Safeguarding public health

MHRA

Public Assessment Report

Mutual Recognition Procedure

Serevent Evohaler/Salmeterol 25 micrograms per actuation pressurised inhalation suspension

UK/H/880-883/001/MR

UK licence no: PL 10949/0369, 71-73

Glaxo Wellcome UK Ltd

Lay Summary

The MHRA granted Glaxo Wellcome UK Ltd Marketing Authorisations (licenses) for the medicinal product Serevent Evohaler and three duplicate licences approved under the name Salmeterol 25 micrograms per actuation pressurised inhalation suspension (PL 10949/0369, 71-73) on 28th October 2005. The MHRA then acted as Reference Member State (RMS) in the Mutual Recognition Procedure for this product. This procedure was completed on 28th June 2006.

These are prescription only medicines (POM) for the treatment of:

> Regular symptomatic add-on treatment of reversible airways obstruction in patients with asthma, including those with nocturnal asthma, who are inadequately controlled on inhaled corticosteroids in accordance with current treatment guidelines. Treatment of chronic obstructive pulmonary disease (COPD). Prevention of exercise-induced asthma.

Salmeterol 25 micrograms per actuation pressurised inhalation suspension contains the active ingredient salmeterol xinafoate. Salmeterol xinafoate is a 'long-acting bronchodilator'. It helps the airways in the lungs to stay open.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Serevent Evohaler/Salmeterol 25 micrograms per actuation pressurised inhalation suspension outweighed the risks, hence Marketing Authorisations were granted.

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Module 1

Product Name	UK/H/0880/001/MR: Serevent Evohaler 25 microgram per actuation pressurised inhalation suspension UK/H/0881/001/MR: Salmeterol 25 microgram per actuation pressurised inhalation suspension UK/H/0882/001/MR: Salmeterol 25 microgram per actuation pressurised inhalation suspension UK/H/0883/001/MR: Salmeterol 25 microgram per actuation pressurised inhalation suspension
Type of Application	Full Dossier, 8.3 [formerly Article 8.3(i)]
Active Substance	Salmeterol xinafoate
Form	25 micrograms per actuation pressurised inhalation suspension
Strength	25 micrograms per actuation
MA Holder	Glaxo Wellcome UK Ltd, Stockley Park West, Uxbridge, Middlesex UB11 1BT UK
RMS	UK
CMS	UK/H/0880/001/MR: Austria, Belgium, Denmark, Estonia, Finland, Germany, Hungary, Iceland, Ireland, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Slovak Republic, Slovenia , Sweden (licence cancelled in Finland 26/03/2008) UK/H/0881/001/MR: Belgium, Germany, Ireland, Lithuania, Luxembourg, Netherlands, Poland (licence cancelled in Ireland 20/12/2006, and cancelled in Belgium and Luxembourg 17/12/2007) UK/H/0882/001/MR: Germany, The Netherlands UK/H/0883/001/MR: Germany, The Netherlands
Procedure Number	UK/H/0880-3/001/MR
Timetable	Day 90 – 28th June 2006

Module 2

European Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Serevent Evohaler ▼ 25 micrograms per actuation pressurised inhalation suspension.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One metered dose (ex-valve) contains 25 micrograms salmeterol (as xinafoate). This is equivalent to a delivered dose (ex-actuator) of 21 micrograms salmeterol (as xinafoate).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pressurised inhalation suspension.

White to off white suspension sealed in an aluminium canister in a green actuator.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Regular symptomatic add-on treatment of reversible airways obstruction in patients with asthma, including those with nocturnal asthma, who are inadequately controlled on inhaled corticosteroids in accordance with current treatment guidelines. Treatment of Chronic Obstructive Pulmonary Disease (COPD). Prevention of exercise-induced asthma.

4.2 Posology and method of administration

Serevent Evohaler is for inhalation use only.

Serevent Evohaler should be used regularly. The full benefits of treatment will be apparent after several doses of the medicinal product. As there may be adverse reactions associated with excessive dosing with this class of medicinal product, the dosage or frequency of administration should only be increased on medical advice.

Recommended Doses:

Asthma

Adults and adolescents 12 years and older:

Two actuations of 25 micrograms salmeterol twice daily.

In asthma patients with more severe airways obstruction up to four inhalations of 25 micrograms of salmeterol twice daily may be of benefit.

Children aged 4 years and older:

Two actuations of 25 micrograms salmeterol twice daily.

Children below 4 years of age:

Serevent Evohaler is not recommended for use in children below four years of age due to insufficient data on safety and efficacy.

COPD

Adults: Two actuations of 25 micrograms salmeterol twice daily.

Children: There is no relevant indication for use of Serevent Evohaler in children.

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 on the use of Serevent Evohaler in patients with hepatic impairment.

INSTRUCTIONS FOR USE:
Patients should be carefully instructed in the proper use of their inhaler (see Patient Information Leaflet).

1. Patients should remove the mouthpiece cover by gently squeezing the sides of the cover.

2. Patients should check inside and outside of the inhaler including the mouthpiece for the presence of loose objects.

3. Patients should shake the inhaler well to ensure that any loose objects are removed and that the contents of the inhaler are evenly mixed. Before using for the first time or if the inhaler has not been used for a week patients should release one puff into the air to make sure that it works.

4. Patients should hold the inhaler upright between fingers and thumb with their thumb on the base, below the mouthpiece.

5. Patients should breathe out as far as is comfortable and then place the mouthpiece in their mouth between their teeth and close their lips around it. Patients should be instructed not to bite the mouthpiece.

6. Just after starting to breathe in through their mouth patients should press down on the top of the inhaler to release salmeterol while still breathing in steadily and deeply.

7. While holding their breath, patients should take the inhaler from their mouth and take their finger from the top of the inhaler. They should continue holding their breath for as long as is comfortable.

8. If patients are going to take a further puff, they should keep the inhaler upright and wait about half a minute before repeating steps 3 to 7.

9. After use patients should always replace the mouthpiece cover to keep out dust and fluff.

10. Patients should replace the mouthpiece cover by firmly pushing and snapping the cap into position.

Important:
Patients should not rush stages 5, 6 and 7. It is important that they start to breathe in as slowly as possible just before operating their inhaler.

Patients should practise in front of a mirror for the first few times. If they see "mist" coming from the top of their inhaler or the sides of their mouth they should start again from stage 2.

Serevent Evohaler should be used with a Volumatic spacer device by patients who find it difficult to synchronise aerosol actuation with inspiration of breath which is often the case for children and the elderly.

Cleaning:
The inhaler should be cleaned at least once a week by:
1. Removing the mouthpiece cover.

2. Wiping the inside and outside of the mouthpiece and the plastic casing with a dry cloth or tissue.

3. Replacing the mouthpiece cover.

The canister must not be removed from the plastic casing when cleaning the inhaler.

PATIENTS MUST NOT PUT THE METAL CANISTER INTO WATER.

4.3 Contraindications
Serevent Evohaler is contraindicated in patients with hypersensitivity to salmeterol xinafoate or to the excipient (see Section 6.1).

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.

Salmeterol should not be used (and is not sufficient) as the first treatment for asthma.

Salmeterol is not a replacement for oral or inhaled corticosteroids. Its use is complementary to them. Patients must be warned not to stop steroid therapy and not to reduce it without medical advice even if they feel better on salmeterol.

Salmeterol should not be used to treat acute asthma symptoms for which a fast and short-acting inhaled bronchodilator is required. Patients should be advised to have their medicinal product to be used for the relief of acute asthma symptoms available at all times.

Increasing use of short-acting bronchodilators to relieve asthma symptoms indicates deterioration of asthma control. The patient should be instructed to seek medical advice if short-acting relief bronchodilator treatment becomes less effective or more inhalations than usual are required. In this situation the patient should be assessed and consideration given to the need for increased anti-inflammatory therapy (e.g. higher doses of inhaled corticosteroid or a course of oral corticosteroid). Severe exacerbations of asthma must be treated in the normal way.

Although Serevent may be introduced as add-on therapy when inhaled corticosteroids do not provide adequate control of asthma symptoms, patients should not be initiated on Serevent during an acute severe asthma exacerbation, or if they have significantly worsening or acutely deteriorating asthma.

Serious asthma-related adverse events and exacerbations may occur during treatment with Serevent. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on Serevent.

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. Under these circumstances daily peak flow monitoring may be advisable. For maintenance treatment of asthma salmeterol should be given in combination with inhaled or oral corticosteroids. Long-acting bronchodilators should not be the only or the main treatment in maintenance asthma therapy (see Section 4.1).

Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of Serevent. Regular review of patients as treatment is stepped down is important. The lowest effective dose of Serevent should be used.

Salmeterol should be administered with caution in patients with thyrotoxicosis.

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

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

Potentially serious hypokalaemia may result from β2 agonist therapy. Particular caution is advised in acute severe asthma as this effect may be potentiated by hypoxia and by concomitant treatment with xanthine derivatives, steroids and diuretics. Serum potassium levels should be monitored in such situations.

Data from a large clinical trial (the Salmeterol Multi-Center Asthma Research Trial, SMART) suggested African-American patients were at increased risk of serious respiratory-related events or deaths when using salmeterol compared with placebo (see section 5.1). It is not known if this was due to pharmacogenetic or other factors. Patients of black African or Afro-Caribbean ancestry should therefore be asked to continue treatment but to seek medical advice if asthma symptoms remained uncontrolled or worsen whilst using Serevent.

Patients should be instructed in the proper use of their inhaler and their technique checked to ensure optimum delivery of the inhaled medicinal product to the lungs.

As systemic absorption is largely through the lungs, the use of a spacer plus metered dose inhaler may vary the delivery to the lungs. It should be noted that this could potentially lead to an increase in the risk of systemic adverse effects so that dose adjustment may be necessary.

4.5 Interaction with other medicinal products and other forms of interaction

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

Potentially serious hypokalaemia may result from β_2 agonist therapy. Particular caution is advised in acute severe asthma as this effect may be potentiated by concomitant treatment with xanthine derivatives, steroids and diuretics.

4.6 Pregnancy and lactation

There are insufficient data on the use of salmeterol or this medicinal product during pregnancy and lactation in women to assess the possible harmful effects. In animal studies fetal abnormalities occur after administration of beta-2-adrenoreceptor agonists (see Section 5.3).

Use of Serevent Evohaler during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus.

It is unknown whether salmeterol is excreted in human breast milk. Animal studies in rats have shown excretion of salmeterol in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Serevent Evohaler should be made taking into account the benefit of breast-feeding to the child and the benefit of Serevent Evohaler therapy to the woman.

Studies of HFA-134a revealed no effects on the reproductive performance and lactation of adult or two successive generations of rats or on the fetal development of rats or rabbits.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: very common (≥ 1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000) and very rare (<1/10,000) including isolated reports. Common and uncommon events were generally determined from clinical trial data. The incidence on placebo was not taken into account. Very rare events are generally determined from post-marketing spontaneous data.

The following frequencies are estimated at the standard dose of 50mcg twice daily. Frequencies at the higher dose of 100mcg twice daily have also been taken to account where appropriate.

System Organ Class	*Adverse Reaction*	*Frequency*
Immune System Disorders	***Hypersensitivity reactions with the following manifestations:*** ***Rash (itching and redness)*** ***Anaphylactic reactions including oedema and angioedema, bronchospasm and anaphylactic shock***	 ***Uncommon*** ***Very Rare***
Metabolism & Nutrition Disorders	***Hypokalaemia*** ***Hyperglycaemia***	***Rare*** ***Very Rare***
Psychiatric Disorders	***Nervousness*** ***Insomnia***	***Uncommon*** ***Rare***
Nervous System Disorders	***Headache*** ***Tremor*** ***Dizziness***	***Common*** ***Common*** ***Rare***
Cardiac Disorders	***Palpitations*** ***Tachycardia*** ***Cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia and extrasystoles).***	***Common*** ***Uncommon*** ***Very Rare***
Respiratory, Thoracic & Mediastinal Disorders	***Oropharyngeal irritation*** ***Paradoxical bronchospasm***	***Very Rare*** ***Very Rare***
Gastro-Intestinal Disorders	***Nausea***	***Very Rare***
Musculoskeletal & Connective Tissue Disorders	***Muscle cramps*** ***Arthralgia***	***Common*** ***Very Rare***
General Disorders and Administration Site Conditions	***Non-specific chest pain***	***Very Rare***

The pharmacological side effects of beta-2 agonist treatment, such as tremor, headache and palpitations have been reported, but tend to be transient and to reduce with regular therapy. Tremor and tachycardia occur more commonly when administered at doses higher than 50mcg twice daily.

As with other inhalational therapy paradoxical bronchospasm may occur with an immediate increase in wheezing and fall in peak expiratory flow rate (PEFR) after dosing. This should be treated immediately with a fast-acting inhaled bronchodilator. Serevent Evohaler should be discontinued immediately, the patient assessed, and if necessary alternative therapy instituted (see Section 4.4).

4.9 Overdose

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.

Additionally hypokalaemia can occur and therefore serum potassium levels should be monitored. Potassium replacement should be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Selective beta-2-adrenoreceptor agonists.

ATC Code: R03AC12

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.

These pharmacological properties of salmeterol offer more effective protection against histamine-induced bronchoconstriction and produce a longer duration of bronchodilation, lasting for at least 12 hours, than recommended doses of conventional short-acting β_2 agonists. In man salmeterol inhibits the early and late phase response to inhaled allergen; the latter persisting for over 30 hours after a single dose when the bronchodilator effect is no longer evident. Single dosing with salmeterol attenuates bronchial hyper-responsiveness. These properties indicate that salmeterol has additional non-bronchodilator activity, but the full clinical significance is not yet clear. The mechanism is different from the anti-inflammatory effect of corticosteroids which should not be stopped or reduced when salmeterol is prescribed.

Salmeterol has been studied in the treatment of conditions associated with COPD and has been shown to improve symptoms, pulmonary function and quality of life.

The Salmeterol Multi-center Asthma Research Trial (SMART)

SMART was a multi-centre, randomised, double-blind, placebo-controlled, parallel group 28-week study in the US which randomised 13,176 patients to salmeterol (50µg twice daily) and 13,179 patients to placebo in addition to the patients' usual asthma therapy. Patients were enrolled if ≥12 years of age, with asthma and if currently using asthma medication (but not a LABA). Baseline ICS use at study entry was recorded, but not required in the study. The primary endpoint in SMART was the combined number of respiratory-related deaths and respiratory-related life-threatening experiences.

Key findings from SMART: primary endpoint

Patient group	Number of primary endpoint events /number of patients		Relative Risk (95% confidence intervals)
	salmeterol	placebo	
All patients	50/13,176	36/13,179	1.40 (0.91, 2.14)
Patients using inhaled steroids	23/6,127	19/6,138	1.21 (0.66, 2.23)
Patients not using inhaled steroids	27/7,049	17/7,041	1.60 (0.87, 2.93)
African-American patients	**20/2,366**	**5/2,319**	**4.10 (1.54, 10.90)**

(Risk in bold is statistically significant at the 95% level.)

Key findings from SMART by inhaled steroid use at baseline: secondary endpoints

	Number of secondary endpoint events /number of patients		Relative Risk (95% confidence intervals)
	salmeterol	placebo	
Respiratory -related death			
Patients using inhaled steroids	10/6127	5/6138	2.01 (0.69, 5.86)
Patients not using inhaled steroids	14/7049	6/7041	2.28 (0.88, 5.94)
Combined asthma-related death or life-threatening experience			
Patients using inhaled steroids	16/6127	13/6138	1.24 (0.60, 2.58)
Patients not using inhaled steroids	**21/7049**	**9/7041**	**2.39 (1.10, 5.22)**
Asthma-related death			
Patients using inhaled steroids	4/6127	3/6138	1.35 (0.30, 6.04)
Patients not using inhaled steroids	9/7049	0/7041	*

(*=could not be calculated because of no events in placebo group. Risk in bold is statistically significant at the 95% level. The secondary endpoints in the table above reached statistical significance in the whole population.) The secondary endpoints of combined all-cause death or life-threatening experience, all cause death, or all cause hospitalisation did not reach statistical significance in the whole population.

5.2 Pharmacokinetic properties

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 active substance in plasma due to the low plasma concentrations at therapeutic doses (approximately 200 picogram/ml or less) achieved after inhaled dosing.

5.3 Preclinical safety data

The only findings in animal studies with relevance for clinical use were the effects associated with exaggerated pharmacological activity.

In reproduction and development toxicity studies with salmeterol xinafoate there were no effects in rats. In rabbits, typical beta-2 agonist embryo fetal toxicity (cleft palate, premature opening of the eye lids, sternebral fusion and reduced ossification rate of the frontal cranial bones) occurred at high exposure levels (approximately 20 times the maximum recommended human daily dose based on the comparison of AUCs).

Salmeterol xinafoate was negative in a range of standard genotoxicity studies.

The non-CFC propellant, norflurane, has been shown to have no toxic effect at very high vapour concentrations, far in excess of those likely to be experienced by patients, in a wide range of animal species exposed daily for periods of up to two years including no effects on the reproductive performance or embryofetal development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Norflurane (HFA 134a), a hydrofluoroalkane (non-chlorofluorocarbon) propellant

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Replace the mouthpiece cover firmly and snap it into position.

