AUSTRALIAN PRODUCT INFORMATION

SEREVENT ACCUHALER (salmeterol xinafoate) Powder for inhalation

1 NAME OF THE MEDICINE

Salmeterol xinafoate.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SEREVENT ACCUHALER is a moulded plastic device containing a foil strip with regularly placed blisters. Each blister contains 50 micrograms of salmeterol, as salmeterol xinafoate.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Powder for inhalation.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Adults:

Salmeterol is suitable for long-term regular treatment of reversible airways obstruction in asthma (including nocturnal asthma and exercise-induced asthma), in patients who are receiving inhaled or oral corticosteroids. It should not be used in patients whose asthma can be managed by occasional use of short-acting inhaled beta-2 agonists.

Salmeterol also provides long-lasting (12 hour) bronchodilation for the reversible component of airways obstruction due to chronic obstructive pulmonary disease (COPD).

Children aged 4 years and over:

Long-term regular treatment of reversible airways obstruction in asthma (including nocturnal asthma and exercise-induced asthma), in patients who are receiving inhaled or oral corticosteroids. It should not be used in patients whose asthma can be managed by occasional use of short-acting inhaled beta-2 agonists.

4.2 DOSE AND METHOD OF ADMINISTRATION

In order to gain full therapeutic benefit regular usage of salmeterol is recommended in the treatment of reversible airways obstruction. The full benefits will be apparent after the first few doses of the drug. The bronchodilator effects of salmeterol usually last for 12 hours, this is particularly useful in the treatment of nocturnal symptoms in asthma and COPD and in the management of exercise-induced asthma. In the management of exercise-induced asthma, it is not appropriate to use salmeterol immediately before exercise as the onset of action of salmeterol occurs usually in 10-30 minutes and the full benefit may only occur after a longer period of time or with repeated doses.

With salmeterol therapy the requirement for other symptomatic bronchodilator therapy is usually reduced and can sometimes be stopped. If symptoms persist, patients should take a short-acting inhaled beta-2 agonist (eg salbutamol) for relief but this need is usually an indication that control of their airways obstruction is suboptimal and that further treatment should be considered. This may involve treatment with other medications or increased doses of current medications.

As there may be adverse effects associated with excessive dosing, the dosage or frequency of administration should only be increased on medical advice. Patients should be instructed not to take additional doses of salmeterol to treat symptoms arising between the regular dosing intervals but to take a short-acting inhaled beta-2 agonist.

Refer to Section 2 QUALITATIVE AND QUANTITATIVE COMPOSITION for further information.

ADULTS:

SEREVENT ACCUHALER is administered by the inhaled route only.

The usual dose for asthma and COPD is 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 required.

Children aged 4 years and over:

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

There are insufficient clinical data at present to recommend the use of salmeterol in children under 4 years of age. Data from controlled clinical trials beyond 12 months are limited.

Elderly: There is no need to adjust the dose in the elderly.

Impaired Renal Function: In patients with impaired renal function there is no need to adjust the dose.

4.3 CONTRAINDICATIONS

Hypersensitivity to any ingredient of the preparation (see Section 2 QUALITATIVE AND QUANTITATIVE COMPOSITION and Section 6.1 LIST OF EXCIPIENTS).

Contraindicated in patients with severe milk protein allergy.

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.

Corticosteroids:

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. Any change in corticosteroid dosage should be made ONLY after clinical evaluation.

Salmeterol is not a substitute for inhaled or oral corticosteroids. When salmeterol treatment is initiated in patients with asthma or COPD, corticosteroids should not be stopped or reduced.

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

Acute symptoms:

Salmeterol is not designed to relieve acute asthmatic symptoms, for which an inhaled short-acting bronchodilator (eg salbutamol) is required. Patients should be advised to have such rescue medication available. Salmeterol should not be initiated in patients with significantly worsening or acutely deteriorating asthma.

