New Zealand Data Sheet

1 PRODUCT NAME
Meterol

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Salmeterol xinafoate (equivalent to 25 mcg salmeterol base per actuation)

3 PHARMACEUTICAL FORM
Meterol Inhaler with a dose counter is a pressurised metered-dose inhaler that delivers salmeterol xinafoate equivalent to 25 mcg per actuation into a specifically designed actuator. Meterol Inhaler consists of a pressurised aluminium canister filled with microcrystalline salmeterol xinafoate (salmeterol hydroxynaphthoate) suspended in the non-CFC HFA-134a propellant (norflurane). The aluminium canister has a metering valve and is placed within a plastic actuator. A dose counter is incorporated into the actuator, which shows how many actuations of medicine remain in the canister. One Meterol Inhaler delivers 120 actuations of medicine. The actuator is fitted with a plastic dust cap.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Asthma:
Meterol Inhaler is indicated in the regular therapy of asthma and prevention of bronchospasm in individuals aged 4 years and older with reversible obstructive airway disease, including those with symptoms of nocturnal asthma, when used in combination with a long-term asthma prevention medicine such as an inhaled corticosteroid.

Meterol Inhaler is NOT indicated for acute asthma treatment, for which a fast-acting inhaled bronchodilator (e.g. salbutamol) should be used.

Exercise-induced bronchospasm:
Meterol Inhaler is indicated in the regular prevention of exercise-induced bronchospasm in individuals aged 4 years and older.

Chronic obstructive pulmonary disease:
Meterol Inhaler is indicated in the regular maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease.

4.2 Dose and method of administration
Meterol Inhaler is for oral inhalation only. Babies, children and patients who experience difficulties with the coordination of a pressurised metered dose inhaler may use a spacer device with Meterol Inhaler. Ask your doctor or pharmacist to explain how to use it or follow the instructions provided with the spacer.

Each actuation of Meterol Inhaler contains 25 micrograms of salmeterol.

Approved dosing of Meterol Inhaler is tabulated below:

	Adults	Children (aged ≥ 4 years)
Asthma	50 micrograms (2 actuations) twice a day	50 micrograms (2 actuations) twice a day
More severe airway obstruction	Up to 100 micrograms (4 actuations) twice a day	_
Chronic obstructive pulmonary disease	50 micrograms (2 actuations) twice a day	_

Meterol Inhaler is not recommended for children aged less than 4 years due to inadequate clinical data.

Medical advice should be sought before adjusting the dosage or frequency of administration of Meterol Inhaler and before stopping treatment. The recommended dosage should not be exceeded. Patients should not stop using Meterol Inhaler even if they feel improvement.

In patients with asthma, Meterol Inhaler must only be prescribed in combination with inhaled corticosteroids or other anti-inflammatory treatment. Patients should be advised to use a SABA (short-acting inhaled β_2 (beta-2) agonist) to treat symptoms rather than additional doses of Meterol Inhaler.

Effective bronchodilation (FEV 1 improvement by >15%) commences within 10-20 minutes with Meterol Inhaler in patients with asthma. After the initial doses of salmeterol the benefits will be evident and will usually continue for twelve hours. In the treatment of patients who experience chronic bronchitis symptoms at night, COPD, asthma and exercise induced asthma, this is of particular use.

Patients who have asthma should begin medication with anti inflammatory therapy at the same time as Meterol Inhaler if they have not been prescribed this already.

Excessive dosing of Meterol inhaler may lead to adverse effects; therefore, increases in frequency or dosage should only be performed on medical recommendation.

Special Patient Groups
The dosage of Meterol Inhaler does not require adjustment in the elderly or in individuals with hepatic or renal impairment.

4.3 Contraindications
Meterol Inhaler is contraindicated in individuals with hypersensitivity to any of its components (see section 4.1).

4.4 Special warnings and precautions for use
Asthma management

The management of asthma should normally follow a stepwise programme. Meterol Inhaler should not be used (and is not sufficient) as the first treatment for asthma. Meterol Inhaler is not a substitute for inhaled or oral corticosteroids. Meterol is recommended to be administered twice a day for the control of asthma (reversible airways obstruction) symptoms and is suitable for regular, long term treatment.

It has been reported that when salmeterol has been administered in patients with deteriorating or unstable asthma, serious acute respiratory episodes that includes death may occur. It is important to note that it cannot be determined whether salmeterol failed to alleviate the worsening asthma in these reports or whether salmeterol may have been

responsible for these adverse events. Regardless, the use of Meterol Inhaler in this worsening asthma situation is not appropriate.

Corticosteroid therapy should not be discontinued or reduced at any stage by the patient, even if the patient is feeling an improvement. Dosage administration change in Meterol Inhaler should only be performed on medical advice.

When treating asthma, Meterol Inhaler should only be used as additional therapy in patients not adequately controlled on other asthma-controller medications (e.g. low-dose to medium-dose inhaled corticosteroids). Anti-inflammatory asthma medications should not be reduced or withdrawn when Meterol Inhaler is initiated. If the patient has not already been prescribed anti-inflammatory treatment this should be administered when starting treatment with Meterol Inhaler.