Do not store above 30°C.

Pressurised container. Do not expose to temperatures higher than 50°C. Do not puncture, break or burn even when apparently empty.

6.5 Nature and contents of container

The suspension is contained in an internally lacquered, 8ml aluminium alloy pressurised container sealed with a metering valve. The containers are fitted into plastic actuators incorporating an atomising mouthpiece and fitted with dustcaps. One pressurised container delivers 120 actuations.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

GlaxoWellcome UK Ltd
Trading as Allen & Hanburys
Stockley Park West
Uxbridge
Middlesex UB11 1BT.
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

PL 10949/0369

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/10/2005

10 DATE OF REVISION OF THE TEXT

11/06/2007

1. NAME OF THE MEDICINAL PRODUCT

Salmeterol ▼25 micrograms per actuation pressurised inhalation suspension.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One metered dose (ex-valve) contains 25 micrograms salmeterol (as xinafoate). This is equivalent to a delivered dose (ex-actuator) of 21 micrograms salmeterol (as xinafoate).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pressurised inhalation suspension.

White to off white suspension sealed in an aluminium canister in a green actuator.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Regular symptomatic add-on treatment of reversible airways obstruction in patients with asthma, including those with nocturnal asthma, who are inadequately controlled on inhaled corticosteroids in accordance with current treatment guidelines. Treatment of Chronic Obstructive Pulmonary Disease (COPD). Prevention of exercise-induced asthma.

4.2 Posology and method of administration

Salmeterol Evohaler is for inhalation use only.

Salmeterol Evohaler should be used regularly. The full benefits of treatment will be apparent after several doses of the medicinal product. As there may be adverse reactions associated with excessive dosing with this class of medicinal product, the dosage or frequency of administration should only be increased on medical advice.

Recommended Doses:
Asthma
Adults and adolescents 12 years and older:
Two actuations of 25 micrograms salmeterol twice daily.

In asthma patients with more severe airways obstruction up to four inhalations of 25 micrograms of salmeterol twice daily may be of benefit.

Children aged 4 years and older:
Two actuations of 25 micrograms salmeterol twice daily.

Children below 4 years of age:
Salmeterol Evohaler is not recommended for use in children below four years of age due to insufficient data on safety and efficacy.

COPD
Adults: Two actuations of 25 micrograms salmeterol twice daily.
Children: There is no relevant indication for use of Salmeterol Evohaler in children.

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 on the use of Salmeterol Evohaler in patients with hepatic impairment.

INSTRUCTIONS FOR USE:
Patients should be carefully instructed in the proper use of their inhaler (see Patient Information Leaflet).

1. Patients should remove the mouthpiece cover by gently squeezing the sides of the cover.

2. Patients should check inside and outside of the inhaler including the mouthpiece for the presence of loose objects.

3. Patients should shake the inhaler well to ensure that any loose objects are removed and that the contents of the inhaler are evenly mixed. Before using for the first time or if the inhaler has not been used for a week patients should release one puff into the air to make sure that it works.

4. Patients should hold the inhaler upright between fingers and thumb with their thumb on the base, below the mouthpiece.

5. Patients should breathe out as far as is comfortable and then place the mouthpiece in their mouth between their teeth and close their lips around it. Patients should be instructed not to bite the mouthpiece.

6. Just after starting to breathe in through their mouth patients should press down on the top of the inhaler to release salmeterol while still breathing in steadily and deeply.

7. While holding their breath, patients should take the inhaler from their mouth and take their finger from the top of the inhaler. They should continue holding their breath for as long as is comfortable.

8. If patients are going to take a further puff, they should keep the inhaler upright and wait about half a minute before repeating steps 3 to 7.

9. After use patients should always replace the mouthpiece cover to keep out dust and fluff.

10. Patients should replace the mouthpiece cover by firmly pushing and snapping the cap into position.

Important:
Patients should not rush stages 5, 6 and 7. It is important that they start to breathe in as slowly as possible just before operating their inhaler.

Patients should practise in front of a mirror for the first few times. If they see "mist" coming from the top of their inhaler or the sides of their mouth they should start again from stage 2.

Salmeterol Evohaler should be used with a Volumatic spacer device by patients who find it difficult to synchronise aerosol actuation with inspiration of breath which is often the case for children and the elderly.

Cleaning:
The inhaler should be cleaned at least once a week by:
1. Removing the mouthpiece cover.

2. Wiping the inside and outside of the mouthpiece and the plastic casing with a dry cloth or tissue.

3. Replacing the mouthpiece cover.

The canister must not be removed from the plastic casing when cleaning the inhaler.
PATIENTS MUST NOT PUT THE METAL CANISTER INTO WATER.

4.3 Contraindications

Salmeterol Evohaler is contraindicated in patients with hypersensitivity to salmeterol xinafoate or to the excipient (see Section 6.1).

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.

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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. Under these circumstances daily peak flow monitoring may be advisable. For maintenance treatment of asthma salmeterol should be given in combination with inhaled or oral corticosteroids. Long-acting bronchodilators should not be the only or the main treatment in maintenance asthma therapy (see Section 4.1).

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Salmeterol should be administered with caution in patients with thyrotoxicosis.

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

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

Potentially serious hypokalaemia may result from β2 agonist therapy. Particular caution is advised in acute severe asthma as this effect may be potentiated by hypoxia and by concomitant treatment with xanthine derivatives, steroids and diuretics. Serum potassium levels should be monitored in such situations.

Data from a large clinical trial (the Salmeterol Multi-Center Asthma Research Trial, SMART) suggested African-American patients were at increased risk of serious respiratory-related events or deaths when using salmeterol compared with placebo (see section 5.1). It is not known if this was due to pharmacogenetic or other factors. Patients of black African or Afro-Caribbean ancestry should therefore be asked to continue treatment but to seek medical advice if asthma symptoms remained uncontrolled or worsen whilst using Salmeterol.

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As systemic absorption is largely through the lungs, the use of a spacer plus metered dose inhaler may vary the delivery to the lungs. It should be noted that this could potentially lead to an increase in the risk of systemic adverse effects so that dose adjustment may be necessary.

4.5 Interaction with other medicinal products and other forms of interaction

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

Potentially serious hypokalaemia may result from β_2 agonist therapy. Particular caution is advised in acute severe asthma as this effect may be potentiated by concomitant treatment with xanthine derivatives, steroids and diuretics.

4.6 Pregnancy and lactation

There are insufficient data on the use of salmeterol or this medicinal product during pregnancy and lactation in women to assess the possible harmful effects. In animal studies fetal abnormalities occur after administration of beta-2-adrenoreceptor agonists (see Section 5.3).

Use of Salmeterol Evohaler during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus.

It is unknown whether salmeterol is excreted in human breast milk. Animal studies in rats have shown excretion of salmeterol in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Salmeterol Evohaler should be made taking into account the benefit of breast-feeding to the child and the benefit of Salmeterol Evohaler therapy to the woman.

Studies of HFA-134a revealed no effects on the reproductive performance and lactation of adult or two successive generations of rats or on the fetal development of rats or rabbits.

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4.8 Undesirable effects

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: very common (≥ 1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000) and very rare (<1/10,000) including isolated reports. Common and uncommon events were generally determined from clinical trial data. The incidence on placebo was not taken into account. Very rare events are generally determined from post-marketing spontaneous data.

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Metabolism & Nutrition Disorders	***Hypokalaemia*** ***Hyperglycaemia***	***Rare*** ***Very Rare***
Psychiatric Disorders	***Nervousness*** ***Insomnia***	***Uncommon*** ***Rare***
Nervous System Disorders	***Headache*** ***Tremor*** ***Dizziness***	***Common*** ***Common*** ***Rare***
Cardiac Disorders	***Palpitations*** ***Tachycardia*** ***Cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia and extrasystoles).***	***Common*** ***Uncommon*** ***Very Rare***
Respiratory, Thoracic & Mediastinal Disorders	***Oropharyngeal irritation*** ***Paradoxical bronchospasm***	***Very Rare*** ***Very Rare***
Gastro-Intestinal Disorders	***Nausea***	***Very Rare***
Musculoskeletal & Connective Tissue Disorders	***Muscle cramps*** ***Arthralgia***	***Common*** ***Very Rare***
General Disorders and Administration Site Conditions	***Non-specific chest pain***	***Very Rare***

The pharmacological side effects of beta-2 agonist treatment, such as tremor, headache and palpitations have been reported, but tend to be transient and to reduce with regular therapy. Tremor and tachycardia occur more commonly when administered at doses higher than 50mcg twice daily.

As with other inhalational therapy paradoxical bronchospasm may occur with an immediate increase in wheezing and fall in peak expiratory flow rate (PEFR) after dosing. This should be treated immediately with a fast-acting inhaled bronchodilator. Salmeterol Evohaler should be discontinued immediately, the patient assessed, and if necessary alternative therapy instituted (see Section 4.4).

4.9 Overdose

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.

Additionally hypokalaemia can occur and therefore serum potassium levels should be monitored. Potassium replacement should be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Selective beta-2-adrenoreceptor agonists.

ATC Code: R03AC12

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.

These pharmacological properties of salmeterol offer more effective protection against histamine-induced bronchoconstriction and produce a longer duration of bronchodilation, lasting for at least 12 hours, than recommended doses of conventional short-acting β2 agonists. In man salmeterol inhibits the early and late phase response to inhaled allergen; the latter persisting for over 30 hours after a single dose when the bronchodilator effect is no longer evident. Single dosing with salmeterol attenuates bronchial hyper-responsiveness. These properties indicate that salmeterol has additional non-bronchodilator activity, but the full clinical significance is not yet clear. The mechanism is different from the anti-inflammatory effect of corticosteroids which should not be stopped or reduced when salmeterol is prescribed.

Salmeterol has been studied in the treatment of conditions associated with COPD and has been shown to improve symptoms, pulmonary function and quality of life.

The Salmeterol Multi-center Asthma Research Trial (SMART)

SMART was a multi-centre, randomised, double-blind, placebo-controlled, parallel group 28-week study in the US which randomised 13,176 patients to salmeterol (50μg twice daily) and 13,179 patients to placebo in addition to the patients' usual asthma therapy. Patients were enrolled if ≥12 years of age, with asthma and if currently using asthma medication (but not a LABA). Baseline ICS use at study entry was recorded, but not required in the study. The primary endpoint in SMART was the combined number of respiratory-related deaths and respiratory-related life-threatening experiences.

Key findings from SMART: primary endpoint

Patient group	Number of primary endpoint events /number of patients		Relative Risk (95% confidence intervals)
	salmeterol	placebo	
All patients	50/13,176	36/13,179	1.40 (0.91, 2.14)
Patients using inhaled steroids	23/6,127	19/6,138	1.21 (0.66, 2.23)
Patients not using inhaled steroids	27/7,049	17/7,041	1.60 (0.87, 2.93)
African-American patients	**20/2,366**	**5/2,319**	**4.10 (1.54, 10.90)**

(Risk in bold is statistically significant at the 95% level.)

Key findings from SMART by inhaled steroid use at baseline: secondary endpoints

	Number of secondary endpoint events /number of patients		Relative Risk (95% confidence intervals)
	salmeterol	placebo	
Respiratory -related death			
Patients using inhaled steroids	10/6127	5/6138	2.01 (0.69, 5.86)
Patients not using inhaled steroids	14/7049	6/7041	2.28 (0.88, 5.94)
Combined asthma-related death or life-threatening experience			
Patients using inhaled steroids	16/6127	13/6138	1.24 (0.60, 2.58)
Patients not using inhaled steroids	**21/7049**	**9/7041**	**2.39 (1.10, 5.22)**
Asthma-related death			
Patients using inhaled steroids	4/6127	3/6138	1.35 (0.30, 6.04)
Patients not using inhaled steroids	9/7049	0/7041	*

(*=could not be calculated because of no events in placebo group. Risk in bold is statistically significant at the 95% level. The secondary endpoints in the table above reached statistical significance in the whole population.) The secondary endpoints of combined all-cause death or life-threatening experience, all cause death, or all cause hospitalisation did not reach statistical significance in the whole population.

5.2 Pharmacokinetic properties

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 active substance in plasma due to the low plasma concentrations at therapeutic doses (approximately 200 picogram/ml or less) achieved after inhaled dosing.

5.3 Preclinical safety data

The only findings in animal studies with relevance for clinical use were the effects associated with exaggerated pharmacological activity.

In reproduction and development toxicity studies with salmeterol xinafoate there were no effects in rats. In rabbits, typical beta-2 agonist embryo fetal toxicity (cleft palate, premature opening of the eye lids, sternebral fusion and reduced ossification rate of the frontal cranial bones) occurred at high exposure levels (approximately 20 times the maximum recommended human daily dose based on the comparison of AUCs).

Salmeterol xinafoate was negative in a range of standard genotoxicity studies.

The non-CFC propellant, norflurane, has been shown to have no toxic effect at very high vapour concentrations, far in excess of those likely to be experienced by patients, in a wide range of animal species exposed daily for periods of up to two years including no effects on the reproductive performance or embryofetal development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Norflurane (HFA 134a), a hydrofluoroalkane (non-chlorofluorocarbon) propellant

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Replace the mouthpiece cover firmly and snap it into position.

Do not store above 30°C.

Pressurised container. Do not expose to temperatures higher than 50°C. Do not puncture, break or burn even when apparently empty.

6.5 Nature and contents of container

The suspension is contained in an internally lacquered, 8ml aluminium alloy pressurised container sealed with a metering valve. The containers are fitted into plastic actuators incorporating an atomising mouthpiece and fitted with dustcaps. One pressurised container delivers 120 actuations.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

GlaxoWellcome UK Ltd
Trading as Allen & Hanburys
Stockley Park West
Uxbridge
Middlesex UB11 1BT.
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 10949/0371
PL 10949/0372
PL 10949/0373

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/10/2005

10 DATE OF REVISION OF THE TEXT

11/06/2007

Module 3
Package Leaflet

Rare (affects less than 1 person in 1,000):

- Feeling dizzy
- Being unable to sleep or finding sleep difficult
- A reduction in the amount of potassium in your blood (you may get an uneven heartbeat, muscle weakness, cramp).

Very rare (affects less than 1 person in 10,000):

- **Breathing difficulties or wheezing that gets worse straight after taking Serevent. If this happens stop using your Serevent Evohaler. Use your fast-acting 'reliever' inhaler to help your breathing and tell your doctor straight away.**
- Uneven heartbeat or your heart gives an extra beat (arrhythmias). If this happens do not stop using Serevent but tell your doctor.
- Sore mouth or throat
- Feeling sick (nausea)
- Aching, swollen joints or chest pain.

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.

5 How to store Serevent Evohaler

- **Keep out of the reach and sight of children.**
- Straight after use, replace the mouthpiece cover firmly and click it into position. Do not use excessive force.
- Do not store above 30°C.
- The metal canister contains a pressurised liquid. Do not puncture, break or burn it even if you think it is empty.
- Do not use Serevent after the expiry date which is stated on the label and carton. The expiry date refers to the last day of the month.

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 Serevent Evohaler contains

- Each puff provides 25 micrograms of the active ingredient salmeterol.
- There are 120 puffs in each canister.
- The other ingredient is norflurane (HFA 134a).

What Serevent Evohaler looks like and contents of the pack

Pressurised inhalation, suspension. The pressurised canister contains a white to off white suspension for inhalation.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
GlaxoWellcome UK Ltd.
trading as Allen & Hanburys
Stockley Park West
Uxbridge
Middlesex UB11 1BT

Manufacturer
Glaxo Wellcome Production
Zone Industrielle No.2
23 Rue Lavoisier
27000 Evreux
France

Other formats:

To listen to or request a copy of this leaflet in Braille, large print or audio please call, free of charge:

0800 198 5000 (UK Only)

Please be ready to give the following information:

Product name	**Serevent Evohaler 25 micrograms per actuation**
Reference number	10949/0369

This is a service provided by the Royal National Institute of the Blind.

Leaflet date: June 2007

ALLEN & HANBURYS

ALLEN & HANBURYS

Package Leaflet: Information for the User

Serevent™ Evohaler™

25 micrograms per actuation (per puff)
Pressurised inhalation, suspension
salmeterol

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 Serevent Evohaler is and what it is used for

- Serevent Evohaler contains the medicine salmeterol. It is a 'long-acting bronchodilator'. It helps the airways in the lungs to stay open. This makes it easier for air to get in and out. The effects are usually felt within 10 to 20 minutes and last for 12 hours or more.
- The doctor has prescribed it to help prevent breathing problems. These could be caused by asthma. Taking Serevent Evohaler regularly will help prevent asthma attacks. This also includes asthma brought on by exercise or at night.
- Taking Serevent Evohaler regularly will also help prevent breathing problems caused by other chest illnesses such as Chronic Obstructive Pulmonary Disease (COPD).
- Serevent Evohaler helps to stop breathlessness and wheezing coming on. It does not work once you are breathless or wheezy. If that happens you need to use a fast acting 'reliever' medicine, such as salbutamol.
- Serevent Evohaler is supplied to you in an inhaler. You breathe the medicine directly into your lungs.
- Serevent Evohaler contains norflurane. This is less harmful to the environment than older inhalers. Older inhalers may taste differently to Serevent Evohaler. This will make no difference to how your medicine works.

