide 50/250 Accuhaler	50/250	Inhalation powder, pre-dispensed	Inhalation	Blister. Double foil 28 or 60 dose	1x28, 1x60, 2x60, 3x60, 10x60 doses
SPAIN	Glaxo Wellcome S.A. Parque Tecnologico de Madrid, Calle Severo Ochoa 2, 28760, Tres Cantos, Madrid	Seretide 50/100 Accuhaler	50/100	Inhalation powder, pre-dispensed	Inhalation	Blister. Double foil 28 or 60 dose	1x28, 1x60, 2x60, 3x60, 10x60 doses
Sweden	GlaxoSmithKline AB P.O. Box 263 SE-431 23 Molndal	Seretide Diskus	50/100, 50/250 and 50/500	Inhalation powder, pre-dispensed	Inhalation	Blister. Double foil 28 or 60 dose	1x28, 1x60, 2x60, 3x60, 10x60 doses
UK	Glaxo Wellcome UK Limited: trading as Allen & Hanburys Stockley Park West; Uxbridge, Middx, UB11 1BT	Seretide Accuhaler	50/100	Inhalation powder, pre-dispensed	Inhalation	Blister. Double foil 28 or 60 dose	28,60,120,180 and 600 actuations
UK	Glaxo Wellcome UK Limited: trading as Allen & Hanburys Stockley Park West; Uxbridge, Middx, UB11 1BT	Seretide Accuhaler	50/250	Inhalation powder, pre-dispensed	Inhalation	Blister. Double foil 28 or 60 dose	28,60,120,180 and 600 actuations
UK	Glaxo Wellcome UK Limited: trading as Allen & Hanburys Stockley Park West; Uxbridge, Middx, UB11 1BT	Seretide Accuhaler	50/500	Inhalation powder, pre-dispensed	Inhalation	Blister. Double foil 28 or 60 dose	28,60,120,180 and 600 actuations

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF SALMETEROL AND FLUTICASONE PROPIONATE FIXED COMBINATION MEDICINAL PRODUCTS (see Annex I)

The CPMP considered that the restricted indication (i.e. "*symptomatic treatment of patients with severe COPD (FEV_1 <50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy*") more closely mirrors the current clinical recommendations on the management of COPD (e.g. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (GOLD) guidelines). In patients with advanced COPD, 10% improvement in FEV1 for the combination compared to placebo would be clinically beneficial. Also the fixed combination shows an advantage in lung function over its separate components. The dose response curve is not steep for either of the components and neither has a narrow therapeutic window. Therefore, it can be anticipated that the requirement to titrate the individual components will be small. Consequently little clinical freedom will be lost through the use of a fixed dose combination. Moreover, the separate components, a long acting β-agonist and an inhaled steroid, are standard pharmacological interventions in the management of advanced COPD; their availability in the same delivery system could represent a simplification of treatment for patients. The adverse event profile of salmeterol and fluticasone fixed combination in patients with COPD was in general similar to that seen with other inhaled steroids and does not preclude its use in the proposed therapeutic indication.

GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS

Whereas

- Salmeterol and fluticasone fixed combination has been shown to be effective in patients with severe COPD (FEV_1 <50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy;

- The available safety data does not support the existence of major unexpected risks;

- Overall the balance of risks and benefits of the above-concerned medicinal products is favourable for the new restricted indication (i.e.: "*symptomatic treatment of patients with severe COPD (FEV_1 <50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy*")

the CPMP has recommended the granting of the variation of the Marketing Authorisations for which the amended Summary of Product Characteristics is set out in Annex III for salmeterol and fluticasone propionate fixed combination medicinal products (see Annex I).

ANNEX III

AMENDED SUMMARY OF PRODUCT CHARACTERISTICS OF THE REFERENCE MEMBER STATE

Note: This SPC is the one that was annexed to the Commission Decision on this Article 7(5) referral for salmeterol/fluticasone propionate containing medicinal products. The text was valid at that time.

After the Commission Decision, the Member State competent authorities will update the product information as required. Therefore, this SPC may not necessarily represent the current text.