A large study (SMART) was completed in the United States which compared the safety of salmeterol (50 mcg taken twice a day) and a placebo which were both an additional asthma therapy to the current treatment. The data from this study showed patients that were receiving the salmeterol compared to patients on the placebo had an increase in asthma related deaths. Over 28 weeks, 13 deaths occurred out of 13,176 patients on salmeterol compared to 3 deaths in 13,179 patients taking the placebo. This study also suggested that patients of African-American decent may have a higher risk of serious respiratory related illnesses or death when prescribed salmeterol instead of the placebo. It is unsure whether this was a result of other factors or pharmacogenetic. Patients that did not receive inhaled corticosteroids as a component of their regular therapy at the beginning of the study had 9 out of 7,049 asthma related deaths in comparison to the placebo group which had 0 out of 7,041. The salmeterol or placebo treatment group at the beginning of the study had no significant differences. Corticosteroids and Long acting beta-2 agonists (LABA's) should be prescribed jointly.

Meterol Inhaler 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 short-acting inhaled bronchodilator for the relief of acute asthma symptoms available at all times.

Salmeterol has a slower action onset of 10-20 minutes so therefore should not be administered for acute symptoms of asthma treatment. A short acting β_2 (beta-2) agonist which is faster acting (less than 5 minutes) should be used in this circumstance. A short acting beta agonist (e.g salbutamol) should be prescribed and used for this purpose and patients kept well advised and reminded of this.

Asthma deterioration

Meterol Inhaler should not be initiated in patients with acutely declining or significantly worsening asthma, which could be regarded as a life threatening condition. Increasing corticosteroid therapy should be considered in patients with progressive and sudden deterioration of asthma control.

Asthma may deteriorate acutely over a period of hours or chronically over several days or longer and can be life-threatening. The patient should be advised to seek medical advice if their required 'on-demand' use of their short-acting β_2 (beta-2) agonist increases or appears less effective. Under these circumstances, the patient's asthma therapy plan should be re-evaluated, with their inhaler technique checked and special consideration given to increasing corticosteroid treatment.

Parenteral corticosteroids, parenteral bronchodilators, nebulisers and other supportive measures should be used for the treatment of severe exacerbations.

Pharmacological side-effects such as headaches, tremor, and subjective palpitations have been recorded against beta-2 agonist treatment. This tends to reduce with recurring therapy.

Paradoxical bronchospasm
Similar to that seen with other inhalation therapy, paradoxical bronchospasm that is potentially life-threatening may occur immediately after using inhaled salmeterol. If this occurs, the patient should be administered a short-acting bronchodilator. The patient should be treated with an alternative therapy and the salmeterol inhaler should be discontinued without any delay.

Hypokalaemia
Adrenergic bronchodilators such as salmeterol may cause decreases in serum potassium concentrations. Although this effect is typically transient and does not require supplementation, clinically significant hypokalaemia may occur in some patients, with the potential to cause adverse cardiovascular effects. Serum potassium levels should be monitored in patients with severe asthma, as the risk of hypokalaemia is increased by concomitant use of xanthine derivatives, corticosteroids and diuretics and by hypoxia.

Cardiovascular effects
Clinically significant cardiovascular effects, such as systolic blood pressure increases, pulse rate and cardiac symptoms, may occur with β_2 (beta-2) agonists such as salmeterol. Meterol Inhaler should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias and hypertension.

Co-existing conditions
Meterol Inhaler should be administered with caution in patients with co-existing hyperthyroidism, or ketoacidosis.

Other medical conditions
Patients with a history of diabetes mellitus should be prescribed Meterol with caution as there have been reports of blood glucose levels increasing in very rare instances (see section 4.8). Patients with thyrotoxicosis should be prescribed Meterol with caution.

Administration of high therapeutic doses of sympathomimetic drugs may cause serum potassium to decrease. Due to this Meterol should be prescribed with caution in patient's that have a predisposition to lower levels of serum potassium.

Spacer Devices
To obtain optimum delivery of salmeterol to the lungs, the inhaler technique of the patient should be monitored to make sure that the patient's inhalation is synchronised correctly with the aerosol actuation.

Inhalers used conjointly with a spacer device will benefit most patients, especially patients that have an inadequate inhaler technique. The quantity of salmeterol deposited in the mouth and throat will decrease with the use of a spacer (in turn this will decrease the incidence of a hoarse voice and 'thrush' side effects).

Where the type of spacer device is changed, this may in turn cause a change in the amount of salmeterol that is delivered to the pulmonary tissue. The patient should be closely observed for any loss of control of asthma symptoms as the clinical significance of this is unknown.

If a spacer is required, Meterol Inhaler is to be actuated into the spacer and the patient is then to breathe in as slowly and deeply as possible. The breath should be held for as long as

possible within a comfortable range prior to releasing the breath gradually. This step is to be repeated for each dose required of Meterol Inhaler. Delays between the actuation of Meterol Inhaler into the space and inhalation should be kept as short as possible.

