NEW ZEALAND DATA SHEET

1. PRODUCT NAME

SEREVENT Accuhaler, 50 micrograms, inhalation powder

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each delivered dose contains 50 micrograms of salmeterol as salmeterol xinafoate.

Excipients with known effect:

SEREVENT Accuhaler also contains the excipient lactose (see Section 4.3 Contraindications).

For full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Inhalation powder.

SEREVENT Accuhaler is a moulded plastic device containing a foil strip with regularly placed blisters.

4. CLINICAL PARTICULARS

4.1 Indications

Asthma

SEREVENT is indicated for long-term regular treatment of reversible airways obstruction in asthma (including nocturnal asthma and exercise-induced asthma) in adults and children aged 4 years and over who are receiving inhaled or oral corticosteroids.

SEREVENT should be used only as an adjunct to corticosteroids in the management of asthma.

SEREVENT should not be used in the treatment of acute asthmatic symptoms, or in patients whose asthma can be managed by occasional use of short-acting beta-2 agonists.

Chronic Obstructive Pulmonary Disease (COPD)

SEREVENT is indicated for long-lasting (12 hour) bronchodilation in adults with reversible airways obstruction due to COPD.

4.2 Dose and method of administration

Dose

SEREVENT Accuhaler is administered by the inhaled route only.

Patients must be warned not to stop steroid therapy and not to reduce it without medical advice even if they feel better on SEREVENT.

Asthma

In the management of reversible airways obstruction due to asthma, SEREVENT (as with other long-acting beta-2 agonists) **must only be administered in combination with anti-inflammatory therapy such as inhaled corticosteroids (ICS).** In asthma patients not already receiving anti-inflammatory therapy, this must be initiated at the same time as SEREVENT.

Adults:
One inhalation (50 micrograms of salmeterol) twice daily.

In asthma patients with more severe airways obstruction up to 2 inhalations (2 x 50 micrograms of salmeterol) twice daily may be of benefit.

Children over 4 years of age:
One inhalation (50 micrograms of salmeterol) twice daily.

There are insufficient clinical data at present to recommend the use of SEREVENT in children under 4 years of age.

Patients should be instructed not to take additional doses to treat symptoms but to take a short-acting inhaled beta-2 agonist.

The onset of effective bronchodilation (>15% improvement in FEV 1) with SEREVENT occurs within 10 to 20 minutes in asthma patients. The full benefits will be apparent after the first few doses of the drug. The bronchodilator effects of SEREVENT usually last for 12 hours. This is particularly useful in the treatment of nocturnal symptoms in asthma, COPD and chronic bronchitis, and in the management of exercise induced asthma.

As there may be adverse effects associated with excessive dosing of this class of drug, the dosage or frequency of administration should only be increased on medical advice.

COPD

Adults:
One inhalation (50 micrograms of salmeterol) twice daily.

Special populations

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

4.3 Contraindications

Hypersensitivity to any ingredient of the preparation (see section 6.1 List of Excipients).

Contraindicated in patients with severe milk protein allergy.

4.4 Special warnings and precautions for use

The onset of effective bronchodilation (>15% improvement in FEV 1) with SEREVENT occurs within 10 to 20 minutes in asthma patients. The full benefits will be apparent

after the first few doses of the drug. The bronchodilator effects of SEREVENT usually last for 12 hours. This is particularly useful in the treatment of nocturnal symptoms in asthma, COPD and chronic bronchitis, and in the management of exercise induced asthma.

SEREVENT should not be initiated in patients with unstable or acutely deteriorating asthma, which may be a life threatening condition. Serious acute respiratory events, including fatalities have been reported when salmeterol has been initiated in the situation. Although it is not possible from these reports to determine whether salmeterol contributed to these adverse events or failed to relieve the deteriorating asthma, the use of salmeterol in this setting is inappropriate.

Use with corticosteroids for asthma

SEREVENT is a long acting beta-2 agonist and should be used only as an adjunct to corticosteroids in the management of asthma. SEREVENT is not a replacement or substitute for oral or inhaled corticosteroids. Its use is complementary to them.

Patients must be warned not to stop or reduce corticosteroid therapy, even if they feel better. Any change in corticosteroid dosage should be made ONLY after clinical evaluation.

In asthma patients not already receiving anti-inflammatory therapy, this should be initiated when starting therapy with SEREVENT.