Salmeterol should not be used to treat acute symptoms of asthma. It is crucial to inform patients of this and prescribe a short-acting inhaled beta-2 agonist for this purpose and to warn them that increasing inhaled beta-2 agonist use is a signal of deteriorating asthma or COPD.

As salmeterol has a slower onset of action, a faster acting beta-2 agonist should be used when rapid bronchodilator action is required.

Deterioration:

Sudden and progressive deterioration in asthma control is potentially life-threatening and consideration should be given to starting or increasing corticosteroid therapy. In patients at risk, daily peak flow monitoring may be instituted. Increasing use of bronchodilators, in particular short-acting inhaled beta-agonists to relieve symptoms, indicates deterioration of asthma control. If patients find that short-acting relief bronchodilator treatment becomes less effective or they need more inhalations than usual, medical attention must be sought. In this situation, patients should be reassessed and consideration given to the need for increased anti-inflammatory therapy (eg higher doses of inhaled corticosteroids or a course of oral corticosteroids). Severe exacerbations of asthma must be treated in the normal way with nebulised or parenteral bronchodilators and parenteral corticosteroids, together with other supportive measures. Patients should be advised to have such rescue medication available.

Salmeterol 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 this 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.

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. Due to

the potential increased risk of cardiovascular adverse events, the concomitant use of salmeterol with strong CYP3A4 inhibitors (e.g. ketoconazole, atazanavir, ritonavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir) is not recommended (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS and Section 5.2 PHARMACOKINETIC PROPERTIES).

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

Salmeterol should be administered with caution in patients with thyrotoxicosis.

As with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. If that happens, a short-acting inhaled bronchodilator should be given immediately. SEREVENT should be discontinued and alternative therapy instituted (See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

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 may reduce with regular therapy (See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE 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.

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

Use in the elderly

There is no need to adjust the dose in the elderly.

Paediatric use

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

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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). This increase in plasma salmeterol may cause a prolongation of QTc interval. (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 5.2 PHARMACOKINETIC PROPERTIES).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy

(Pregnancy Category B3)

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 during pregnancy should be considered only if the expected benefit to the mother is greater than any possible risk to the foetus.

Studies in rats showed slight retardation of ossification and prolongation of gestation at oral doses above 0.5 mg/kg/day. In rabbits, cleft palate and other fetal abnormalities were observed at maternal doses above 0.6 mg/kg/day. These effects are similar to those observed with some other beta-2 agonists, and occurred at maternal plasma 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.

Use in lactation

Plasma levels of salmeterol after inhaled therapeutic doses are negligible and therefore levels in milk should be correspondingly low. Nevertheless as there is no 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: common ($\geq$1/100 to $<$1/10), uncommon ($\geq$1/1000 to $<$1/100), and very rare ($<$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.

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 may 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.

Peripheral vasodilation and a compensatory small increase in heart rate may occur in some patients.

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 suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

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, 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 information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Mode of Action: Salmeterol belongs to a new class of selective long-acting beta-2 adrenoceptor agonists and at dosages of less than 100 microgram twice daily has little measurable cardiovascular effect. Salmeterol xinafoate is a racemate, the R-enantiomer being active.

The pharmacological properties of salmeterol offer a slower onset of action, but more effective protection against histamine-induced bronchoconstriction and a longer duration of bronchodilation (lasting for approximately 12 hours) than recommended doses of conventional short-acting beta-2 agonists. The onset of effective bronchodilation (> 15% improvement in FEV_1) occurs within 10 to 30 minutes and peak effect occurs between 3 to 4 hours.

In vitro tests have shown salmeterol is a potent and long-lasting inhibitor of the release, from human lung fragments, of mast cell mediators, such as histamine, leukotrienes and prostaglandin D2. In one study 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 hyperresponsiveness. 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

Clinical trials

Asthma

Adults: Approximately 2500 adults with mild to severe asthma were treated with salmeterol in randomised, double blind studies in the clinical trial program.