If you are being treated for asthma, you should always be given both a Serevent and a steroid inhaler to use together.

2 Before you use Serevent Evohaler

Do not take Serevent Evohaler if:

you are allergic (hypersensitive) to salmeterol or to the other ingredient norflurane (HFA 134a).

Take special care with Serevent Evohaler

- **If your asthma or breathing gets worse tell your doctor straight away.** You may find that you feel more wheezy, your chest feels tight more often or you may need to use more of your fast acting 'reliever' medicine. If any of these happen, do not increase your number of puffs of Serevent. Your chest condition may be getting worse and you could become seriously ill. See your doctor as you may need a change in asthma treatment.
- If you have been prescribed Serevent for your asthma, continue to use any other asthma medication you are already taking. These could include a steroid inhaler or steroid tablets. Continue taking the same doses as before, unless your doctor tells you otherwise. Do this even if you feel much better. **Do not stop taking your steroid inhaler (or any steroid tablets) when you start using Serevent.**
- Your doctor may want to check your health regularly if you have an overactive thyroid gland, diabetes mellitus (Serevent may increase your blood sugar) or heart disease, including an irregular or fast heartbeat.

Taking other medicines

- Please tell your doctor if you are taking or have recently taken any other medicines. This includes those for asthma or any other medicines obtained without a prescription. This is because Serevent may not be suitable to be taken with other medicines.

- Beta-Blockers should be avoided when taking Serevent, unless your doctor tells you to. Beta-blockers, including atenolol, propranolol and sotalol, are mostly used for high blood pressure or other heart conditions. Please tell your doctor if you are taking beta-blockers or have recently been prescribed beta-blockers as they may reduce or abolish the effects of salmeterol.
- Serevent can reduce the amount of potassium in your blood. If this happens you may notice an uneven heartbeat, muscle weakness or cramp. This is more likely to happen if you take Serevent with medicines used to treat high blood presssure (diuretics) and other medicines used to treat breathing problems such as theophylline or steroids. Your doctor may ask for you to have blood tests to check the amount of potassium in your blood. If you have any concerns discuss them with your doctor.

Pregnancy and breast-feeding

If you are pregnant, planning to get pregnant or breast-feeding, talk to your doctor before taking Serevent. Your doctor will assess whether you can take Serevent during this time.

Driving and using machines

The possible side effects associated with Serevent are unlikely to affect your ability to drive or use machines.

3 How to use Serevent Evohaler

- **If you are being treated for asthma, you should always be given both a Serevent and a steroid inhaler to use together.**
- Use Serevent every day, until your doctor advises you to stop.
- You will start to feel your medicine working within the first day of use.

Serevent is for inhalation by mouth only.

Adults and adolescents aged 12 years and older with Asthma

- The usual starting dose is 2 puffs twice a day.
- For people with more severe asthma, your doctor may increase your dose to 4 puffs twice a day.

Children with Asthma

- In children aged 4 to 12 the usual dose is 2 puffs twice a day.
- Serevent is not recommended for use in children below 4 years of age.

Adults with Chronic Obstructive Pulmonary Disease (COPD) including bronchitis and emphysema

- The usual starting dose is 2 puffs twice a day.
- Not applicable for children and adolescents.

Instructions for use

Your doctor, nurse or pharmacist should show you how to use your inhaler. They should check how you use it from time to time. Not using the inhaler properly or as prescribed, may mean that the medicine will not help your asthma or COPD as it should.

The medicine is contained in a pressurised canister in a plastic casing with a mouthpiece.

Testing your inhaler

1 When using your inhaler for the first time, test that it is working. Remove the mouthpiece cover by gently squeezing the sides with your thumb and forefinger and pull apart.

2 To make sure that it works, shake it well, point the mouthpiece away from you and press the canister to release a puff into the air. If you have not used the inhaler for a week or more, release one puff of medicine into the air.

Using your inhaler

It is important to start to breathe in as slowly as possible just before using your inhaler.

1 Stand or sit upright when using your inhaler.

2 Remove the mouthpiece cover (as shown in the first picture). Check inside and outside to make sure that the mouthpiece is clean and free of objects.

3 Shake the inhaler 4 or 5 times to ensure that any loose objects are removed and that the contents of the inhaler are evenly mixed.

4 Hold the inhaler upright with your thumb on the base, below the mouthpiece. Breathe out as far as is comfortable.

5 Place the mouthpiece in your mouth between your teeth. Close your lips around it. Do not bite.

6 Breathe in through your mouth. Just after starting to breathe in, press down on the top of the canister to release a puff of medicine. Do this while still breathing in steadily and deeply.

7 Hold your breath, take the inhaler from your mouth and your finger from the top of the inhaler. Continue holding your breath for a few seconds, or as long as is comfortable.

8 Wait about half a minute between taking each puff of medicine and then repeat steps 3 to 7.

9 After use always replace the mouthpiece cover immediately to keep out dust. Replace the cover by firmly pushing and snapping the cap into position.

Practise in front of a mirror for the first few times. If you see a 'mist' coming from the top of your inhaler or the sides of your mouth you should start again

If you or your child find it difficult to use Serevent Evohaler, it may be used with other devices to make its use easier e.g. a Haleraid$_{TM}$ or Volumatic$_{TM}$ spacer device. Serevent is also available in an alternative device. Talk to your doctor, nurse or pharmacist for further advice.

Cleaning your inhaler

To stop your inhaler blocking up, it is important to clean it at least once a week.

To clean your inhaler:

- Remove the mouthpiece cover.
- Do not remove the metal canister from the plastic casing at any time.
- Wipe the inside and outside of the mouthpiece and the plastic casing with a dry cloth or tissue.
- Replace the mouthpiece cover.

Do not put the metal canister in water.

If you use more Serevent Evohaler than you should

It is important to use the inhaler as instructed. If you accidentally take a larger dose than recommended, talk to your doctor or pharmacist. You may notice your heart beating faster than usual and that you feel shaky. You may also have a headache, muscle weakness and aching joints.

If you forget to use Serevent Evohaler

If you forget to use your inhaler, take your next dose when it is due. Do not take a double dose to replace the one you forgot.

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

4 Possible side effects

Like all medicines, Serevent can cause side effects, although not everybody gets them. To reduce the chances of side effects, your doctor will prescribe the lowest dose of Serevent to control your asthma or COPD. These are the side effects reported by people taking Serevent.

Allergic reactions: you may notice your breathing suddenly gets worse after using Serevent. You may be very wheezy and cough. You may also notice itching and swelling (usually of the face, lips, tongue or throat). If you get these effects or they happen suddenly after using Serevent, **tell your doctor straight away.** Allergic reactions to Serevent are very rare (they affect less than 1 person in 10,000).

Other side effects are listed below:

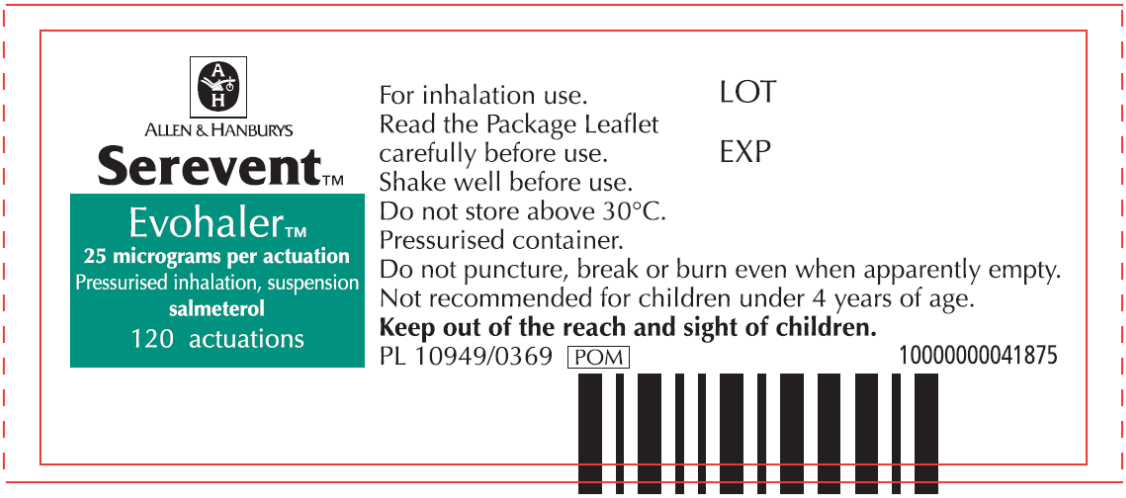
Common (affects less than between 1 person in 10):

- Muscle cramps
- Feeling shaky; fast or uneven heartbeat (palpitations), headache, shaking hands (tremor). Tremors are more likely if you are taking more than two puffs twice daily. These side effects do not last long and happen less as treatment with Serevent continues.

Uncommon (affects less than 1 person in 100):

- Rash
- Very fast heart rate (tachycardia). This is more likely to happen if you are taking more than two puffs twice daily.
- Feeling nervous.

Module 4
Labelling



Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considered that the applications for Serevent Evohaler/Salmeterol 25 micrograms per actuation pressurised inhalation suspension in the treatment of reversible airways obstruction in patients with asthma, including those with nocturnal asthma or chronic obstructive pulmonary disease (COPD), could be approved. National marketing authorisations were granted on 28th October 2005.

These applications concern complete applications submitted by Glaxo Wellcome UK Ltd, trading as Allen & Hanburys, under Article 8.1(a) of Directive 2001/83/EC for line extensions to their existing products, Serevent Diskhaler 50 micrograms, inhalation powder (PL 10949/0069) and Serevent Inhaler (25 micrograms per actuation, pressurised inhalation suspension) (PL 10949/0068).

Salmeterol xinafoate is a selective long-acting $beta_2$ adrenoceptor agonist and is a potent and long-lasting inhibitor of the release from the human lung of mast cell mediators such as histamine, leukotrienes and prostaglandin D_2. Salmeterol inhibits the early and late phase response to inhaled allergen, inhibition of the late phase response persisting for over 30 hours following a single dose. Salmeterol also attenuates bronchial hyperresponsiveness. Salmeterol produces bronchodilatation which lasts for at least 12 hours. The drug is particularly useful in patients with reversible airways obstruction who continue to experience symptoms despite treatment with an anti-inflammatory agent such as an inhaled corticosteroid. Guidelines for the management of reversible airways obstruction and particularly asthma recommends the addition of a long-acting $beta_2$ agonist to the treatment regimen in these patients and studies have shown that the addition of a long-acting $beta_2$ agonist provides better control of asthma than increasing the dose of inhaled corticosteroid. The mechanism of action of the two drugs is different; the corticosteroid should not be discontinued or the dose reduced when salmeterol is added to the treatment regimen. Salmeterol is administered via the orally inhaled route.

Salmeterol first received marketing approval for the treatment of Reversible Obstructive Airways Disease, in adults at doses of 50-100 μg BID in October 1990 and for use in children aged 4 years and above at a dose of 50 μg BID in July 1992, and has now been approved in more than 120 countries worldwide. Salmeterol xinafoate is also approved in over 40 countries, at a dose of 50 μg BID, for the treatment of COPD or chronic bronchitis. In addition, the salmeterol xinafoate/fluticasone propionate combination has been marketed as an MDI formulated with HFA 134a since June 2000.

Salmeterol xinafoate is formulated with the hydrofluoroalkane 1,1,1,2-tetrafluoroethane, propellant HFA-134a, as a non-chlorofluorocarbon (CFC) alternative propellant.

With the UK as reference member state a mutual recognition procedure (MRP) was undertaken. The marketing authorisation holder (Glaxo Wellcome UK Ltd, trading as Allen & Hanburys) applied for marketing authorisations in Austria, Belgium, Denmark, Estonia, Finland, Germany, Hungary, Ireland, Iceland, Lithuania, Luxembourg, Malta, The Netherlands, Norway, Poland, Sweden, Slovenia and Slovakia, although not all these markets applied for all four licences (see Module 1).

The UK was assured that acceptable standards of GMP are in place for this product at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

For manufacturing sites within the community, the UK has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the UK has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	UK/H/0880/001/MR: Serevent Evohaler 25 microgram per actuation pressurised inhalation suspension UK/H/0881/001/MR: Salmeterol 25 microgram per actuation pressurised inhalation suspension UK/H/0882/001/MR: Salmeterol 25 microgram per actuation pressurised inhalation suspension UK/H/0883/001/MR: Salmeterol 25 microgram per actuation pressurised inhalation suspension
Name(s) of the active substance(s) (INN)	Salmeterol (as xinafoate)
Pharmacotherapeutic classification (ATC code)	Adrenergic inhaled selective beta-2-adrenoceptor agonist (R03A C12)
Pharmaceutical form and strength(s)	25 micrograms per actuation
Reference numbers for the Mutual Recognition Procedure	UK/H/0880-3/001/MR
Reference Member State	United Kingdom
Member States concerned	UK/H/0880/001/MR: Austria, Belgium, Denmark, Estonia, Finland, Germany, Hungary, Iceland, Ireland, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Slovak Republic, Slovenia , Sweden (licence cancelled in Finland 26/03/2008) UK/H/0881/001/MR: Belgium, Germany, Ireland, Lithuania, Luxembourg, Netherlands, Poland (licence cancelled in Ireland 20/12/2006, and cancelled in Belgium and Luxembourg 17/12/2007) UK/H/0882/001/MR: Germany, The Netherlands UK/H/0883/001/MR: Germany, The Netherlands
Marketing Authorisation Number(s)	PL 10949/0369, 371-3
Name and address of the authorisation holder	Glaxo Wellcome UK Ltd, Stockley Park West, Uxbridge, Middlesex UB11 1BT UK

III SCIENTIFIC OVERVIEW AND DISCUSSION

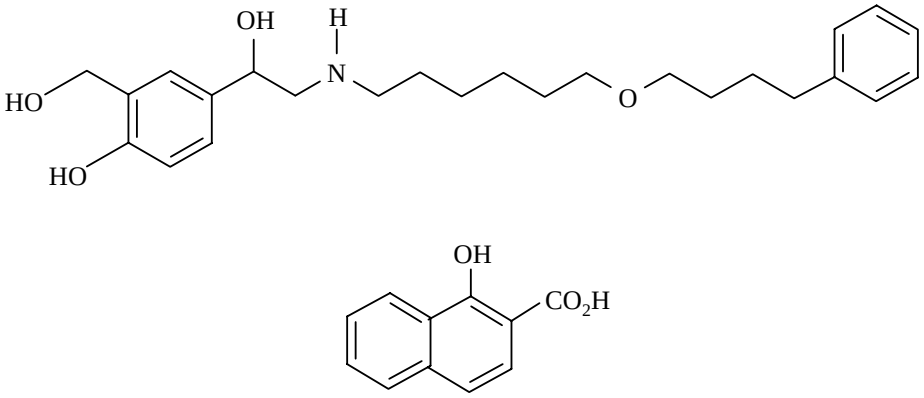
III.1 QUALITY ASPECTS

S. Active substance

INN/Ph.Eur name: Salmeterol xinafoate

Chemical name: (*RS*)-5-{1-Hydroxy-2-[6-(4-phenylbutoxy)hexylamino]ethyl}salicyl alcohol xinafoate

Structural formula:



Molecular formula: $C_{25}H_{37}NO_4C_{11}H_8O_3$

Appearance: A white to off-white powder

Molecular weight: 603.8

Salmeterol xinafoate has a European Pharmacopoeia monograph.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance, with suitable test methods and limits. The methods of testing and limits for residual solvents are in compliance with current guidelines. Batch analysis data are provided and comply with the proposed specification.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Suitable certificates of analysis have been provided for all reference standards used.

The active substance is packaged in polyethylene bags, which are placed in high density polyethylene drums and sealed.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug. The data support a retest period of 48 month for unmicronised salmeterol xinafoate and 36 month for the micronised drug.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipient norflurane (HFA 134a), a hydrofluoroalkane (non-chlorofluorocarbon) propellant. The excipient complies with current guidelines and contains no materials of animal or human origin.

Pharmaceutical development

The final formulation has been evaluated in line with the 'Note for guidance on requirements for pharmaceutical documentation for pressurised metered dose inhalation products' for appropriate parameters.

The manufacturing process development is consistent with the manufacture of other HFA-containing pressurised-metered dose inhalers by Glaxo Wellcome that have already been granted Marketing Authorisations.

The product is manufactured to comply with the specifications of the European Pharmacopoeia for microbial quality of inhaled preparations.

Manufacturing Process

A satisfactory batch formula has been provided for the manufacture of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container-Closure System

The suspension is contained in an internally lacquered, 8ml aluminium alloy pressurised container, sealed with a metering valve. The containers are fitted into plastic actuators, incorporating an atomising mouthpiece and fitted with dustcaps. One pressurised container delivers 120 actuations.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the relevant regulations regarding materials for use in contact with food.

