Serevent Diskus

1. NAME OF THE MEDICINAL PRODUCT

Serevent Diskus

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Serevent Diskus is a moulded plastic device containing a foil strip with regularly spaced blisters each containing 50 micrograms of salmeterol (as xinafoate).

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Inhalation powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Salmeterol is a selective β_2-agonist indicated for reversible airways obstruction in patients with asthma and chronic obstructive pulmonary disease (COPD).

In asthma (including nocturnal asthma and exercise induced symptoms) it is indicated for those treated with inhaled corticosteroids who require a long-acting beta agonist in accordance with current treatment guidelines.

4.2 Posology and method of administration

Serevent Diskus is not a replacement for inhaled or oral corticosteroids which should be continued at the same dose, and not stopped or reduced, when treatment with Serevent Diskus is initiated.

Serevent Diskus is for inhalation use only.

Serevent Diskus should be used regularly. The full benefits of treatment will be apparent after several doses of the drug.

In asthma
Adults (including the elderly): One inhalation (50 micrograms) twice daily, increasing to two inhalations (2 x 50 micrograms) twice daily if required.

Children 4 years and over: One inhalation (50 micrograms) twice daily.

The dosage or frequency of administration should only be increased on medical advice.

There are insufficient clinical data to recommend the use of Serevent Diskus in children under the age of four.

In chronic obstructive pulmonary disease
Adults (including the elderly): One inhalation (50 micrograms) twice daily.
Children: Not appropriate.

Special patient groups: There is no need to adjust the dose in patients with impaired renal function.

Using the Diskus:

The Diskus should be used in a standing or sitting position. The device is opened and primed by sliding the lever. The mouthpiece is then placed in the mouth and the lips closed round it. The dose can then be inhaled and the device closed.

4.3 Contraindications

Hypersensitivity to salmeterol xinafoate or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

The management of asthma should normally follow a stepwise programme.

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

Serevent is not a replacement for inhaled or oral corticosteroids in asthma (see section 4.1). Its use is complementary to them. Asthmatic patients must be warned not to stop steroid therapy, and not to reduce it without medical advice, even if they feel better on salmeterol.

Serevent 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 bronchodilators, in particular short-acting inhaled β_2-agonists, to relieve symptoms, indicates deterioration of asthma control. In this case, the patient should be instructed to seek medical advice.

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.

Paradoxical bronchospasm
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 Diskus should be discontinued immediately, the patient assessed, and if necessary alternative therapy instituted (see section 4.8).

The pharmacological side effects of beta-$_2$ agonist treatment, such as tremor, subjective palpitations and headache have been reported, but tend to be transient and to reduce with regular therapy (see section 4.8).

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

Thyrotoxicosis
Serevent should be administered with caution in patients with thyrotoxicosis.
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Blood glucose levels
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.

Hypokalaemia
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 hypoxia and by concomitant treatment with xanthine derivatives, steroids and diuretics. Serum potassium levels should be monitored in such situations.

Respiratory-related events
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.

Ketoconazole
Concomitant use of systemic ketoconazole significantly increases systemic exposure to salmeterol. This may lead to an increase in the incidence of systemic effects (e.g. prolongation in the QTc interval and palpitations). Concomitant treatment with

ketoconazole or other potent CYP3A4 inhibitors should therefore be avoided unless the benefits outweigh the potentially increased risk of systemic side effects of salmeterol treatment (see section 4.5).

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

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Beta-adrenergic blockers may weaken or antagonise the effect of salmeterol. Both non-selective and selective β-blockers should be avoided 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 hypoxia and by concomitant treatment with xanthine derivatives, steroids and diuretics.

Potent CYP3A4 inhibitors
Co-administration of ketoconazole (400 mg orally once daily) and salmeterol (50 mcg inhaled twice daily) in 15 healthy subjects for 7 days resulted in a significant increase in plasma salmeterol exposure (1.4-fold Cmax and 15-fold AUC). This may lead to an increase in the incidence of other systemic effects of salmeterol treatment (e.g. prolongation of QTc interval and palpitations) compared with salmeterol or ketoconazole treatment alone (see section 4.4).