Data from a large US study (SMART) comparing the safety of salmeterol (50 micrograms inhaler twice daily) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol versus those on placebo (13 out of 13,176 vs 3 out of 13,179 over 28 weeks). Data from this study suggested that African-American patients may be at greater risk of serious respiratory-related events or deaths when using salmeterol compared to placebo. It is not known if this was due to pharmacogenetic or other factors. Patients on salmeterol who did not receive inhaled corticosteroids as part of their usual therapy at the start of the study experienced a greater number of asthma-related deaths compared to those taking placebo (9 out of 7,049 vs. 0 out of 7,041). There were no significant differences between the salmeterol and placebo treatment groups among patients who were receiving inhaled corticosteroids at the start of the study. Long-acting beta-2–agonists, such as salmeterol, should be prescribed with corticosteroids

Acute asthma symptoms

SEREVENT is suitable for long-term regular, twice-daily treatment to control symptoms of reversible airways obstruction.

In view of its slower onset of action (10 to 20 minutes) it should not be used to relieve acute symptoms of asthma, for which a faster acting (within 5 minutes) inhaled bronchodilator (e.g. short-acting beta-2 agonists such as salbutamol) should be given.

It is crucial to inform patients of this and prescribe a short-acting inhaled beta-2 agonist for this purpose.

Deterioration of asthma control

Sudden and progressive deterioration of asthma control is potentially life threatening and considerations should be given to increasing corticosteroid therapy. In patients at risk, daily peak flow monitoring may be instituted.

Increasing use of bronchodilators, in particular short-acting inhaled beta-2 agonists, to relieve symptoms indicates deterioration of asthma control. Severe exacerbations of asthma must be treated in the normal way with nebulised or parenteral bronchodilators and parenteral corticosteroids, together with other supportive measures. Use in patients with other medical conditions.

As with other inhalational therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. This should be treated immediately with a fast-acting inhaled bronchodilator. SEREVENT should be discontinued immediately, the patient assessed, and if necessary alternative therapy instituted.

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.

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, SEREVENT should be used with caution in patients with pre-existing cardiovascular disease.

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

SEREVENT should be administered with caution to patients with thyrotoxicosis.

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

4.5 Interaction with other medicines and other forms of interaction

It was observed in a drug interaction study that concomitant use of systemic ketoconazole increases exposure to salmeterol. This may lead to prolongation in the QTc interval. Caution must be exercised when strong CYP3A4 inhibitors (eg ketoconazole) are co-administered with salmeterol (see section 4.4 Special warnings and precautions for use and 5.2 Pharmacokinetic Properties).

Both non-selective and selective beta-blockers should be avoided in patients with reversible obstructive airways disease, unless there are compelling reasons for their use.

Co-administration of ketoconazole and salmeterol resulted in a significant increase in plasma salmeterol exposure (1.4-fold C_{max} and 15-fold AUC) and this may cause a prolongation of the QTc interval (see section 4.4 Special warnings and precautions for use and 5.2 Pharmacokinetic Properties).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well controlled studies of salmeterol in pregnant women. The effect of salmeterol on human pregnancy is unknown.

As with any medicine, use of SEREVENT during pregnancy should be considered only if the expected benefit to the mother is greater than any possible risk to the foetus.

In animal studies, some effects on the foetus, typical for a beta-2 agonist, occurred at exposure levels substantially higher than those that occur with therapeutic use. Extensive experience with other beta-2 agonists has provided no evidence that such effects are relevant for women receiving clinical doses.

Breast-feeding

Plasma levels of salmeterol after inhaled therapeutic doses are low and therefore levels in milk should be correspondingly low. Nevertheless as there is limited experience of the use of salmeterol in nursing mothers its use in such circumstances should only be considered if the expected benefit to the mother is greater than any possible risk to the infant.

Studies in lactating animals support the view that salmeterol is likely to be secreted in only very small amounts into breast milk.

Fertility

There are no data on human fertility.

4.7 Effects on the ability to drive and operate machines

None reported.

4.8 Undesirable Effects

Summary of the safety profile

Adverse events 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) and very rare (<1/10,000) including isolated reports. Common and uncommon events were generally determined from clinical trial data. The incidence of placebo was not taken into account. Very rare events were generally determined from post-marketing spontaneous data.

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

Tabulated list of adverse reactions

Immune system disorders

Hypersensitivity Reactions:

Uncommon: Rash.

Very rare: Anaphylactic reactions including oedema and angioedema, bronchospasm and anaphylactic shock.

Metabolism and nutrition disorders

Very rare: Hyperglycaemia.

Nervous system disorders

Common: Tremor and headache (see section 4.4 Special warnings and precautions for use).