Stability of the product

Stability studies were performed on batches of the finished product in the packaging proposed for marketing and in accordance with current guidelines. All results from

stability studies were within specified limits. These data support a shelf-life of 2 years with the storage conditions ‘Replace the mouthpiece cover firmly and snap it into position’, ‘Do not store above 30°C’ and ‘Pressurised container. Do not expose to temperatures higher than 50°C. Do not puncture, break or burn even when apparently empty’.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels
The SPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA during the Mutual Recognition Procedure along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Not all licences are to be marketed at this current time. The marketing authorisation holder has committed to submitting the patient information leaflet and packaging for all products for approval before marketing.

MAA forms
The MAA forms are pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
The grant of marketing authorisations is recommended.

III.2 PRE-CLINICAL ASPECTS

FORMULATION AND DEVICE

The active ingredient salmeterol complies with the same specifications as applied for Salmeterol/Fluticasone Propionate Inhaler and *Diskus*.

The only excipient used is the propellant HFA 134a (Norflurane).

To minimise deposition of the drug on the MDI can walls, a specified fluoropolymer coating is used. The coating is identical to that used in the other currently licensed GlaxoWellcome HFA 134a inhalation products.

GLP STATUS

The repeat-dose 'bridging' toxicity studies and the definitive embryo-foetal development (EFD) study were performed in full compliance with Good Laboratory Practice (GLP) regulations. With the exception of the initial 14-day study, the studies with the early ethanolic formulations, and the preliminary EFD study, performed to establish suitable dose levels for use in the definitive study, were also performed in accordance with GLP, but were not fully compliant in that the reports were not audited.

The initial 14-day repeat-dose study and the preliminary EFD study, performed to validate the method of dose administration in the rabbit, were performed according to the principles of GLP.

PHARMACOLOGY

No further pharmacodynamic studies in animals were considered to be necessary to support the use of salmeterol xinafoate formulated in HFA134a in the same population which the CFC formulation is already licensed to treat.

PHARMACOKINETICS

Analytical methods used to detect salmeterol formulated in HFA 134a, were identical to those used during the toxicokinetic investigations with the dry powder formulation previously assessed at the Agency.

Repeat-dose pharmacokinetics of salmeterol xinafoate, formulated in HFA 134a were obtained by monitoring plasma concentrations in repeat dose toxicity studies (see below).

The results of these studies validate the 'bridging' toxicity studies conducted with salmeterol xinafoate formulated in HFA 134a.

TOXICOLOGY

A "full" programme of pharmaco-toxicological studies was not performed to support this application on the grounds that the active constituents have well-established medicinal use with recognised efficacy and acceptable levels of safety. In addition, a comprehensive "bridging" programme of studies was performed, using the salmeterol/fluticasone dry powder formulation. This approach is considered to be acceptable.

REPRODUCTIVE TOXICOLOGY

In the embryo-foetal development study with salmeterol xinafoate formulated in HFA 134a, the patterns of changes were generally consistent with those seen at comparable plasma concentrations of salmeterol xinafoate, formulated in CFC propellants 11 and 12, in previous studies conducted by the oral route of administration

GENOTOXICITY AND CARCINOGENCITY

No new genotoxicity or carcinogenicity studies have been performed with salmeterol xinafoate or HFA 134a alone, or with salmeterol xinafoate formulated in HFA 134a.

DISCUSSION

The applicant has conducted a satisfactory "bridging" package of studies for the proposed new formulation. The non-clinical studies conducted with salmeterol xinafoate formulated in HFA 134a alone, the proposed clinical formulation, confirm that HFA 134a does not alter the expected class related effects of salmeterol xinafoate. All findings were consistent with the known effects of administration of high doses of β_2-agonists observed in previous studies with salmeterol xinafoate formulated in CFC propellants 11 and 12.

Similarly, the propellant did not influence the toxicokinetics or extent of systemic exposure to salmeterol.

Salmeterol xinafoate formulated in HFA 134a has not been evaluated in juvenile toxicity studies. However, there is no evidence to suggest that the new propellant alters the known toxicity of salmeterol xinafoate.

Furthermore, clinical data obtained in adults indicate that systemic exposure to salmeterol xinafoate following administration of the MDI formulation with HFA 134a is not higher than for the CFC formulation. Therefore, there are unlikely to be any additional safety concerns for administration of this formulation, over and above those associated with the use of the CFC formulation, to either adults or children aged 4-11 years.

The applicant's Non-clinical Overview contains a good summary of the studies performed on this product and on the dry powder formulation. A brief overview of studies performed by the applicant on HFA 134a has been included.

EXTRACTABLES AND LEACHABLES AND IMPURITIES

The impurity profile of the salmeterol xinafoate/HFA 134A drug product is qualitatively similar to the impurity profile of salmeterol xinafoate formulated in CFC propellants 11 and 12. Furthermore, the impurity profile of the salmeterol xinafoate/HFA 134a drug product is qualitatively similar to the impurity profile of the input salmeterol xinafoate and drug-related impurities do not increase on manufacture or storage of the salmeterol xinafoate/134a drug product. Thus the impurities have been adequately qualified in the previously provided toxicity studies performed with salmeterol xinafoate.

The safety assessment of potential extractives and leachables from the valve was based on a guidance document prepared by the Inhalation Technology Focus Group of the American Association of Pharmaceutical Scientists (ITFG) and the International Pharmaceutical

Aerosol Consortium on Regulation and Science, and indicated that there were no safety issues for patients with the container closure system and actuator proposed for Serevent HFA MDI.

SUMMARY of PRODUCT CHARACTERISTICS (SPC)

Sections 4.3 (Contra-indications), 4.5 (Interactions with other Medicaments), 4.6 (Pregnancy and Lactation) and 5.3 (Preclinical Safety Data) of the SPC are identical to the approved text for the current formulations.

CONCLUSION

It is concluded that there are no preclinical reasons why marketing authorisations should not be granted for these products.

III.3 CLINICAL ASPECTS

For the purposes of this report the name Serevent Evohaler will be used throughout to describe the four identical products that are the subject of these applications. In addition, salmeterol formulated with propellant HFA-134a will be described as salmeterol HFA MDI; salmeterol as currently formulated with chlorofluorocarbon propellants, the reference product and the applicant's original product, Serevent Inhaler 25 micrograms per actuation will be described as salmeterol CFC MDI. This terminology is in-line with that used by the applicant in their dossier. If a specific strength or dose is being described the strength or dose will replace the term MDI, for example salmeterol HFA 50µg or salmeterol CFC 50µg.

Background

Under the terms of Montreal Protocol (1987) parties to the agreement agreed to phase-out the use of CFCs including use in medicinal products due to concern over the contribution of CFCs to the depletion of the ozone layer. Initially the phase-out of such use was to have taken place by the end of 1999; currently the target for phase-out for long-acting $beta_2$ adrenoceptor agonists is the end of 2006.

In October 1994 GlaxoWellcome UK Limited (GlaxoSmithKline) applied to the then CPMP (now CHMP) for approval for the use of the non-CFC propellant, HFA-134a (Norflurane) as an alternative propellant in metered dose inhalers (MDIs) for use primarily in the management of asthma and chronic obstructive lung diseases. This hydrofluoroalkane propellant would then replace the CFCs used in the GlaxoSmithKline range of pressurised MDIs (trichlorofluoromethane, propellant 11 and dichlorodifluoromethane, propellant 12).

The conclusions reached following the assessment of the dossier on GlaxoWellcome Inhalation Grade are as follows:

- In animal studies HFA-134a was shown to have no significant pharmacological effects other than at very high exposure concentrations when narcosis and a relatively weak cardiac sensitising effect were seen. The potency of the cardiac sensitisation was less than that of CFCs 11 and 12.
- No significant biotransformation of HFA-134a was detected in man. HFA-134a was eliminated rapidly by exhalation after administration and did not accumulate in the human body.
- In studies to detect toxicity, repeated high dose levels of HFA-134a indicated that safety margins, based on exposure, would be of the order of 2880, 3429, 167 and 1380 for rat, mouse, rabbit and dog with respect to humans.
- Studies of HFA-134a revealed no effects on the reproductive performance and lactation of adult or two successive generations of rats or on the foetal development of rats or rabbits.
- There were no reasons to consider HFA-134a as a potential mutagen, clastogen and carcinogen judged from *in vitro* and *in vivo* studies including long-term administration by inhalation in rodents.

The CPMP conclusions were as follows:

1. The Committee considered that the GlaxoWellcome Inhalation Grade HFA-134a, could be a suitable alternative to CFCs currently used in the formulation of medicinal products, including metered dose inhalers for treatment of asthma.
2. Compatibility with an active substance would have to be established *(cf. CPMP Note for Guidance: Replacement of Chlorofluorocarbons (CFCs) in Metered Dose Inhalation Products, III/5378/93 - Final*).
3. The Committee attached great importance to having adequate reassurance on bronchial hyperreactivity and nasal ciliary problems. These issues were to be very carefully addressed in both the 3 month clinical and the post-marketing surveillance studies described in the *CPMP Note for Guidance: III/5378/93.*
4. The Company was asked to consider and report to the CPMP as soon as possible, any alternative approaches which might better address the concerns of the Committee on the effects of the new propellant on nasal ciliary problems and bronchial hyperreactivity.

Good Clinical Practice

A statement is made in the Clinical Overview that *all studies were undertaken in accordance with standard operating procedures of the GlaxoSmithKline Group of Companies, which comply with the principles of Good Clinical Practice. All studies were conducted with the approval of Ethics Committees or Institutional Review Boards. Informed consent was obtained for all subjects, and the studies were performed in accordance with the version of the Declaration of Helsinki that applied at the time the studies were conducted. Where regulatory approval was required, this was obtained from the relevant Health Authority.*

Paediatric Development Plan

The applicant requests use of these products in children aged 4 years and older and this is in line with the recommendations for use in children for the reference product, the applicant's original product, Serevent Inhaler 25 micrograms per actuation pressurised metered dose inhaler, PL 10949/0068.

The applicant has submitted a pivotal study which examined repeat dosing over 12 weeks duration in 547 children with asthma (aged between 4 and 11 years) in which salmeterol formulated with propellant HFA-134a was compared with salmeterol formulated with CFC propellants (the applicant's original product, Serevent Inhaler) each administered at a dose of 50 micrograms (2 x 25 micrograms) twice daily, in an attempt to demonstrate that the two formulations were clinically equivalent.

In conclusion it may be considered that the single study described is acceptable in respect of both efficacy and safety and that salmeterol reformulated with propellant HFA-134a may be used in children across the same age range for which the original product formulated with chlorofluorocarbon propellants is authorised.

Spacing Device
The Volumatic spacing device is named in the SPC as the only spacing device to be used in conjunction with these products. This stipulation is on the advice of the UK advisory committee.

CLINICAL PHARMACOLOGY

The clinical pharmacology of salmeterol has been investigated previously and effects in human subjects are well known and consistent with the effects of a $beta_2$ adrenoceptor agonist. The non-CFC propellant HFA-134a administered alone either in single dose or in repeat dose studies has been shown to be well tolerated and a number of clinical studies have now been carried out in which active drugs have been formulated in an excipient mix including propellant HFA-134a and these have confirmed the safety of this propellant. In the light of the extensive data available on salmeterol and HFA-134a the applicant presents a limited clinical pharmacology programme comprising only three studies. Two of these studies were set up to compare the safety, tolerability and systemic pharmacodynamic effects and one of which also compared the pharmacokinetics of salmeterol formulated with HFA-134a with the reference product, currently marketed and formulated with CFC propellants; the third study assessed differences between CFC-free and CFC-containing formulations as observed by experienced users of the metered dose inhaler, including salmeterol CFC and salmeterol CFC-free. Of the three studies only one study, was carried out using the product proposed for the market, the other two studies used an earlier version and now superseded container closure system. In Module 3, the Quality Module, batch data are presented for the batch used in one study no data are presented on the batches used in the other two studies.

Pharmacodynamics
Study Number: SLGB10006
A randomised, double blind, placebo controlled, crossover study to compare the systemic pharmacodynamic effects and pharmacokinetics of salmeterol delivered by the non-CFC propellant (HFA-134a; GR106642X) and the CFC propellant (propellant 11/12) metered dose inhalers in healthy subjects.

Study Number: C92-038
To evaluate the safety, tolerability and systemic pharmacodynamic effects of single, cumulative doses of the salmeterol/GR106642X inhaler in healthy volunteers.

Two of the three clinical pharmacology studies compared the pharmacodynamics of salmeterol HFA MDI with the pharmacodynamics of salmeterol CFC MDI. Both studies were carried out in healthy volunteers and were designed as equivalence studies. At therapeutic doses salmeterol has only minimal systemic pharmacodynamic effects and therefore both studies used supra-therapeutic doses of salmeterol in order that pharmacodynamic effects could be demonstrated and compared.

Both of the above studies are described well in study summaries and are discussed in the Clinical Overview.

Study SLGB10006 was carried out in Australia, 30 healthy male volunteers aged between 19 and 32 years were recruited, of whom 26 completed all five treatment days and each subject received four active treatments and one placebo treatment. Each formulation of salmeterol was studied at three dose levels, 50μg, 150μg and 300μg and for each patient the four active treatments were made up of two of the salmeterol doses each administered from a CFC-free inhaler and from a CFC-containing inhaler. Each study day was separated by at least 7 days.

The primary objective of this study was to determine whether the systemic pharmacodynamic response in respect of heart rate and serum potassium levels following inhalation of salmeterol HFA MDI and salmeterol CFC MDI are equivalent. The study employed a randomised, double blind, placebo controlled, 5-way incomplete block crossover design.

The second study, Study C92-038, a single centre study carried out in the UK saw the recruitment of 12 healthy male subjects, aged between 19 and 40 years, all of whom completed the study. The study used a randomised, double blind, crossover design with inhalation of placebo (placebo HFA MDI), salmeterol HFA MDI and salmeterol CFC MDI on three study days each separated by at least 7 days. Salmeterol was inhaled at doses of 50, 50, 100 and 200 micrograms at 60-minute intervals over a period of three hours, to cumulative total doses of 50, 100, 200 and 400 micrograms. The objective of this study was to demonstrate acceptable safety and tolerability and to compare the systemic pharmacodynamic response to cumulative doses of salmeterol formulated with HFA-134a with cumulative doses of salmeterol formulated with CFC propellants.

The endpoints in the two studies were similar and as in the table below:

	SLGB10006	**C92-038**
Primary Endpoint	Maximum heart rate 0-12 hours (50μg dose) Minimum serum potassium level 0-4 hours (50μg dose)	Pulse rate (final value), Plasma potassium (final value)
Secondary Endpoints	Maximum heart rate 0-12 hours (150 and 300μg doses) Minimum serum potassium level 0-4 hours (150 and 300μg doses) Minimum diastolic blood pressure, Maximum systolic blood pressure, Maximum QTc interval, Maximum plasma glucose levels (0-4 hours).	Pulse rate (regression slope), Plasma potassium (regression slope) Diastolic blood pressure, Systolic blood pressure, QTc Interval, Plasma glucose Tremor

In Study SLGB10006, all subjects fasted from midnight on the day prior to dosing until four hours post-dosing, and blood sampling and safety evaluations were carried out to 12 hours post-dosing.

In Study C92-038, measurements were made prior to dosing and at 30 and 55 minutes

after each dose increment on each study day.

In the sample size considerations the applicant reviews data from a previous study with salmeterol which indicated a within standard deviation post-dosing with salmeterol 400µg from a MDI of 6.5 bpm for heart rate and concludes that with completion of 24 subjects and assuming no difference between the two treatments it could estimated that the study would have over 90% power to confirm equivalence of the two treatments with respect to maximum heart rate and minimum potassium level post-dosing. The applicant estimated that with a sample size of 24 completed subjects the treatments would be deemed to be equivalent if the 95% confidence intervals (CI) for the mean difference between the two treatments were contained within +/- 10 beats per minute (bpm) for heart/pulse rate in both studies and +/- 0.33mmol/L in Study SLGB10006 and +/- 0.3mmol/L in Study C92-038 for serum/plasma potassium.

The findings were as follows:

Study SLGB1006

Summary of Results for Maximum Heart Rate (bpm) (0-12h)

	Least Squares Mean Values		Treatment Difference	
Comparison of Interest	**HFA (bpm)**	**CFC (bpm)**	**Difference**	**95% CI**
HFA 50µg versus CFC 50µg	69.68	73.74	-4.06	-8.12, -0.01
HFA 150µg versus CFC 150µg	74.80	82.23	-7.43	-11.69, -3.18
HFA 300µg versus CFC 300µg	86.68	88.37	-1.69	-5.79, 2.41
HFA 50µg versus Placebo	69.68	68.11	1.56	-2.19, 5.31
HFA 150µg versus Placebo	74.80	68.11	6.68	2.84, 10.52
HFA 300µg versus Placebo	86.68	68.11	18.57	14.72, 22.42
CFC 50µg versus Placebo	73.74	68.11	5.62	1.80, 9.45
CFC 150µg versus Placebo	82.23	68.11	14.12	10.13, 18.11
CFC 300µg versus Placebo	88.37	68.11	20.26	16.41, 24.10

HFA = salmeterol HFA MDI; CFC = salmeterol CFC MDI

Both formulations of salmeterol produced dose-related beta agonist pharmacodynamic effects, demonstrating increases in heart rate compared with placebo.