Clinically significant effects were not seen on blood pressure, heart rate, blood glucose and blood potassium levels. Co-administration with ketoconazole did not increase the elimination half-life of salmeterol or increase salmeterol accumulation with repeat dosing.

The concomitant administration of ketoconazole should be avoided, unless the benefits outweigh the potentially increased risk of systemic side effects of salmeterol treatment. There is likely to be a similar risk of interaction with other potent CYP3A4 inhibitors (e.g. itraconazole, telithromycin, ritonavir).

Moderate CYP 3A4 inhibitors
Co-administration of erythromycin (500mg orally three times a day) and salmeterol (50µg inhaled twice daily) in 15 healthy subjects for 6 days resulted in a small but non-statistically significant increase in salmeterol exposure
(1.4-fold Cmax and 1.2-fold AUC). Co-administration with erythromycin was not associated with any serious adverse effects.

4.6 Fertility, pregnancy and lactation

Pregnancy
A moderate amount of clinical data on pregnant women (between 300 to 1000 pregnancy outcomes) indicate no malformative or feto/ neonatal toxicity of salmeterol.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity with the exception of evidence of some harmful effects on the fetus at very high dose levels (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of Serevent during pregnancy.

Breast-feeding
Available pharmacodynamic/toxicological data in animals have shown excretion of salmeterol in milk. A risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Serevent therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

4.7 Effects on the 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 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), 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)	Uncommon
	Anaphylactic reactions including oedema and angioedema,bronchospasm and anaphylactic shock	Very Rare
Metabolism & Nutrition Disorders	Hypokalaemia	Rare
	Hyperglycaemia	Very Rare
Psychiatric Disorders	Nervousness	Uncommon
	Insomnia	Rare
Nervous System Disorders	Headache (see section 4.4)	Common
	Tremor (see section 4.4)	Common
	Dizziness	Rare
Cardiac Disorders	Palpitations (see section 4.4)	Common

System Organ Class	Adverse Reaction	Frequency
	Tachycardia	Uncommon
	Cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia and extrasystoles).	Very Rare
Respiratory, Thoracic & Mediastinal Disorders	Oropharyngeal irritation	Very Rare
	Paradoxical bronchospasm (see section 4.4)	Very rare
Gastrointestinal Disorders	Nausea	Very Rare
Musculoskeletal & Connective Tissue Disorders	Muscle cramps	Common
	Arthralgia	Very Rare
General Disorders and Administration Site Conditions	Non-specific chest pain	Very Rare

The pharmacological side effects of β_2-agonist treatment, such as tremor, subjective palpitations and headache, 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/
Additionally, you should also report to GSK Israel (il.safety@gsk.com).

4.9 Overdose

Symptoms and signs
The signs and symptoms of salmeterol overdosage are those typical of excessive β_2-adrenergic stimulation including dizziness, increases in systolic blood pressure, tremor, headache and tachycardia.

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

Treatment
If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Selective β_2-adrenoreceptor agonists.

ATC Code: R03AC12

Salmeterol is a selective long-acting (usually 12 hours) β_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 bronchodilatation, lasting for at least 12 hours, than recommended doses of conventional short-acting β_2-agonists. *In vitro* tests have shown that salmeterol is a potent and long-lasting inhibitor of the release from the human lung of mast cell mediators, such as histamine, leukotrienes and prostaglandin D2. In man, salmeterol inhibits the early and late phase response to inhaled allergen; the latter persisting for over 30 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 Serevent Diskus is prescribed.

Salmeterol has been studied in the treatment of conditions associated with COPD, and has been shown to improve symptoms and pulmonary function, and quality of life. Salmeterol acts as a β_2-agonist on the reversible component of the disease. *In vitro* salmeterol has also been shown to increase cilial beat frequency of human bronchial epithelial cells, and also reduce a ciliotoxic effect of *Pseudomonas* toxin on the bronchial epithelium of patients with cystic fibrosis.

<u>Asthma Clinical Trials</u>

The Salmeterol Multi-centre 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.

<u>Key findings from SMART: primary endpoint</u>

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.