1. NAME OF THE MEDICINAL PRODUCT

<Invented name> 50/100 microgram/dose inhalation powder, pre-dispensed.
<Invented name> 50/250 microgram/dose inhalation powder, pre-dispensed.
<Invented name> 50/500 microgram/dose inhalation powder, pre-dispensed.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Inhalation powder, pre-dispensed.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Asthma

<Invented name> 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: <invented name> 50/100 microgram strength is not appropriate in adults and children with severe asthma.

Chronic Obstructive Pulmonary Disease

<Invented name> is indicated for the symptomatic treatment of patients with severe COPD (FEV_1 < 50 % predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy.

4.2 Posology and method of administration

<Invented name> is for inhalation use only.

Patients should be made aware that <invented name> must be used daily for optimum benefit, even when asymptomatic.

Patients should be regularly reassessed by a doctor, so that the strength of <invented name> 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 <invented name> 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 <invented name> containing the appropriate fluticasone propionate dosage for the severity of their disease. 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.

Children 4 years and older:

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

There are no data available for use of <invented name> 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 <invented name> 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

<Invented name> is contraindicated in patients with hypersensitivity to any of the active substances or to the excipient.

4.4 Special warnings and special 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.

<Invented name> 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. <Invented name> is not intended for the initial management of asthma until the need for and approximate dosage of corticosteroids has been established.

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 <invented name> has failed to give adequate control of asthma.

For patients with asthma or COPD, consideration should be given to additional corticosteroid therapies.

Treatment with <invented name> 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, <invented name> should be administered with caution in patients with pulmonary tuberculosis.

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

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. <Invented name> should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

<Invented name> 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 <invented name> 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 adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. It is important, therefore, for asthma patients that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control is maintained.

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

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.

4.5 Interaction with other medicinal products and other forms of interaction

Due to the very low plasma concentrations achieved after inhaled dosing clinically significant drug interactions are in general unlikely. Care should be taken when co-administering known strong CYP3A4 inhibitors (e.g. ketoconazole, ritonavir) as there is potential for increased systemic exposure to fluticasone propionate. Any increased exposure during long-term concomitant treatment may can result in enhanced cortisol suppression. A few cases of such significant drug interactions have been reported (see 4.4 'Special Warnings and Precautions for Use').
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.

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 <invented name> 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 <invented name> 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 <invented name> 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. As with other inhalation therapy, paradoxical bronchospasm may occur.
Adverse events which have been associated with salmeterol or fluticasone propionate are given below.

Salmeterol:

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.

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

There have been reports of arthralgia, myalgia, muscle cramps, oropharyngeal irritation and hypersensitivity reactions, including rash, oedema and angioedema.

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 using the product. Symptomatic candidiasis can be treated with topical anti-fungal therapy whilst still continuing with the <invented name>.

Cutaneous hypersensitivity reactions have been reported.

Rare cases of facial and oropharyngeal oedema have been reported.

Possible systemic effects include 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').

<Invented name> clinical trials:

The following undesirable effects were commonly (> 1/100 and < 1/10) reported:
Hoarseness/dysphonia, throat irritation, headache, candidiasis of mouth and throat and palpitations.

4.9 Overdose

There are no data available from clinical trials on overdose with <invented name>, 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 <invented name> 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 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. However, if higher than recommended dosage is continued over prolonged periods, some degree of adrenal suppression may result. Monitoring of adrenal reserve may be necessary. In cases of fluticasone propionate overdose <invented name> therapy may still be continued at a suitable dosage for symptom control (see 4.4 'Special Warnings and Precautions for Use').

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Adrenergics and other anti-asthmatics, ATC code: R03AK06

<Invented name> COPD clinical trials:

Placebo-controlled clinical trials, over 6 and 12 months, have shown that regular use of <invented name> 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:

<Invented name> 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 (1150 ml/min), a large volume of distribution at steady-state (approximately 300 l) 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.

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 Instructions for use and handling

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

To be completed as appropriate

8. MARKETING AUTHORISATION NUMBER(S)

To be completed as appropriate

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be completed as appropriate

10. DATE OF REVISION OF THE TEXT

To be completed as appropriate