The difference in the Least Squares [LS] means between the active treatments at the 50µg dose was -4.06 bpm (95% CI –8.12, -0.01), indicating equivalence with the 95% CI for the difference in heart rate falling within the pre-defined range of +/- 10 bpm. However although the two formulations were shown to be equivalent for the primary endpoint in respect of maximum heart rate following the 50µg dose, treatment comparisons at the higher dose levels, secondary endpoints, may be more robust as at these doses differences were observed between active treatments and placebo. In the comparisons between active treatments and placebo at the lowest dose, 50µg although a slight increase was seen on active treatment compared with placebo the difference was small and the 95% confidence intervals fell within the range of +/- 10 bpm.

As can be seen in the table above the equivalence criterion was met in the comparison of the 300ug doses but not for the 150µg doses. For the latter the lower 95% CI for the

difference fell outside the +/- 10 bpm range – the difference in the LS means was –7.43 bpm (95% CI -11.69, -3.18).

It is noted that the increase in heart rate following salmeterol HFA MDI was consistently lower than that following salmeterol CFC MDI at each dose level.

The analysis of change in heart rate with dose showed evidence of a dose-response relationship for both formulations of salmeterol.

Summary of Results for Minimum Serum Potassium (mmol/L) (0-4h)

	Least Squares Mean Values		Treatment Difference	
Comparison of Interest	**HFA mmol/L**	**CFC mmol/L**	**Difference**	**95% CI**
HFA 50µg versus CFC 50µg	3.90	3.81	0.08	-0.02, 0.18
HFA 150µg versus CFC 150µg	3.75	3.52	0.23	0.13, 0.34
HFA 300µg versus CFC 300µg	3.48	3.33	0.15	0.05, 0.26
HFA 50µg versus Placebo	3.90	3.94	-0.04	-0.14, 0.05
HFA 150µg versus Placebo	3.75	3.94	-0.18	-0.28, -0.09
HFA 300µg versus Placebo	3.48	3.94	-0.45	-0.55, -0.36
CFC 50µg versus Placebo	3.81	3.94	-0.12	-0.22, -0.03
CFC 150µg versus Placebo	3.52	3.94	-0.42	-0.52, -0.32
CFC 300µg versus Placebo	3.33	3.94	-0.61	-0.70, -0.51

HFA = salmeterol HFA MDI; CFC = salmeterol CFC MDI

The findings in respect of the change in serum potassium were similar to the findings seen in respect of the increase in heart rate following salmeterol formulated with either propellant HFA-134a or CFC propellants and compared with placebo. Both formulations of salbutamol produced dose-related beta agonist pharmacodynamic effects, demonstrating a consistent fall in serum potassium compared with placebo.

The difference in the LS means between the two formulations of salmeterol at the 50µg dose level was 0.08mmol/L (95% CI –0.02, 0.18), indicating equivalence with the 95% CI for the difference in serum potassium falling within the pre-defined range of +/- 0.33mmol/L. As with the findings in respect of heart rate there were no real differences between the active treatments and placebo at the lowest dose level and although the fall in serum potassium was increased following salmeterol HFA 150µg the difference from placebo remained small with the 95% CI for the difference falling within the pre-defined range of +/- 0.33mmol/L. Again the equivalence criterion was met for the comparison of salmeterol HFA 300µg and salmeterol CFC 300µg but in the comparison of the 150µg dose levels the upper limit of the 95% CI for the difference fell just outside the pre-defined range, with a difference in the LS means of 0.23mmol/L (95% CI 0.13, 0.34). The falls seen in serum potassium were consistently less following salmeterol HFA MDI than following salmeterol CFC MDI at all dose levels. Analysis of the change in serum potassium with dose showed evidence of a dose-response relationship for both formulations.

The findings were similar for the other secondary endpoints, QTc interval and plasma glucose. Dose-related effects were seen and effects following salmeterol HFA MDI were consistently less than those seen with salmeterol CFC MDI. The findings in respect of both systolic and diastolic blood pressure were unremarkable. There were no apparent differences in mean maximum systolic blood pressure or in mean minimum diastolic blood pressure between the two formulations of salmeterol at any dose level.

Study C92-038

Significant differences were seen between salmeterol HFA MDI and placebo for all parameters measured as might be expected following administration of such a high cumulative dose. As in the previous study this confirms that the design was sensitive enough to detect differences between treatments. The two formulations of salmeterol behaved similarly in respect of their effects on the endpoints measured as the dose was increased to the cumulative maximum dose. Effects were dose-related. In respect of the two primary endpoints both active formulations showed equivalent effects on pulse rate (mean treatment different 1 bpm, 95% CI for the difference -4, 6 bpm) and on serum potassium (mean treatment difference 0.12mmol/L, 95% CI for the difference 0.02, 0.22mmol/L), although a smaller effect was seen with the HFA-containing formulation compared with the CFC-containing formulation.

Tremor was also measured in this study. Cumulative dosing with salmeterol HFA MDI to a final cumulative dose of 400µg resulted in an increase in mean tremor (95% CI) of 110% (67, 165) compared with placebo. Although slightly increased tremor was seen in the salmeterol HFA MDI treatment group at the final cumulative dose (mean difference 4%, 95% CI -17, 30), there were no significant differences between the two formulations.

Pharmacokinetics

The pharmacokinetics of salmeterol HFA MDI were compared with those of salmeterol CFC MDI in healthy subjects at three dose levels, 50, 150 and 300µg, in Study SLGB10006. Blood samples for determination of salmeterol plasma concentrations were taken pre-administration of study treatments and then at 5, 10, 20, 30 and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12 hours post-administration of study treatments. Pharmacokinetic profiles were similar in shape and a dose-related increase in salmeterol plasma concentration was seen at all time points for all six study treatments (salmeterol HFA 50µg, 150µg and 300µg and salmeterol CFC 50µg, 150µg and 300µg). Salmeterol was measurable in most samples across the sampling period, however for salmeterol HFA 50µg levels were only measurable to five hours post-administration.

Summary of derived geometric mean (95% CI) plasma salmeterol pharmacokinetic parameters following administration of salmeterol HFA MDI

Parameter	Salmeterol Dose		
	50µg	**150µg**	**300µg**
C_{max} (pg/ml)	224.0 (71.0, 706.7)	700.8 (220.7, 2225.5)	1482.0 (453.4, 4844.7)
t_{max}[1] (h)	0.083 [0.083, 0.083]	0.083 [0.083, 0.167]	0.083 [0.083, 0.167]
$AUC_{(0-t)}$ pg.h/mL)	80.6 (14.3, 453.1)	558.9 (134.5, 2339.0)	1612.7 (618.9, 4202.1)

1. Data provided as median [range]
C_{max} – maximum plasma concentration
T_{max} – time to maximum plasma concentration
$AUC_{(0-t)}$ – area under the plasma concentration versus time curve between zero hours and the last quantifiable concentration

Summary of derived geometric mean (95% CI) plasma salmeterol pharmacokinetic parameters following administration of salmeterol CFC MDI

Parameter		Salmeterol Dose	
	50µg	**150µg**	**300µg**
C_{max} (pg/ml)	541.1 (136.5, 2145.3)	1286.6 (269.7, 6136.3)	2005.5 (735.4, 5469.2)
t_{max}[1] (h)	0.083 [0.083, 0.100]	0.083 [0.083, 0.167]	0.083 [0.083, 0.167]
$AUC_{(0-t)}$ pg.h/mL)	278.6 (39.4, 1972.0)	1233.3 (278.0, 5472.7)	2254.5 (984.3, 5163.6)

1. Data provided as median [range]
C_{max} – maximum plasma concentration
T_{max} – time to maximum plasma concentration
$AUC_{(0-t)}$ – area under the plasma concentration versus time curve between zero hours and the last quantifiable concentration

Salmeterol levels achieved following administration of salmeterol formulated with HFA-134a were consistently lower than those obtained following the same dose of salmeterol formulated with CFC propellants. Both C_{max} and $AUC_{(o-t)}$ were lower following administration of salmeterol HFA MDI than following administration of salmeterol CFC MDI at each dose level. For each of the comparisons the 95% CI for comparison were consistently less than unity (with the exception of the comparison of $AUC_{(o-t)}$ for the 300µg does level where the upper limit of the 95% confidence interval just included unity at 1.00). With the exception of this one comparison when all data at all dose levels are considered the data suggest that the systemic exposure to salmeterol is lower following administration of the drug when formulated with propellant HFA-134a as compared with the systemic exposure when formulated with CFC propellants.

The time to obtain maximum concentration, t_{max} appeared in the main to be synonymous with the first sampling time of five minutes post-administration of both formulations of

salmeterol at all dose levels. However it is accepted that the true C_{max} and t_{max} might be earlier of the 5-minute time point.

Comparisons between salmeterol HFA MDI and salmeterol CFC MDI for salmeterol $AUC_{(0-t)}$ and C_{max} values

Comparison	Parameter	Ratio	95% CI
HFA 50µg/CFC 50µg	C_{max} (pg/mL)	0.40	(0.31, 0.52)
	$AUC_{(0-t)}$ (pg.h/mL)	0.28	(0.19, 0.39)
HFA 150µg/CFC 150µg	C_{max} (pg/mL)	0.56	(0.43, 0.74)
	$AUC_{(0-t)}$ (pg.h/mL)	0.46	(0.32, 0.67)
HFA 300µg/CFC 300µg	C_{max} (pg/mL)	0.73	(0.56, 0.94)
	$AUC_{(0-t)}$ (pg.h/mL)	0.70	0.49, 1.00)

HFA = salmeterol HFA MDI
CFC = salmeterol CFC MDI

A Perception Study

Study Number: C94-022

A study on the perception by asthmatic patients of differences in the inhalations from metered dose inhalers of salbutamol, salmeterol, fluticasone propionate or beclometasone dipropionate containing either the current propellant or a non-CFC propellant, GR106642X (HFA-134a).

This study was set up to ascertain whether or not patients with asthma could perceive and describe differences between their usual inhaler formulated with CFC propellants and the inhaler formulated with HFA-134a (and containing the same active drug substance). Approximately 50% of the patients studied and who received salmeterol-containing formulations were able to correctly identify the HFA-134a-containing formulation of the active drug. Perceived differences between formulations were minor and the most commonly mentioned differences were taste and *feel in the mouth*. Comments were evenly balanced in terms of those favourable to one or other formulation.

Assessor's Comments - Pharmacodynamics

At a dose of 50µg the systemic pharmacodynamic effects of salmeterol whether formulated with propellant HFA-134a or with CFC propellants were equivalent. Salmeterol HFA 50µg appeared to have no significant effect on heart rate, serum potassium, QTc interval, systolic and diastolic blood pressure or plasma glucose. Single doses of salmeterol HFA 150µg and salmeterol HFA 300µg produced dose-related beta agonist pharmacodynamic effects but these appeared to be consistently less than those seen with salmeterol formulated with CFC propellants and administered at the same dose level.

At the lowest dose studied, the therapeutic dose of 50µg salmeterol HFA MDI was not associated with any significant pharmacodynamic effects when compared with placebo HFA MDI.

Assessor's Comments - Pharmacokinetics

The pharmacokinetic findings indicate that the maximum plasma salmeterol concentration and area under the plasma concentration versus time curve from time zero

to the last quantifiable concentration were lower for salmeterol HFA MDI when compared with salmeterol CFC MDI. At the highest dose studied, 300μg, C_{max} was 27% lower and $AUC_{(o-t)}$ 30% lower following administration of salmeterol HFA MDI compared with salmeterol CFC MDI.

This lower systemic exposure together with similar or lesser systemic pharmacodynamic effects when salmeterol is formulated with propellant HFA-134a compared with the original formulation with CFC propellants would indicate that the new HFA-134a formulation would be safe at single doses up to 300μg.

CLINICAL EFFICACY

Overview

In December 1993 the CPMP published a *Note for Guidance: Replacement of Chlorofluorocarbons (CFCs) in Metered Dose Inhalation Products III/5378/93 – Final*. Following the assessment of the submission from GlaxoWellcome UK Limited (see 1.2, *Background*, above) in which approval for the use of propellant HFA-134a in the clinical development of active drugs formulated in an excipient mix including HFA-134a as a propellant was gained, it was recommended that such clinical development should take full account of this *Note for Guidance*.

The clinical programme submitted with these applications comprises nine studies. Only two of the nine studies, Studies SMO30006 and SMO30007 are described by the applicant as pivotal clinical studies as they are the only studies to have been carried out using the final product as proposed for marketing. All other studies presented used products with different container closure systems. In Module 3 of the dossier, batch data are presented for the batches used in the two pivotal studies; no data are presented on the batches used in the other seven clinical studies.

The remaining seven studies are described by the applicant as simply supporting studies, they are ranked in hierarchical order. Two studies, Studies SLGT39 and SLPT18 are described as key studies and the remaining five studies, Studies SLGT41 and SLGT42, and SLGT40, SLGT43 and SMO30003 are described as supporting studies.

Since only two of the nine studies were carried out with the product proposed for marketing (the pivotal studies) and batch data for the clinical trial supplies have been provided, this Assessment Report will concentrate on these two studies; all other studies will be reviewed but will not form a major part of this Report.

All nine clinical studies presented have assessed the efficacy of salmeterol HFA MDI in patients with asthma. No studies have been carried out in patients with chronic obstructive pulmonary disease.

Tabular study summaries for all nine studies are presented in Module 2 of the dossier.

Pivotal Studies

Study Number: SMO30006

A multicentre, randomised, double blind, 12-week parallel group study to compare salmeterol xinafoate 50μg bd delivered either via a HFA metered dose inhaler or via a CFC metered dose inhaler, in the treatment of adults, aged 12 years and over, with asthma.

Study Number: SMO30007

A multicentre, randomised, double blind, 12-week parallel group study to compare salmeterol xinafoate 50μg bd delivered either via a HFA metered dose inhaler or via a CFC metered dose inhaler, in the treatment of children aged 4-11 years with asthma.

These studies will be described together initially as they both share a very similar study design, the major difference between the two studies being the population of patients studied. Study SMO30006 sees recruitment of adult patients aged 12 years and over, Study SMO30007 sees recruitment of children with asthma aged between 4 and 11 years. Both studies were carried out in Europe.

The objective of both studies was to demonstrate non-inferiority of salmeterol HFA MDI to salmeterol CFC MDI based on mean morning peak expiratory flow rate (PEFR) in patients with a clinical history of asthma. In both studies salmeterol was administered in a dose of 50μg twice daily (bd) and each study comprised a 2-week run-in period, a 12-week treatment period and a 2-week follow-up period. All patients recruited to these two studies were required to be taking regular inhaled corticosteroids (inhaled beclometasone dipropionate, budesonide or flunisolide in a dose of ≤1000μg/day in the study recruiting adults and adolescents, Study SMO30006 and ≤500μg/day in the study recruiting children, Study SMO30007, or fluticasone propionate at a dose of ≤500μg/day in Study SMO30006 and ≤200μg/day in Study SMO30007) throughout the total duration of each study.

The primary efficacy endpoint in both studies was the mean morning PEFR measured at home each day for 12 weeks and recorded in the daily record card. The secondary efficacy endpoints included the following:

- mean morning PEFR recorded in the DRC over weeks 1-4, 5-8 and 9-12
- mean evening PEFR recorded in the DRC over weeks 1-12
- percentage of symptom free days
- percentage of symptom free nights
- percentage of rescue free days
- percentage of rescue free nights
- clinic visit forced expiratory volume in one second (FEV_1) in all patients in the adult study and wherever possible in the study in children
- per cent predicted mean morning PEFR in the study in children, Study SMO30007.

(PEFR as a percentage of predicted normal may be a better assessment of treatment effects than absolute PEFR in children in the light of the wide variation seen in this measurement in different age and height groups).

Neither study included a placebo treatment group. Therefore the absolute effects of treatment could not be determined. The applicant cites the *CPMP Note for Guidance: Replacement of CFCs in Metered Dose Inhalation Products III/5378/93 – Final* and the *CPMP Note for Guidance: Choice of Control Group in Clinical Trials – CPMP/ICH/364/96*, which approve the use of an active control when it can be assumed that the control would be effective under the conditions of the study.

In both studies patients recruited entered a 2-week run-in period at the end of which the following inclusion criteria had to be met:

- a symptom score (daytime plus night-time) totalling ≥1 on at least four of the last seven consecutive days of the run-in period,
- a mean morning PEFR (calculated from the last seven days of the run-in period) of between <85% and >50% of their PEFR measured 15 minutes post administration of salbutamol 400μg.
- a need for inhaled corticosteroids (as described above).

On entry to the run-in period the patients' usual short-acting inhaled $beta_2$ agonists were discontinued and each patient was provided with a salbutamol inhaler for as required relief of asthma symptoms.

By ensuring that all patients entering the treatment period had a baseline level of symptoms and pulmonary function measurements which were less than optimal on treatment, populations of adolescents, adults and children would enter the study in whom there was room for improvement in asthma control. Therefore if there were any clinically important differences between treatments there was an increased likelihood of these being detected.