COPD clinical trials

TORCH study

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

	Placebo N = 1524	**Salmeterol 50 N = 1521**	**FP 500 N = 1534**	**Seretide 50/500 N = 1533**
All cause mortality at 3 years				

Number of deaths (%)	231 (15.2%)	205 (13.5%)	246 (16.0%)	193 (12.6%)
Hazard Ratio vs Placebo (CIs) p value	N/A	0.879 (0.73, 1.06) 0.180	1.060 (0.89, 1.27) 0.525	0.825 (0.68, 1.00) 0.052[1]
Hazard Ratio Seretide 50/500 vs components (CIs) p value	N/A	0.932 (0.77, 1.13) 0.481	0.774 (0.64, 0.93) 0.007	N/A

1. Non significant P value after adjustment for 2 interim analyses on the primary efficacy comparison from a log-rank analysis stratified by smoking status

There was a trend towards improved survival in subjects treated with Seretide compared with placebo over 3 years however this did not achieve the statistical significance level $p \leq 0.05$. The percentage of patients who died within 3 years due to COPD-related causes was 6.0% for placebo, 6.1% for salmeterol, 6.9% for FP and 4.7% for Seretide.

The mean number of moderate to severe exacerbations per year was significantly reduced with Seretide as compared with treatment with salmeterol, FP and placebo (mean rate in the Seretide group 0.85 compared with 0.97 in the salmeterol group, 0.93 in the FP group and 1.13 in the placebo). This translates to a reduction in the rate of moderate to severe exacerbations of 25% (95% CI: 19% to 31%; $p<0.001$) compared with placebo, 12% compared with salmeterol (95% CI: 5% to 19%, $p=0.002$) and 9% compared with FP (95% CI: 1% to 16%, $p=0.024$). Salmeterol and FP significantly reduced exacerbation rates compared with placebo by 15% (95% CI: 7% to 22%; $p<0.001$) and 18% (95% CI: 11% to 24%; $p<0.001$) respectively.

Health Related Quality of Life, as measured by the St George's Respiratory Questionnaire (SGRQ) was improved by all active treatments in comparison with placebo. The average improvement over three years for Seretide compared with placebo was -3.1 units (95% CI: -4.1 to -2.1; $p<0.001$), compared with salmeterol was -2.2 units ($p<0.001$) and compared with FP was -1.2 units ($p=0.017$). A 4-unit decrease is considered clinically relevant.

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

5.2 Pharmacokinetic properties

Salmeterol acts locally in the lung, therefore plasma levels are not predictive of therapeutic effects. In addition there are only limited data available on the pharmacokinetics of salmeterol because of the technical difficulty of assaying the drug in plasma because of the

very low plasma concentrations at therapeutic doses (approximately 200 pg/ml or less) achieved after inhaled dosing.

After regular dosing with salmeterol xinafoate, xinafoic acid can be detected in the systemic circulation, reaching steady state concentrations of approximately 100 ng/ml. These concentrations are up to 1000-fold lower than steady state levels observed in toxicity studies. These concentrations in long term regular dosing (more than 12 months) in patients with airways obstruction, have been shown to produce no ill effects.

5.3 Preclinical safety data

In reproduction studies in animals, some effects on the fetus, typical of a β_2-agonist, have been observed at very high doses.

Salmeterol xinafoate produced no genetic toxicity in a range of studies using either prokaryotic or eukaryotic cell systems *in vitro* or *in vivo* in the rat.

Long term studies with salmeterol xinafoate, induced class-related benign tumours of smooth muscle in the mesovarium of rats and the uterus of mice. The scientific literature and our own pharmacological studies provide good evidence that these effects are species-specific and have no relevance for clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose (which contains milk protein).

6.2 Incompatibilities

None reported.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package.

6.5 Nature and contents of container

The powder mix of salmeterol xinafoate and lactose is filled into a blister strip consisting of a formed base foil with a peelable foil laminate lid. The foil strip is contained within the Diskus device. Pack size 60.

6.6 Special precautions for disposal and handling

The powdered medicine is inhaled through the mouth into the lungs.

The Diskus device contains the medicine in individual blisters which are opened as the device is manipulated.

For detailed instructions for use refer to the Patient Information Leaflet in every pack.

7. Manufacturer

Glaxo Wellcome Production, Evreux, France

8 License Holder and Importer

GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva

9. License Number

067-16-28303

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