667 adults with mild to moderate asthma (PEF or FEV_1 60-90%, and reversibility >15%) were entered in a 3 month, pivotal study. Compared to patients who received salbutamol 200 micrograms four times daily (qid), patients on salmeterol 50 micrograms twice daily (bd, n=334) had significantly improved morning PEF (differences of 31 to 36 L/min) and evening PEF (differences of 9 to 14 L/min). Symptom scores and the requirement for “rescue”

bronchodilator medication were also significantly reduced from the first week of treatment onwards.

Similar results were seen in a study comparing salmeterol 50 micrograms bd with salbutamol 400 micrograms qid using dry powder inhalers.

In 2 separate studies, salmeterol 50 micrograms bd also proved more effective than inhaled salbutamol taken on an “as required” basis.

In patients with moderate to severe asthma (n=283, FEV_1 or PEF<50% of predicted normal value, with FEV_1 reversibility > 15%), salmeterol 100 micrograms bd produced significant improvement in morning and evening PEF over salmeterol 50 microgram bd. The higher dose also improved daytime symptoms and reduced bronchodilator use significantly more than 50 micrograms bd. Other symptoms were equally well controlled on 50 micrograms bd.

In all these studies, salmeterol improved nocturnal asthma measures such as number of nocturnal awakenings, and percentage of nights with no awakenings.

Children: 831 children with asthma, aged 4 to 16, were entered in a total of 8 clinical trials. On entry, they had FEV_1 > 60% or PEF diurnal variation > 15%, with >15% reversibility in FEV_1 or PEF.

Salmeterol 50 micrograms bd significantly improved lung function (morning PEF +17L/min; evening PEF +24L/min), and reduced daytime symptoms, compared to placebo with p.r.n. salbutamol.

Compared to salbutamol 200 microgram bd, salmeterol 50 microgram bd achieved significantly greater asthma control with respect to morning and evening PEF (+14L/min and +17L/min respectively with dry powder inhaler, and +9L/min and +8L/min respectively with the metered dose inhaler).

Salmeterol 50 micrograms bd protected against exercise-induced bronchoconstriction for at least 9 hours in children and 12 hours in adults.

The studies in both adult and paediatric patients showed that improvements in lung function were sustained over a 12-month period.

SEREVENT INHALER and ACCUHALER were demonstrated to be clinically equivalent.

COPD

In 3 randomised double-blind studies, a total of 542 adult patients were treated with salmeterol. Two doses of salmeterol were compared against placebo. At entry, patients had between 5-15% airway reversibility, FEV_1 < 70%, and were either current or past smokers. They were either diagnosed as COPD, or had symptoms (cough/sputum) for > 3 months a year in 2 consecutive years.

Over a 16 week treatment period, compared to placebo, 447 patients on salmeterol 50 micrograms bd had significantly improved median symptom scores during the day and night, increased number of symptom-free nights, reduced use of bronchodilator rescue medication, and improved FEV_1 and FVC. Salbutamol was available as rescue medication in all groups.

No significant treatment differences were seen in exacerbation rates or sputum production. No significant treatment differences were detected with respect to distance walked in a 6 minute period; however, the patients experienced significantly less breathlessness (Borg scale). A similar result was seen in a separate study on the effect of treatment on exercise capacity.

In the 16 week study, the improvements produced by salmeterol 50 micrograms bd resulted in significant quality of life gains for COPD patients. Both investigators' and patients' assessment of effectiveness consistently favoured salmeterol 50 micrograms bd over placebo.

The incidence of drug-related adverse events was similar for placebo and salmeterol 50 micrograms bd. There is no experience with salmeterol in COPD patients beyond 16 weeks.