Sample size considerations, analysis populations and treatment comparisons

In both studies the primary endpoint was the mean morning PEFR over weeks 1-12 of the treatment period, calculated from data collected on the daily record card. Non-inferiority was deemed to have been shown if the lower limit of the 95% confidence interval for the estimated treatment difference (between salmeterol HFA MDI and salmeterol CFC MDI) for mean morning PEFR was greater than -15L/min.

From a previous study carried out in adults (Study SLGT39 described as a key study in this clinical programme) in which salmeterol HFA MDI was compared with salmeterol CFC MDI the between groups variance (standard deviation) for mean morning PEFR averaged over weeks 1-12 was found to be 44.1L/min. Therefore in Study SMO30006 (adults) and assuming a non-inferiority limit of -15L/min, a 5% significance level, 90% power and a two-sided t-test, the number of subjects required in the per protocol (PP) population was 182 per treatment group and allowing for a 10% exclusion rate from the

total recruited population, the intention-to-treat (ITT population) it was planned to recruit and randomise 204 subjects per treatment group.

From a previous study carried out in children, (Study SLPT18 also described as a key study in this clinical programme) in which salmeterol HFA MDI was compared with salmeterol CFC MDI the between groups variance (SD) for mean morning PEFR averaged over weeks 1-12 was 47.9L/min. Therefore in Study SMO30007 (children) and with the same assumptions in respect of the non-inferiority limit of -15L/min, a 5% significance level, 90% power and a two-sided t-test, the number of subjects required in the PP population was 215 per treatment group and allowing for a 10% exclusion from the ITT population it was planned that 240 subjects per treatment group should be recruited and randomised to treatments.

The analysis populations included the total population (all subjects who entered the study), the ITT population (all subjects randomised to treatment who took at least one dose of study medication) and the PP population (all subjects in the ITT population who did not have any protocol violations that may have impacted upon the treatment effect). The PP population was used as the primary population of interest for the primary efficacy analysis, the ITT population was the secondary population for the primary efficacy analysis and the primary population for all secondary efficacy analyses and safety tables.

The studies were designed to show non-inferiority of salmeterol HFA MDI to salmeterol CFC MDI. However if the lower bound of the confidence interval exceeded zero, the p-value was assessed in order to determine the strength of evidence for demonstrating superiority.

The number of patients recruited into the two pivotal studies is shown in the table below:

Number of Patients Included in Pivotal Studies

	SMO30006		SMO30007	
	HFA	**CFC**	**HFA**	**CFC**
ITT Population	278	294	274	272[1]
PP Population	258	261	248	253
Power Calculation[2]	182	182	215	215

1. Does not include one subject randomised who received no study treatment
2. Subject numbers defined *a priori* to obtain 90% power in the PP Population

The findings in the two pivotal efficacy studies were as follows:

Study Number: SMO30006 – The adult study, recruiting from age 12 years above
The demographic and baseline characteristics were well matched between the two treatment groups and across the two main analysis populations. A total of 572 patients (247 (43%) males), mean age 46.7 years (range 12-87 years) were recruited to the ITT population. More than 99% of patients were white Caucasians, 29% were current/former smokers and 24% used the Volumatic spacing device for administration of salmeterol. The mean per cent predicted FEV_1 at baseline was 79% with a range from 23-176% predicted. The breakdown of age of patients recruited to this study saw recruitment of only 13 patients aged between 12 and 17 years and 75 patients aged >65 years. Patients

recruited within these age bands were evenly distributed between the two treatment groups.

Ninety-one per cent of the ITT population were included in the PP population – the most common reason for exclusion was the mean PEFR ≤50% of predicted normal at the end of the run-in period.

The use of the Volumatic spacing device was permitted in those subjects who would normally use a spacing device.

The findings in respect of the primary efficacy variable for the PP population are presented in the table below:

Summary of Mean Morning PEFR (L/min) Analysis (PP Population)

Parameter	**PEFR (L/min)**	
	Salmeterol HFA MDI (n=258)	**Salmeterol CFC MDI (n=261)**
Baseline, mean (sd)	373.9 (102.8) n=248	362.6 (101.6) n=250
Weeks 1-12, mean (sd)	403.6 (102.5) n=255	398.8 (106.3) n=254
Weeks 1-12, adjusted mean (se)	405.1 (2.8) n=245	408.3 (2.9) n=244
Mean change from baseline (sd)	33.6 (39.8) n=245	37.1 (37.6) n=244
Adjusted mean change from baseline (se)[1]	37.4 (2.8) n=245	40.5 (2.9) n=244
Treatment Difference (HFA-CFC) (se) **95% CI** **p-value**	-3.2 (3.4) -9.8, 3.4 0.344	

sd: standard deviation, se: standard error
CI: Confidence interval
1. Adjusted for age, sex, country, baseline mean morning PEFR and use of spacing device

Over weeks 1-12 the adjusted mean treatment difference (salmeterol HFA MDI - salmeterol CFC MDI) for mean morning PEFR was -3.2L/min (95% CI -9.8, 3.4 L/min). The 95% confidence interval was above the pre-defined non-inferiority limit of -15L/min and the applicant concludes that non-inferiority of salmeterol HFA MDI to salmeterol CFC MDI has been demonstrated in respect of the primary efficacy endpoint. The findings are confirmed in the ITT analysis, treatment difference (SE) -2.6 (3.2), 95% CI -8.9, 3.7 and p=0.411. The tests for interaction of treatment with other covariates showed no interactions with country, sex or use of the spacing device. A statistically significant interaction was seen with age and baseline PEFR in the PP population. However, the applicant attaches no significance to this finding and describes it as *an artefact of the exclusion criteria from the Per-Protocol population* as it is not seen in the ITT population or in any of the analyses of the secondary variables.

The findings following the analysis of the secondary efficacy variables (ITT population) supported the findings in the analysis of the primary variable and no statistically

significant differences were seen between the treatment groups in any variable excepting clinic visit FEV_1. Clinic FEV_1 was measured at baseline and at each post-randomisation clinic visit at the end of weeks 4, 8 and 12 (end of treatment period). No differences were seen between treatments following 4 and 8 weeks treatment, however a statistically significant difference in favour of salmeterol HFA MDI was seen at week 12 and at endpoint (Last Observation Carried Forward – LOCF), p=0.007 and p=0.008, respectively. The actual treatment difference in favour of salmeterol HFA MDI was 91ml at week 12 and 85ml at endpoint. The applicant states that the magnitude of this difference was not felt to be clinically relevant in a population of patients with asthma with highly reversible airways disease, and particularly in the light of possible lower systemic exposure with salmeterol HFA MDI and the lack of a difference seen in the assessment of the other efficacy variables.

The secondary efficacy findings support the non-inferiority of salmeterol HFA MDI to salmeterol CFC MDI seen in the primary efficacy analysis.

The applicant concludes that non-inferiority of salmeterol HFA MDI 50µg bd when compared with salmeterol CFC MDI 50µg bd has been demonstrated based on the analysis of the primary efficacy variable, mean morning PEFR over weeks 1-12 of the study, in both per protocol and intention-to-treat analysis populations. Comparable efficacy findings were seen in the analyses of the secondary efficacy variables.

Study Number: SMO30007 – The study in children aged between 4 and 11 years
The demographic and baseline characteristics were well matched between the two treatment groups. A total of 639 children were recruited to the study and 547 randomised to study treatments. The most common reasons for withdrawal prior to randomisation included entry criteria not fulfilled and withdrawal of consent. Of those children randomised 546 received at least one dose of study medication. The mean age of the study population was 7.3 years, range 4-11 years and 328 (60%) were male. Ninety-eight per cent were white Caucasian. None smoked and 72% (70% receiving salmeterol HFA MDI and 74% receiving salmeterol CFC MDI) used the Volumatic spacing device (use of which was permitted during the study). Mean per cent predicted FEV_1 was 86.51% with a range of 43.5 to 136.3%.

Ninety-two per cent of the ITT population were included in the PP population – the most common reasons for exclusion were insufficient symptom scores ≥1 recorded in the daily record card at the end of the run-in period and a failure to meet the requirement for inhaled corticosteroid use.

Summary of Mean Morning PEFR (L/min) Analysis (PP Population)

Parameter	PEFR (L/min)	
	Salmeterol HFA MDI (n=248)	**Salmeterol CFC MDI (n=253)**
Baseline, mean (sd)	216.1 (61.9) n=246	213.6 (69.5) n=249
Weeks 1-12, mean (sd)	253.5 (66.4) n=248	248.4 (75.6) n=251
Weeks 1-12, adjusted mean (se)	252.3 (2.1) n=246	249.8 (2.2) n=248
Mean change from baseline (sd)	37.5 (31.2) n=246	34.3 (33.8) n=248
Adjusted mean change from baseline (se)[1]	37.2 (2.1) n=246	34.7 (2.2) n=248
Treatment Difference (HFA-CFC) (se) **95% CI** **p-value**	2.5 (2.7) -2.8, 7.8 0.353	

sd: standard deviation, se: standard error
CI: Confidence Interval
1. Adjusted for age, sex, country, baseline mean morning PEFR and use of spacing device. In the analysis, the countries Greece and Israel were combined.

Over weeks 1-12 the adjusted mean treatment difference (salmeterol HFA MDI – salmeterol CFC MDI) for mean morning PEFR was 2.5L/min (95% CI -2.8, 7.8 L/min). The 95% confidence interval was above the pre-defined non-inferiority limit of -15L/min and the applicant concludes that non-inferiority of salmeterol HFA MDI to salmeterol CFC MDI has been demonstrated in respect of the primary efficacy endpoint. In the ITT population the treatment difference was 2.0 L/min (95% CI -3.2, 7.2 L/min) again above the predefined non-inferiority limit. The results for the ITT population were consistent with and supported the results seen in the PP population with no significant differences seen between treatments, p=0.353 and p=0.451 in the PP population and the ITT population, respectively.

Tests for interaction of treatment with other covariates showed no interactions with sex, use of a spacing device, age or baseline PEFR. An interaction was seen in respect of country but the applicant felt this to be *an artefact of the exclusion criteria from the Per-Protocol population.* No country interaction was seen in the ITT population nor in any of the analyses of the secondary efficacy variables.

The following table presents a summary of the changes from baseline in morning PEFR in the two treatment groups by use of the Volumatic spacing device:

Summary of Mean Morning PEFR (L/min) in VOLUMATIC Spacer and Non-Spacer Users (PP population)

	PEFR (L/min)[1]			
	Spacer Users		Non-Spacer Users	
Parameter	**Salmeterol HFA MDI (n=175)**	**Salmeterol CFC MDI (n=185)**	**Salmeterol HFA MDI (n=73)**	**Salmeterol CFC MDI (n=68)**
Baseline, mean (sd)	209.8 (63.8) n=173	198.7 (65.9) n=184	231.1 (54.7) n=73	255.9 (61.8) n=65
Weeks 1-12, mean (sd)	247.2 (69.2) n=175	233.4 (74.4) n=184	268.6 (56.5) n=73	289.4 (62.9) n=67
Mean change from baseline (sd)	37.6 (30.3) n=173	34.0 (31.7) n=183	37.4 (33.5) n=73	35.1 (39.6) n=65

1. PEFR readings taken within 6 hours of rescue medication use have been excluded.
p-value for treatment by VOLUMATIC spacer use interaction over weeks 1-12 = 0.189. Interaction p-value from an analysis of covariance model for mean morning PEFR, adjusted for baseline mean morning PEFR, country, age and sex, in addition to treatment group and use of spacing device. In the analysis, the countries Greece and Israel have been combined.

No interaction was seen in mean morning PEFR with use of the spacing device.

There were no statistically significant differences between the two treatment groups in the analyses of any of the secondary endpoints. A considerable improvement was seen in mean per cent predicted morning PEFR over weeks 1-12 in both treatment groups, in the salmeterol HFA MDI treatment group the improvement was 15.2% and in the salmeterol CFC MDI treatment group the improvement was 14.0%.

It was noted that approximately 70% of children were able to perform satisfactory measures of FEV_1 (FEV_1 was to be measured whenever possible in this study in children). No significant differences were seen between the two study treatments in clinic FEV_1 at any time point, the treatment difference at week 12 was 0.005L (95% CI – 0.046, 0.056L; p=0.849).

The applicant concludes that non-inferiority of salmeterol HFA MDI 50μg bd compared with salmeterol CFC MDI 50μg bd has been demonstrated in this study based on the findings in respect of the primary efficacy variable, the mean morning PEFR over weeks 1-12 of the study, in both the per protocol and intention-to-treat populations. Comparable efficacy findings were demonstrated following the analyses of the secondary efficacy variables.

Key and Supporting Studies

Of the remaining seven studies presented in the dossier two are described by the applicant as key and five as supporting. All were prospective, randomised and double blind in design and with the exception of one of the key studies (Study SLPT18 which was carried out in children and adolescents, 4-15 years) all studies were carried out in adults.

Key Studies

Study Number: SLGT39 (SLGB3003)

Study Number: SLPT18

These two studies, one in adults (Study SLGT39) and one in children and adolescents (Study SLPT18) were designed to demonstrate equivalence (rather than non-inferiority) between salmeterol HFA MDI and salmeterol CFC MDI administered in a dose of 50µg bd over a treatment period of three months, based on mean morning PEFR recorded daily over the 12-week treatment period. Both studies also incorporated an optional nine-month extension phase during which both efficacy and safety were assessed. Other than the differences described the studies were essentially very similar in their design to the two pivotal studies described at 3.2 above.

In both studies clinical equivalence was deemed to have been demonstrated if the 90% confidence intervals for the estimated treatment difference for the mean morning PEFR were within +/- 15L/min. The applicant reviewed previous studies which estimated that the standard deviation across PEFR values for similar patient populations was 30-40L/min and with this assumption and with the requirement for 80% power to demonstrate equivalence between the two treatments it was estimated that data on 250 evaluable patients (125 evaluable patients per treatment group) were required in each study.

In Study SLGT39 a total of 395 patients were recruited, 357 aged between 18 and 65 years and of whom 174 received salmeterol HFA MDI and 183 salmeterol CFC MDI; 38 patients were aged over 65 years of whom 22 received salmeterol HFA MDI. The mean age of patients recruited was 43.5 years.

In Study SLPT18 a total of 407 children and adolescents were recruited. Two hundred and sixty-two were aged between 4 and 11 years of whom 138 received salmeterol HFA MDI and 124 received salmeterol CFC MDI and 145 were aged between 12 and 15 years of whom 73 received salmeterol HFA MDI. Fifty-nine per cent of patients in Study SLPT18 used the Volumatic spacing device.

It is noted that in both Study SLGT39 and Study SLPT18 a number of subjects did not receive inhaled corticosteroids during the study treatment periods. In Study SLGT39 only 81% of patients in the salmeterol HFA MDI treatment group and 86% in the salmeterol CFC MDI treatment group continued to receive inhaled corticosteroids; in Study SLPT18 only 58% in the salmeterol HFA MDI group and 62% in the salmeterol CFC MDI group continued to receive inhaled steroids.

The findings from the key studies support those of the pivotal studies and the applicant concludes that the key studies support the clinical equivalence of salmeterol HFA MDI and salmeterol CFC MDI when administered in a dose of 50µg bd to both adults, children and adolescents in the two studies presented.

The two key studies provided an option for patients recruited to continue in the study for a further nine months at the end of the initial three-month treatment period, with a clinic

visit every three months. The table below shows the mean morning PEFR for those subjects who entered the nine-month extension phase of the two studies, (90% of the original study population in Study SLGT39 and 93% of the original study population in Study SLPT18). The extension period was not powered in either study to show equivalence at 12 months; however the difference between treatment groups was not statistically significant and not deemed by the applicant to be clinically relevant.

Mean Morning PEFR (L/min) for 1-12 months for Study SLGT39 and Study SLPT18 (Long-Term Population)

	SLGT39		**SLPT18**	
	Salmeterol HFA MDI n=197	**Salmeterol CFC MDI n=178**	**Salmeterol HFA MDI n=202**	**Salmeterol CFC MDI n=178**
Baseline Mean	359	356	275	278
Months 1-12	412	407	325	334
Adjusted mean Change from Baseline	56	50	50	55
Treatment difference [90% CI]	6[-4, 16]		-6[-14, 2]	
p-value	0.326		0.233	

Supporting Studies

Study Number: SLGT41
Study Number: SLGT42
Study Number: SLGT40
Study Number: SLGT43
Study Number: SMO30003

Studies SLGT41 and SLGT42 were designed to assess the clinical equivalence of salmeterol HFA MDI and salmeterol CFC MDI administered in a dose of 50µg bd in adults (aged at least 18 years in study SLGT41 and at least 16 years in Study SLGT42) over a treatment period of one month. The definition of clinical equivalence was the same as that used in the key studies described above.

Studies SLGT40, SLGT43 and SMO30003 differed from the six studies described previously in that they were all single dose and single centre studies designed to investigate the bronchodilatory and bronchoprotective effects of salmeterol HFA MDI compared with salmeterol CFC MDI. The primary objective was to demonstrate equivalence of the two study treatments in Studies SLGT40 and SLGT43 and non-inferiority of salmeterol HFA MDI to salmeterol CFC MDI in Study SM030003, in respect of protection against methacholine-induced bronchoconstriction. In Studies SLGT43 and SMO30003, subjects received salmeterol in a dose of 50µg, in Study SLGT40 subjects received salmeterol in a dose of 100µg.