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

Cardiac disorders

Common: Palpitations (see section 4.4 Special warnings and precautions for use).

Uncommon: Tachycardia.

Tachycardia occurs more commonly when administered at doses higher than 50 micrograms twice daily.

Very rare: Cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia and extrasystoles.

Respiratory, thoracic and mediastinal disorders

Very rare: Oropharyngeal irritation and paradoxical bronchospasm (see section 4.4 Special warnings and precautions for use)

Musculoskeletal and connective tissue disorders

Common: Muscle cramps.

Very rare: Arthralgia.

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via: https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

The expected symptoms and signs of salmeterol overdosage are those typical of excessive beta-2-adrenergic stimulation, including tremor, headache, tachycardia, increases in systolic blood pressure and hypokalaemia and raised blood glucose levels.

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 Poison Information Centre.

For advice on the management of overdose, contact the National Poisons Information Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective beta-2-adrenoreceptor agonists,

ATC code: R03AC12

Mechanism of action

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 to bronchodilation, lasting for at least 12 hours, than recommended doses of conventional short-acting beta-2 agonists. *In vitro* tests have shown salmeterol is a potent and long-lasting inhibitor of the release, from human lung, of mast cell mediators, such as histamine, leukotrienes and prostaglandin D_2. 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 SEREVENT 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 is prescribed.

SEREVENT 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 beta-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 acidiotoxic effect of pseudomonas toxin on the bronchial epithelium of patients with cystic fibrosis.

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 drug in plasma due to the low plasma concentrations at therapeutic doses (approximately 200pg/mL or less) achieved after inhaled dosing.

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

In a placebo-controlled, crossover drug interaction study in 15 healthy subjects, co-administration of salmeterol (50 micrograms twice daily inhaled) and the CYP3A4 inhibitor ketoconazole (400 mg once daily orally) for 7 days resulted in a significant increase in plasma salmeterol exposure (1.4-fold C_{max} and 15-fold AUC). There was no increase in salmeterol accumulation with repeat dosing. Three subjects were withdrawn from salmeterol and ketoconazole co-administration due to QTc prolongation or palpitations with sinus tachycardia. In the remaining 12 subjects, co-administration of salmeterol and ketoconazole did not result in a clinically significant effect on heart rate, blood potassium or QTc duration (see Warnings and Precautions and Interactions).

An *in vitro* study showed that salmeterol is extensively metabolised to α-hydroxysalmeterol (aliphatic oxidation) by cytochrome P450 3A4 (CYP3A4). A repeat dose study with salmeterol and erythromycin in healthy volunteers showed no clinically significant changes in pharmacodynamic effects at 500 mg three times daily doses of erythromycin.

5.3 Preclinical safety data

In reproduction studies in animals, some effects on the foetus, typical of a beta-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.

Carcinogenicity

Oral administration of salmeterol xinafoate to mice at 0.2, 1.4 or 10 mg/kg/day for 18 months resulted in the development of smooth muscle tumours (leiomyomas and possibly leiomyosarcomas) in the uterus. In rats, combined oral/inhalational administration for 24 months at total dose levels of 0.2, 0.7 and 2.6 mg/kg/day resulted in leiomyomas in the suspensory ligament of the ovaries, as well as an increased incidence of benign pituitary tumours. The smooth muscle tumours in both species are thought to result from chronic stimulation of beta-adrenoceptors in these tissues, whereas the mechanism involved in the development of the pituitary tumours is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose (which contains milk protein) (see Section 4.3 Contraindications).

6.2 Incompatibilities

None reported.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Store below 30 °C

Store in a dry place.

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 with a peelable foil laminate lid.

The foil strip is contained within the Accuhaler device. The Accuhaler device is packaged within a foil laminate overwrap.

Each SEREVENT Accuhaler contains 60 inhalations.

6.6 Special preauction for disposal

Any unused medicinal product or waste should be disposed of in accordance with local requirement.

7. MEDICINES SCHEDULE

Prescription Medicine

8. SPONSOR

GlaxoSmithKline NZ Limited

Private Bag 106600
Downtown
Auckland
NEW ZEALAND

Phone: (09) 367 2900
Fax: (09) 367 2910

9. DATE OF FIRST APPROVAL

31 August 1995

10. DATE OF REVISION OF THE TEXT

17 June 2021

Summary table of changes:

Section changed	Summary of new information
2	Added cross reference to contraindication
4.3	Addition of contraindication relating to milk protein allergy

6.1	Added cross reference to contraindication

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