Post-Market Safety Study

Data from a large US study that compared the safety of salmeterol inhaler 50 micrograms twice daily or placebo added to usual asthma therapy showed no difference between treatments for the primary endpoint which was serious respiratory-related episodes or serious asthma-related episodes (including deaths). However, when asthma-related deaths were analysed alone, there was a small but significant increase in patients receiving salmeterol versus those on placebo (13 out of 13,176 vs 3 out of 13,179 over 28 weeks). In this study the overall death rate was lower than expected, hence it is not clear if any differences seen were due to treatment or other confounding factors. Subgroup analyses revealed no significant difference in respiratory or asthma-related episodes in Caucasian patients, but the data suggest the risk for respiratory-related episodes (20 vs. 5), asthma-related episodes (19 vs. 4) and asthma-related death (7 vs. 1) may be greater for African American patients treated with salmeterol (n=2,366) compared to those treated with placebo (n=2,319). 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.

5.2 PHARMACOKINETIC PROPERTIES

Salmeterol acts locally in the lung therefore plasma levels are not predictive of therapeutic effect. In addition there are only limited data available on the pharmacokinetics of salmeterol because of the technical difficulty of assaying very low plasma concentrations (approximately 200 pg/mL or less) of the drug after inhaled dosing.

Following administration, salmeterol xinafoate is extensively bound (95-98%) to plasma proteins. Elimination of radioactivity from plasma following oral administration of radiolabelled salmeterol xinafoate is slow (mean $t_{½}$ is 67 hours). Excretion is predominantly through the faeces and to a lesser extent urine. Aliphatic hydroxylation appears to be the major route of metabolism in humans.

After regular dosing with salmeterol xinafoate, the xinafoate moiety, hydroxynaphthoic 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 and in longer-term regular dosing (more than 12 months) trials in patients with airways obstruction, there have not been adverse effects attributable to hydroxynaphthoic acid reported.

In a placebo-controlled, crossover drug interaction study in 20 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. The increase in the QTc interval observed with the co-administration of salmeterol and ketoconazole compared with salmeterol and placebo administration was not statistically significant. There were no clinically significant effects seen in heart rate or blood potassium levels, which were the primary endpoints of the study (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Metabolism

Aliphatic hydroxylation appears to be the major route of metabolism in humans.

Excretion

Excretion is predominantly through the faeces and to a lesser extent urine.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

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 monohydrate (which contains milk protein) (see Section 4.3 CONTRAINDICATIONS).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Store in a dry place.

6.5 NATURE AND CONTENTS OF CONTAINER

SEREVENT ACCUHALER is a moulded plastic device containing a foil strip with 28 or 60 regularly placed blisters. Each blister strip consists of a formed base foil (polyamide film/aluminium foil/PVC film) with a peelable foil laminate lid (white paper/polyethylene terephthalate film/aluminium foil).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

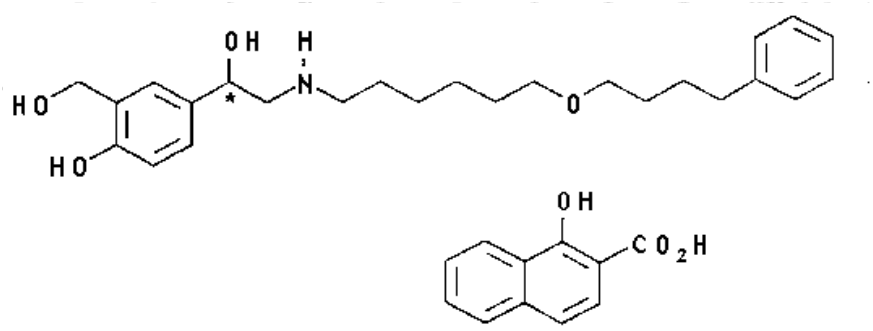
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Name:

4-Hydroxy-*'-[[[6-(4-phenylbutoxy)hexyl]amino]-methyl]-1,3-benzenedimethanol,1-hydroxyl-2-naphthoate.

Chemical structure



* chiral centre

CAS number

94749-08-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

GlaxoSmithKline Australia Pty Ltd

Level 4, 436 Johnston Street,
Abbotsford, Victoria, 3067

9 DATE OF FIRST APPROVAL

27 August 2008

10 DATE OF REVISION

11 August 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.3	Added contraindication for severe milk protein allergy
6.1	Added cross reference to Section 4.3

Version 4.0