The findings in Studies SLGT41 and SLGT42, the two multiple dose studies over one month were similar to those of the key studies, Studies SLGT39 and SLPT18 and the applicant concludes that the findings from these two studies demonstrate clinical equivalence between salmeterol HFA MDI and salmeterol CFC MDI over the four-week treatment period.

Studies SLGT40 and SLGT43 both designed to show equivalence in respect of protection against methacholine-induced bronchoconstriction met their objectives, the 90% confidence intervals for the difference between salmeterol HFA MDI and salmeterol CFC MDI in doubling dose of methacholine did not contain two doubling doses as pre-defined and therefore the applicant concludes that the two formulations are therapeutically equivalent in the populations studied.

Study SMO30003 designed to show non-inferiority between the two formulations in respect of protection afforded against a methacholine challenge did not achieve its objectives and did not demonstrate non-inferiority as the upper limit of the 95% confidence interval for the treatment difference was greater than the pre-defined limit of one doubling dilution. The applicant does not consider that these findings have any relevance to the current applications in the light of the differences in the container/closure system and the very low fine particle mass seen when the clinical batch used in this study and the proposed commercial product are compared; the clinical batch used is not considered to be representative of the product which will ultimately appear on the market.

Studies in special populations – Children.
One pivotal study, Study SMO30007 and one key study, Study SLPT18 have been carried out in children. These studies are described above at 3.2 *Pivotal Studies* and 3.3 *Key and Supporting Studies*.

Ongoing Studies
There are no ongoing studies.

Statistical Assessor's Comment
Studies SMO30006 and SMO30007 are the pivotal efficacy studies for these applications. The studies are fully described above at 3.2 *Pivotal Studies*. From a methodological point of view these studies do not raise any concerns. Improvements at baseline were seen in both treatment groups for all primary and secondary endpoints. Hence it is clear that the similarity of the two treatments was not due to lack of effect of the study medications. The non-inferiority margin was sufficiently small and the studies have been appropriately analysed. Non-inferiority was clearly demonstrated in both studies. All secondary endpoints also showed similar effects in the two treatment groups except for FEV_1 in Study SMO30006. The mean change from baseline in clinic FEV_1 at week 12 in Study SMO30006 was 91mL (95% CI 24mL, 157mL, p = 0.007). A significant difference for this endpoint was not observed in Study SMO30007. The applicant concludes that 91mL is not a clinically relevant difference in FEV_1. This difference is small and even the upper limit of the 95% confidence interval of 157mL can probably be considered clinically unimportant. Therefore this finding is not a cause for concern. The results from the primary endpoint provide clear evidence that salmeterol HFA 50µg is non-inferior to salmeterol CFC 50µg.

Clinical Assessor's Comment
The applicant has submitted an extensive series of clinical studies. However, unfortunately, only two (both described as the pivotal studies) were carried out with the product proposed for marketing and were the only studies for which batch data for the clinical trial supplies have been provided. The remaining seven studies, two described as key and five as supporting studies used products with different container closure systems.

The two pivotal studies include one study in adults and adolescents aged 12 years and over with asthma and one in children aged 4-11 years with asthma. Both studies were appropriately designed, had appropriate endpoints and were appropriately analysed. The patients recruited to the studies underwent a 2-week run-in period at the end of which all patients entering the 12-week treatment period were required to demonstrate a baseline level of symptoms and to have pulmonary function measurements which were less than optimal on treatment such that improvement in asthma control could be demonstrated on treatment with study medications. If there were clinically important differences between the study treatments these entry criteria would provide an increased likelihood of these differences being detected and hence enhance the sensitivity of the study.

Following 12 weeks of study medication, improvements were seen in both treatment groups in both studies for both the primary and the secondary variables and both studies clearly demonstrated that salmeterol formulated with propellant HFA-134a and administered in a dose of 50μg bd was non-inferior to salmeterol formulated with CFC propellants and administered in a dose of 50μg bd. This conclusion was based on the primary efficacy variable, the mean morning PEFR over weeks 1-12 in the per protocol population but was confirmed by the findings of the analysis of the primary efficacy variable in the intention-to-treat population and was supported by the findings in the analyses of secondary efficacy variables.

The only secondary efficacy variable which did not support these findings was the comparison of FEV_1 between the two treatment groups at the end of the 12-week treatment period and at endpoint (last observation carried forward) in the adult study, Study SMO30006. A statistically significant difference was seen in favour of salmeterol formulated with propellant HFA-134a at week 12 and at endpoint with a treatment difference of 91ml and 85ml and p=0.007 and 0.008, respectively. There is an argument in support of the applicant's comment that the magnitude of this difference was not felt to be clinically relevant in a population of patients with asthma with highly reversible airways disease when the timing of these measurements is considered. FEV_1 was measured at all visits after the patients had taken their study medication and hence any treatment differences could be described as differences at peak concentrations. A clinically meaningful treatment difference in FEV_1 in patients with asthma in considered to be an approximate improvement from baseline of 200ml; the observed treatment difference in Study SMO30006 (and the upper limit of the confidence interval, 157ml) was below this clinically meaningful improvement of 200ml.

It is also to be noted that no other endpoints, either primary or secondary, measured in this study would support this difference between the two treatments. Therefore, it is

accepted that this difference in FEV_1 in favour salmeterol formulated with propellant HFA-134a might be considered to be of no clinical significance.

It is also of note that the pharmacokinetic study presented (see 2.2 *Pharmacokinetics* and 2.4 *Assessor's Comments* above) suggests that there might be lower systemic exposure to salmeterol when formulated with propellant HFA-134a than when formulated with CFC propellants.

In both of the pivotal studies, both the study in adults and the study in children, use of the Volumatic spacing device was permitted by those subjects who would normally use a spacing device. In the adult study 24% of patients recruited used the device but in the study in children this figure was much increased with 70% of children receiving salmeterol formulated with HFA-134a and 74% of children receiving salmeterol formulated with CFC propellants using the device. In both studies tests for interaction of treatment with other covariates which included the spacing device were carried out. The comparison of spacer and non-spacer use in the study in children, Study SMO30007 is presented above in Section 3.2 *Pivotal Studies*. No interaction was seen in mean morning PEFR with use of the spacing device.

However, it is of note in the assessment of Module 3 that a slight increase in fine particle mass is seen when the Volumatic spacing device is used and that this increase is further increased after build-up of salmeterol in the spacing device after a week of simulated dosing. Cleaning of the spacing device has no adverse effect on the cascade impaction performance and the fine particle dose is reduced after cleaning of the device has removed the build-up of drug. This is of potential concern as the increase in fine particle mass might effect both clinical efficacy and safety; however the findings in respect of both efficacy as presented above and in respect of safety as presented below would suggest that use of a spacing device is not associated with either enhanced efficacy or worsening of safety. Therefore the applicant's comment that the changes in fine particle mass are not significant is accepted.

In conclusion the clinical study programme presented in respect of efficacy demonstrates that salmeterol when formulated with propellant HFA-134a is at least as effective as salmeterol formulated with CFC propellants in the treatment of adults, adolescents and children aged between 4 and 11 years with asthma. The effects seen were similar whether or not patients used the Volumatic spacing device.

CLINICAL SAFETY

Overview/Exposure

The clinical programme presented in the dossier includes nine clinical studies and the data generated from these have been used to assess the safety profile of salmeterol formulated with propellant HFA-134a and to compare this safety profile with that of salmeterol formulated CFC propellants. Further to these nine clinical studies, three clinical pharmacology studies are presented two of which looked at supra-therapeutic doses of salmeterol formulated with both HFA-134a and CFC propellants.

A total of 986 adults and adolescents aged ≥12 years and 412 children aged between 4 and 11 years have been exposed to at least one dose of salmeterol HFA MDI in the clinical programme presented. In the pivotal studies the number of patient- years of exposure for adults and adolescents (Study SMO30006) and children (Study SMO30007) was 63 patient-years for each population; in the two key studies, studies which comprised an initial 12-week efficacy and tolerability period which was followed by an optional nine-month tolerability extension, exposure to salmeterol in adults (Study SLGT39) and in children and adolescents (SLPT18) totalled 183 patient-years in each population. (In Study SLGT39 168 adults treated with salmeterol HFA MDI completed the 12-month study and in SLPT18 186 patients aged between 4 and 15 years and treated with salmeterol HFA MDI completed the 12-month study).

Safety data were reviewed in the intention-to-treat populations in all studies. The ITT population was defined as all subjects randomised to study treatments and who received at least one dose of study treatment.

[To reiterate previous comments only the two pivotal clinical studies, Studies SMO30006 and SMO30007 and the clinical pharmacology study, Study SLGB10006, were carried out with final product as proposed for marketing. The data generated in these studies can be described as the pivotal safety data generated in support of these applications].

Adverse Events

Pivotal and Key Studies

Studies in Adults – Study SMO30006 (12 weeks) and Study SLGT39 (long-term treatment to 12 months)

During the 12-week pivotal study, Study SMO30006 the incidence of adverse events in the salmeterol HFA MDI treatment group was similar to that in the salmeterol CFC MDI treatment group with 98/278 (35%) patients and 101/294 (34%) patients in the two treatment groups respectively reporting at least one adverse event. The most common adverse events affecting >5% of patients were asthma exacerbations and nasopharyngitis, both of which might be expected in patients with asthma, and headache, a known adverse event seen with beta$_2$ adrenergic agonists. No new safety concerns were identified.

Most Common Adverse Events Affecting >5% of Subjects in either Treatment Group During Treatment Period (ITT Population): SMO30006

	n(%)	
	Salmeterol HFA MDI (n=278)	**Salmeterol CFC MDI (n=294)**
At least one AE[1]	98 (35)	101 (34)
Asthma NOS[2]	24(9)	26(9)
Headache[3]	21(8)	19(6)
Nasopharyngitis	15(5)	7(2)

1. AEs were coded using MedDRA
2. Not otherwise specified; all events were asthma exacerbations
3. AE expected with salmeterol use

The incidence of cardiovascular adverse events was low and similar in the two treatment groups. Three subjects receiving salmeterol HFA MDI experienced four events,

arrhythmia, tachycardia, myocardial ischaemia and palpitations; four subjects receiving salmeterol CFC MDI experienced four events, arrhythmia (in two subjects), tachycardia and paroxysmal tachycardia.

Only 6/278 (2%) and 8/294 (3%) patients in two treatment groups, salmeterol HFA MDI and salmeterol CFC MDI, respectively experienced adverse events deemed by the investigators to be drug-related.

Study SLGT39 the 12-week efficacy and safety study followed by the optional nine-month safety extension saw an increase in the number of subjects reporting adverse events but the incidence of events reported in the salmeterol HFA MDI treatment group remained similar to that seen in the salmeterol CFC MDI treatment group. The most common adverse events affecting >5% of subjects were adverse events frequently reported in a population of patients with asthma and as previously those which might be expected following use of a $beta_2$ adrenergic agonist. No new safety concerns were identified.

The incidence of cardiovascular events was similar across the two treatment groups with 7% reporting such events in the salmeterol HFA MDI group compared with 8% in the salmeterol CFC MDI group. The main events were palpitations, 2% compared with 1% in the two treatment groups, respectively and tachycardia, 1% and <1% in the two treatment groups, respectively.

Over the 12-month treatment period the incidence of adverse events considered to be drug-related was lower in the salmeterol HFA MDI treatment group, 11% compared with 19%. The most common events deemed to be drug-related were those affecting the respiratory tract, the most common of these being asthma exacerbations – 3% in the salmeterol HFA MDI treatment group (5/196 patients) and 5% in the salmeterol CFC MDI treatment group (10/199 patients).

Asthma exacerbations continued to be the most common event reported in both treatment groups and with a similar incidence, 6% versus 8%, during the post-treatment follow-up period. The overall incidence of adverse events reported during this period was similar in the two treatment groups, 19% versus 20%.

Studies in Children ≥4 years – Study SMO30007 (12 weeks) and Study SLPT18 (long-term treatment to 12 months)
As in the adult studies the most common adverse events affecting >5% of children were adverse events which might be expected in a population of patients with asthma or patients receiving a $beta_2$ agonist. The incidence of events seen in the two treatment groups was similar and no new safety concerns were identified.

Most Common Adverse Events Affecting >5% of Subjects in either Treatment Group During Treatment Period (ITT Population): SMO30007

	n(%)	
	Salmeterol HFA MDI (n=274)	**Salmeterol CFC MDI (n=272)**
At least one AE[1]	146(53)	134(49)
Headache[2]	26(9)	22(8)
Rhinitis NOS[3]	23(8)	17(6)
Nasopharyngitis	20(7)	20(7)
Pyrexia	19(7)	15(6)
Cough	18(7)	22(8)
Respiratory tract infection NOS	17(6)	13(5)
Viral infection NOS	16(6)	16(6)
Asthma NOS[4]	16(6)	10(4)
Pharyngitis	15(5)	9(3)

1. AEs were coded using MedDRA
2. AE expected with salmeterol use
3. Not otherwise specified
4. All events were asthma exacerbations

Only one child, receiving salmeterol CFC MDI, experienced a cardiovascular adverse event which was diagnosed as mild cardiac extrasystoles (not specified).

Only few adverse events were deemed to be drug-related, 7/274 (3%) patients receiving salmeterol HFA MDI and 6/272 (2%) patients receiving salmeterol CFC MDI. The only event reported by more than one subject in either treatment group was headache reported by five subjects (2%) receiving salmeterol HFA MDI.

No subject in either treatment group experienced an adverse event for the first time during the post-treatment follow-up period.

In Study SLPT18 when study treatments were inhaled for up to 12 months the number of children reporting adverse events increased with the extended treatment period but the incidence remained similar across the two treatment groups. At least one adverse event was reported by 188/211 (89%) children receiving salmeterol HFA MDI and 168/196 (86%) children receiving salmeterol CFC MDI. As in Study SMO30007 (the 12-week pivotal study in children) the most common events affecting >5% of children were events frequently reported in an asthmatic population and those which might be expected following inhalation of a $beta_2$ agonist. No new safety concerns were identified.

There were no reports of cardiovascular events in either treatment group.

The incidence of adverse events considered by the investigators to be drug-related was similar across the two treatment groups, 15% in those receiving salmeterol HFA MDI and 17% in those receiving salmeterol CFC MDI. The most common events deemed to be drug-related were headache and asthma exacerbations, the former reported by 6% and 5% of children in the two treatment groups, respectively and the latter by 4% and 5% of children in the two treatment groups, respectively.

The post-treatment follow-up period saw a similar incidence of events across the two treatment groups, the most common event being asthma exacerbations reported by 13% of children who had received salmeterol HFA MDI and by 12% of children who had received salmeterol CFC MDI. The overall incidence of adverse events reported during this period across the two treatment groups was 26% and 29% respectively.

Supporting Studies

In the two one-month studies, Studies SLGT41 and SLHT42 the general pattern of events reported was similar to that seen in the studies described above.

In the single dose studies, Studies SLGT40 and SLGT43 the overall incidence of adverse events and those deemed to be drug-related was lower in those receiving salmeterol HFA MDI than in those receiving salmeterol CFC MDI. In Study SLGT40 headache was the most frequently reported event deemed to be drug-related occurring in 15% receiving salmeterol HFA MDI and 20% receiving salmeterol CFC MDI.

In Study SMO30003 and during the washout period, a higher incidence of events was seen in the salmeterol HFA MDI treatment group than in the salmeterol CFC MDI treatment group, 26% compared with 13% of patients reporting at least one event. There were 8 events reported which were deemed by the investigator to be drug-related, five following salmeterol HFA MDI, one following salmeterol CFC MDI and two following placebo CFC MDI. The event reported most frequently was headache, occurring in a higher proportion of patients receiving salmeterol HFA MDI than receiving salmeterol CFC MDI, 8% (3/39 patients) compared with 3% (1/40 patients), respectively.

Withdrawals Due to Adverse Events

Pivotal and Key Studies

Studies in Adults – Study SMO30006 (12 weeks) and Study SLGT39 (long-term treatment to 12 months)

Study SMO30006 saw six adverse event related withdrawals (with a total of eight adverse events reported). Two, one in each treatment group were due to asthma exacerbations requiring hospitalisation and these were both reported as serious adverse events; none of the other events leading to treatment discontinuation occurred in more than one subject. Overall four patients, reporting five events were withdrawn from the salmeterol HFA MDI treatment group and two patients reporting three events from the salmeterol CFC MDI treatment group.

In Study SLGT39 there were 22 adverse event related withdrawals, eight from the salmeterol HFA MDI treatment group and 14 from the salmeterol CFC MDI treatment group. The main reason for these withdrawals was asthma exacerbation, four patients compared with six patients in the two treatment groups, respectively.

Studies in Children ≥4 years – Study SMO30007 (12 weeks) and Study SLPT18 (long-term treatment to 12 months)

Study SMO30007 saw six adverse event related withdrawals (with a total of seven adverse events reported). As in the adult pivotal efficacy study, Study SMO30006 there

were two withdrawals, one in each treatment group due to asthma exacerbations but none of the other events leading to treatment discontinuation occurred in more than one subject. Overall only one patient was withdrawn from the salmeterol HFA MDI treatment group (asthma exacerbation); five patients reporting six events were withdrawn from the salmeterol CFC MDI treatment group.

In Study SLPT18 there were 18 adverse event related withdrawals, eight in patients receiving salmeterol HFA MDI and 10 in patients receiving salmeterol CFC MDI. As in the adult study with the long-term extension, Study SLGT39 the main reason for withdrawal in this study was asthma, in six children receiving salmeterol HFA MDI and in eight receiving salmeterol CFC MDI.

Supporting Studies

There were few withdrawals due to adverse events from the five supporting studies and the incidence of withdrawal from the salmeterol HFA MDI and the salmeterol CFC MDI treatment groups was similar with asthma exacerbations being the most common reason for withdrawal.

Serious Adverse Events

Generally the incidence of serious adverse events across the clinical programme was low. Few were considered related to study treatments and a slightly greater incidence was seen in the salmeterol CFC MDI treatment groups. In the two pivotal studies, Study SMO30006 (adults) and SMO30007 (children), no serious adverse events were considered drug-related. Four out of seven patients in the adult study (of whom only one received salmeterol HFA MDI) were described as due to asthma exacerbations. In the study in children there were no serious adverse events in the salmeterol HFA MDI treatment group and of the three reported in the salmeterol CFC MDI treatment group one was an asthma exacerbation and the other two were respiratory tract infections.

In the long-term study in adults, Study SLGT39 the incidence of severe adverse events was lower in the salmeterol HFA MDI treatment group than in the salmeterol CFC treatment group, 6% compared with 9% of subjects/17 events compared with 30 events in the two treatment groups, respectively. One event in the salmeterol HFA MDI treatment group was described as possibly related to study medication (asthma attack) and this compared with two subjects reporting four events in the salmeterol CFC MDI treatment group considered to possibly be drug-related. These four events included two episodes of status asthmaticus, and two reports of glaucoma. In the 2-week post-treatment follow-up period one patient receiving salmeterol HFA MDI was reported with severe hypokalaemia diagnosed following an abnormal ECG (extrasystoles, repolarisation abnormalities).

In the long-term treatment extension in children, Study SLPT18 the incidence of serious adverse events was similar across the two treatment groups, three events only were considered related to treatment, one following salmeterol HFA MDI (asthma exacerbation) and two following salmeterol CFC MDI (upper respiratory tract infection and asthma attack).

In the supporting studies the incidence of serious adverse events was low and the most common event reported was that of asthma exacerbation.

Deaths
There were a total of five deaths in the clinical programme presented. Four were adults (two patients receiving salmeterol HFA MDI and two patients receiving salmeterol CFC MDI) and one was a child (receiving salmeterol HFA MDI).

The two deaths in adults receiving treatment with salmeterol HFA MDI were in Study SLGT39 and were considered by the investigator to be unrelated to the study drug. One female patient suffered a respiratory and cardiac arrest following a severe respiratory episode on Day 313 of the study (the patient did not appear to be taking inhaled steroids) and the second patient, a male died at home, cause unknown but following a period of hospitalisation for non-cardiac chest pain and a possible transient ischaemic episode. The two deaths in adults receiving salmeterol CFC MDI occurred in Study SLGT41 and were considered by the investigator to be either unrelated (myocardial infarction in a male patient with a history of diabetes, hyperlipidameia and hypertension) or unlikely to be related (male patient with heart failure) to the study drug.

The death of a child occurred in Study SLPT18. The child had received salmeterol HFA MDI for 10 months, developed an exercise-induced asthma crisis and aspiration pneumonia. Death was considered unrelated to study treatment.

Pregnancies
Four pregnancies were reported during the clinical programme, only one in a patient receiving salmeterol HFA MDI. The patient was withdrawn and the applicant provides no information as to the outcome of the pregnancy.

Laboratory Data
Laboratory evaluations were not carried out in the two pivotal studies, Studies SMO30006 and SMO30007.

In the two key studies, Studies SLGT39 and SLPT18 and in the supporting studies the laboratory findings were unremarkable. No safety issues were identified and there was no clear treatment effect on any laboratory parameters (including serum potassium). There was no evidence of an effect of treatment with salmeterol HFA MDI.

Safety in Special Populations
Safety in the Clinical Pharmacology Studies
In Study SLGB10006 the clinical pharmacology study carried out with the product proposed for the market, 24 subjects reported a total of 93 adverse events. The majority (79/93) were described as mild and the most frequently reported events were headache, tremor and palpitations. The incidence of events, and of those deemed to be drug-related events, was similar for all doses and placebo but with the exception of the comparison between salmeterol CFC 300μg and placebo where a markedly higher incidence of adverse events and drug-related events were seen with the active drug. It is noted that

although the number of subjects reporting events on salmeterol HFA 300µg was similar to the number reporting events in the other salmeterol dose groups (150 and 50µg doses) the actual number of events reported by subjects receiving salmeterol HFA 300µg was higher. However the number of events reported at this dose level (300µg) was not as high as the number reported at the corresponding dose level of salmeterol CFC MDI (15 events compared with 26, respectively).

In the other two clinical pharmacology studies, Studies C92-038 and C94-022 very few events were reported following inhalation of salmeterol HFA MDI.

There were no deaths or other serious adverse events reported in the clinical pharmacology programme.

Studies SLGB10006 and C92-038 were set up to look at high doses of salmeterol and changes in serum potassium and plasma glucose concentrations. The findings are discussed above at 2.1 *Pharmacodynamics*.

Safety Related to Drug-Drug Interactions and Other Interactions
No drug interactions were reported in studies included in these applications.

Data from Ongoing Trials
There are no ongoing studies.

Post Marketing Data
No post marketing experience existed with salmeterol formulated with propellant HFA 134a at the time of approval. However, the product has subsequently been launched and has been on the market since December 2005. PSURs containing post-marketing data on salmeterol formulated with propellant HFA 134a are under review.

The *CPMP Note for Guidance: Replacement of Chlorofluorocarbons (CFCs) in Metered Dose Inhalation Products III/5378/93 – Final* requests that applications for Marketing Authorisations for metered dose inhalation products containing propellant HFA-134a should include proposals *to monitor the introduction of the new non-CFC products in order to identify rare and unexpected adverse events. A method such as the use of record linkage schemes should be considered as these could provide a means for prospectively monitoring the new non-CFC propellants against historical data relating to the products using CFC propellants.*

Since the launch of salmeterol formulated with CFC propellants in October 1990 and up until 31 October 2003 the estimated use provides approximately 21.8 million patient-years of exposure.

These applications are the fourth submission from the applicant for an inhaled medicine formulated with the non-CFC propellant, HFA-134a. The clinical studies submitted at the time of these previous submissions and post-marketing experience have confirmed that propellant HFA-134a is a suitable alternative to CFC propellants in pressurised

metered dose inhalers. Salbutamol, fluticasone propionate and the combination of salmeterol and fluticasone propionate have all been reformulated with propellant HFA-134a and are available on the market as Ventolin Evohaler, Flixotide Evohaler and Seretide Evohaler, respectively. All three products are formulated with HFA-134a alone (with no other excipients). Ventolin Evohaler and Flixotide Evohaler have been available on the market in the UK since June 1997 and Seretide Evohaler since June 2000 and the applicant has included in this submission the study report for Study EP140069, the report on the post-marketing experience with the salmeterol/fluticasone propionate combination (Seretide Evohaler) formulated with propellant HFA-134a.

The estimated cumulative patient exposure to these three reformulated (with propellant HFA-134a) inhalers up to 31 October 2003 is 20.9 million patient-years which includes 2.2 million patient-years of exposure to the reformulated salmeterol/fluticasone propionate combination inhaler, Seretide Evohaler.

The types of adverse reactions and the reporting rates following introduction of the reformulated inhalers have been similar to those seen with the original CFC-containing formulations.

In the light of extensive post-marketing experience with the above listed active drugs formulated with propellant HFA-134a and in the knowledge that one of the previously marketed reformulated inhalers is a combination inhaler containing salmeterol, the applicant requests that the requirement to generate post-marketing data with this new CFC-free formulation of salmeterol be waived.

Excipients
The sole excipient in this formulation is the non-chlorofluorocarbon propellant HFA-134a (Norflurane).

Preclinical testing of HFA-134a has been carried out by the applicant and in October 1994 the applicant applied to the CPMP for approval for the use of HFA-134a as an alternative propellant in metered dose inhalers. The conclusions reached by the CPMP are stated above at 1.2 *Background*.

Assessor's Comment
The safety assessment of salmeterol formulated with propellant HFA-134a shows a comparable safety profile to that of salmeterol formulated with CFC propellants in respect of adverse events. Both formulations appear well tolerated and no unusual or unexpected adverse events were reported in either adults, adolescents or in children four years of age and older.

The most commonly reported adverse events were events which might be expected in a population of patients with asthma or in patients receiving $beta_2$ adrenergic agonists. The incidence of cardiovascular events was low. Few patients were withdrawn from the clinical programme and the most common reason for withdrawal was asthma exacerbation. The incidence of serious adverse events was also low, few were considered

related to study treatments and again asthma exacerbation was the most common event reported. (A slightly greater incidence of serious adverse events was seen in the salmeterol CFC MDI treatment groups).

Of note are the five deaths in the clinical programme presented (described at 4.5 *Deaths* above) and of the five, the three which occurred in patients receiving salmeterol HFA MDI (two adults and one child) none was considered related to study treatment.

In the clinical pharmacology studies salmeterol HFA 50µg appeared to have no significant effect on heart rate, serum potassium, QTc interval, systemic and diastolic blood pressure or plasma glucose. However dose-related beta agonist pharmacodynamic effects are seen as the dose of salmeterol HFA was increased to 150µg and 300µg. It is of note that the dose-related effects seen did appear to be consistently less when compared with the beta agonist effects seen with salmeterol formulated with CFC propellants and administered at the same dose level. The pharmacokinetic findings indicate lower systemic exposure when salmeterol is formulated with propellant HFA-134a than when formulated with CFC propellants.

The applicant states that no adverse effects of withdrawal are reported in the studies presented, that there are no data on overdose and that there is no evidence of abuse potential. Extrapolation from the clinical pharmacology data might suggest that the effects of overdose would be no worse when salmeterol is formulated with propellant HFA-134a than when formulated with CFC propellants.

Post Marketing Experience

Although there is no post-marketing experience with salmeterol formulated with propellant HFA-134a the applicant does make reference to the post-marketing experience with their combination inhaler containing salmeterol and fluticasone propionate and formulated with propellant HFA-134a (Seretide Evohaler) and to their other products available on the market and formulated with propellant HFA-134a (salbutamol as Ventolin Evohaler and fluticasone propionate (alone) as Flixotide Evohaler). The applicant argues that in the light of extensive post-marketing experience with these reformulated products, all reformulated with propellant HFA-134a (estimated cumulative patient exposure to the three reformulated inhalers to 31 October 2003 is 20.9 million patient-years), and in the knowledge that one of the previously marketed reformulated inhalers is a combination inhaler containing salmeterol (salmeterol/fluticasone propionate combination inhaler, Seretide Evohaler, with 2.2 million patient-years of exposure) it might be considered that the requirement to generate post-marketing data with this new CFC-free formulation of salmeterol could be waived.

These arguments can be accepted; it is felt that the requirement for a Phase IV post-marketing surveillance study could indeed be waived on this occasion.

CLINICAL OVERVIEW/CLINICAL EXPERT

This was written by an appropriately qualified person.

PRODUCT LITERATURE

Summary of Product Characteristics (SPC)

The SPCs for these four products are identical apart from product name. These are considered to be medically satisfactory.

Patient Information Leaflet

These are medically satisfactory.

Product Labelling

These are medically satisfactory.

CONCLUSIONS

Clinical Pharmacology

Pharmacodynamics

At a dose of 50μg the systemic pharmacodynamic effects of salmeterol whether formulated with propellant HFA-134a or with CFC propellants were equivalent. Salmeterol formulated with propellant HFA-134a and administered in a dose of 50μg appeared to have no significant effect on heart rate, serum potassium, QTc interval, systolic and diastolic blood pressure or plasma glucose. Salmeterol formulated with HFA-134a and administered in single doses of 150μg and 300μg produced dose-related beta agonist pharmacodynamic effects but these appeared to be consistently less than those seen with salmeterol formulated with CFC propellants and administered at the same dose level.

Pharmacokinetics

The pharmacokinetic findings would suggest lower systemic exposure with similar or lesser systemic pharmacodynamic effects when salmeterol is formulated with propellant HFA-134a compared with the original formulation of salmeterol formulated with CFC propellants.

Clinical Efficacy

The clinical programme presented in respect of efficacy demonstrates that salmeterol when formulated with propellant HFA-134a is at least as effective as salmeterol formulated with CFC propellants in the treatment of adults, adolescents and children aged between 4 and 11 years with asthma. The effects seen were similar whether or not patients used the Volumatic spacing device.

Safety

The safety assessment of salmeterol formulated with propellant HFA-134a shows a comparable safety profile to that of salmeterol formulated with CFC propellants in respect of adverse events. Both formulations appear well tolerated and no unusual or unexpected adverse events were reported in either adults and adolescents or in children 4 years of age and older.

In the light of the applicant's post-marketing experience with inhaled active substances formulated with propellant HFA-134a alone (without other excipients) and in the light of post-marketing experience with the combination inhaler containing salmeterol

and fluticasone propionate formulated with propellant HFA-134a, the applicant's request that the requirement to generate post-marketing data with this new CFC-free formulation of salmeterol alone be waived, is accepted.

Paediatric Development Plan
The applicant requests use of these products in children aged 4 years and older and this is in line with the recommendations for use in children for the reference product, the applicant's original product, Serevent Inhaler 25 micrograms per actuation pressurised metered dose inhaler, PL 10949/0068.

The applicant has submitted a pivotal study examining repeat dosing over 12 weeks duration in 547 children with asthma (aged between 4 and 11 years) in which salmeterol formulated with propellant HFA-134a is compared with salmeterol formulated with CFC propellants (the applicant's original product, Serevent Inhaler) each administered at a dose of 50 micrograms (2 x 25 micrograms) twice daily, in an attempt to demonstrate that the two formulations are clinically equivalent. The study is discussed in Sections 3.2, 3.7, 4.2.1, 4.3.1, 4.4, 4.5, 4.7, 4.13 and 7.2 of this Report.

In conclusion, it may be considered that the single study described is acceptable in respect of both efficacy and safety and that salmeterol reformulated with propellant HFA-134a may be used in children across the same age range for which the original product formulated with chlorofluorocarbon propellants is authorised.

Risk/Benefit
The data presented confirm that the risk/benefit ratio for salmeterol formulated with propellant HFA-134a is acceptable.

CLINICAL AND PRECLINICAL ASSESSORS' CONCLUSIONS
It is recommended that Marketing Authorisations be granted for these products.

Module 6

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

The following “non-confidential” changes have been made to these licences in the reference member state since the conclusion of the first-wave MRP:

Date submitted	Application type	Scope	Outcome
10/11/2006	Type II	To include a combination pack in addition to the single inhaler pack already approved for Salmeterol Inhaler 25 micrograms per actuation pressurised inhalation suspension, which will only be marketed in Nehterlands (UK/H/0883/001/MR only).	Granted 29/01/2007
17/01/2007	Type IB	To change the registered tradename of Salmeterol Inhaler from "Salmeterol inhalator 25 microgram, aërosol suspensie 25 microgram per dosis" to "Serevent Volumatic Inhalator 25 CFK-vrij, aërosol suspensie 25 microgram/dosis" in the Netherlands (UK/H/0883/001/MR only).	Granted 03/03/2007
26/09/2006	Type II	To modify the sections 4.4 (Special warnings) and 5.1 (Pharmacodynamic properties) as requested by the CHMP Pharmacovigilance working party following a review of the safety of long-acting beta2-agonists.	Granted 04/10/2007
07/12/2006	Type IA	To register the addition of GlaxoSmithKline Pharmaceuticals S.A., ul. Grunwaldzka 189, 60 - 322 Pozan, Poland as a site of batch release of the finished product.	Granted 19/12/2006
17/01/2007	Type IB	To change the registered tradename of Salmeterol Inhaler from "Salmeterol inhalator 25 microgram, aërosol suspensie 25 microgram per dosis" to "Serevent Volumatic Inhalator 25 CFK-vrij, aërosol suspensie 25 microgram/dosis" in the Netherlands *(UK/H/0883/001/MR only).*	Granted 24/04/2007
26/03/2007	Type II	To update sections 4.2 (Posology and method of administration) and 6.4 (Special precautions for storage) of the SPC and PIL in order to ensure consistent guidance on use, handling and storage. To also correct some typographic errors and make name changes in the leaflet.	Granted 24/07/2007

Date submitted	Application type	Scope	Outcome
15/11/2007	Type IA	To register a change of the marketing authorisation holder in Slovenia only, from 'GlaxoSmithKline d.o.o., družba za promet s farmacevtskimi izdelki, Ljubljana, Knezov štradon 90, 1000 Ljubljana, Slovenija', to 'Montrose d.o.o., Ribičičeva ulica 33, 1000 Ljubljana, Slovenija'.	Granted 15/11/2007