Variability of drug delivery may occur due to static on the spacer walls. It is important that patients are informed that detergent and warm water are to be used to wash the spacer without rinsing. The spacer must be air dried instead of dried with a cloth. Cleaning should be completed prior to initial use and at least once a month.

4.5 Interaction with other medicines and other forms of interaction

Cytochrome P450 3A4 inhibitors

Due to the potentially increased risk of cardiovascular adverse events, the concomitant use of Meterol Inhaler with strong CYP3A4 inhibitors (e.g. ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir and telithromycin) is not recommended as this can lead to increasing salmeterol exposure.

Monoamine oxidase inhibitors and tricyclic antidepressants

Salmeterol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of salmeterol on the vascular system may be potentiated by these agents.

β-adrenoceptor antagonists

Meterol Inhaler should not generally be prescribed in patients treated with non-selective β (beta) antagonists, such as propranolol, as these block the pulmonary effects of salmeterol and may produce severe bronchospasm. If there is no acceptable alternative to the use of β (beta) antagonists (such as prophylaxis after myocardial infarction), then cardioselective β (beta) antagonists, such as atenolol, could be considered, although these should be administered with caution.

Patients with asthma or reversible obstructive airways disease should avoid the use of both selective and non-selective beta-blockers, unless there is a very convincing reason to do so.
Plasma salmeterol exposure was significantly increased by 1.4 fold C_{max} and 15 fold AUC to lengthening of the QTc interval with the administration of both salmeterol and ketoconazole (see section 5.2).

4.6 Fertility, pregnancy and lactation

Pregnancy

The effects of salmeterol xinafoate on human fertility are not known due to inadequate information being available.

Meterol Inhaler should only be considered during pregnancy if the potential benefit to the mother exceeds any potential risk to the foetus.

In animal studies, there is evidence of some harmful effects on the foetus at very high dose levels of β_2 (beta-2) agonists. Other β_2 (beta-2) agonist studies have resulted in nil evidence that these effects are significant for pregnant women receiving normal doses of salmeterol.

Breast feeding

Salmeterol is likely to be excreted into breast milk in negligible amounts; however, it is not known whether this has a harmful effect on the breast-feeding child. It is not recommended that lactating women use salmeterol unless the potential benefit to the mother exceeds any possible risk to the child.

In lactating animals, studies have shown that minimal amount of salmeterol is secreted in into breast milk.

Fertility
No data available.

4.7 Effects on ability to drive and use machines
Presumed to be safe or unlikely to produce an effect on the capability to drive or use machinery.

4.8 Undesirable effects
Cardiovascular system
Hypertension (4%); palpitations, tachycardia (more common in doses higher than 50mcg administered twice a day); arrhythmias, including atrial fibrillation, extrasystoles, and supraventricular tachycardia (postmarketing).

Nervous system
Headache (17%); dizziness (4%); anxiety, migraine, nervousness, paresthesia, sleep disturbance (1% to 3%); tremor.

Headache and tremor side effects tend to reduce as therapy continues. Tremor is more prevalent in doses higher than 50mcg administered twice a day.

Gastrointestinal system
Nausea/vomiting (3%); dental pain, dyspepsia, gastrointestinal infections, hyposalivation, oral/throat candidiasis, oral mucosal abnormality (1% to 3%); gastrointestinal signs/symptoms (1% to 2%).

Immune system
Immediate hypersensitivity reactions (eg, angioedema, bronchospasm, oedema, rash); anaphylaxis (postmarketing).

Dermatological
Rash (4%); urticaria (3%); contact dermatitis, eczema (1% to 3%); photodermatitis (1% to 2%).

Eyes, ears, nose and throat
Nasal sinus congestion, pallor (9%); throat irritation (7%); pharyngitis (6%); rhinitis (5%); ear signs/symptoms, nasal blockage/congestion, sinusitis (4%); conjunctivitis, keratitis, sinus headache (1% to 3%).

Respiratory system
Bronchitis, tracheitis (7%); cough, viral respiratory tract infection (5%); asthma (4%); lower respiratory signs/symptoms (1% to 2%); irritation or swelling (including stridor or choking), laryngeal spasm, oropharyngeal irritation, paradoxical bronchospasm, serious exacerbations of asthma (some fatal) (postmarketing).

In a meta-analysis of 215 randomised controlled trials comparing salmeterol with placebo or any non-long-acting β (beta) agonist in patients with asthma (n=106, 575), the odds ratio for asthma mortality with salmeterol was 2.7 (95% CI 1.4 to 5.3). In 54 placebo controlled studies the risk of death from asthma in salmeterol recipients not prescribed concomitant inhaled corticosteroids was 7.3 (95% CI 1.8 to 29.4). In 127 studies in which patients were co-prescribed inhaled corticosteroids, the risk of asthma death was 2.1 (95% CI 0.6 to 7.9).

Musculoskeletal system
Skeletal muscle pain (12%); muscle cramps/spasms (3%); arthralgia, articular rheumatism, bone/skeletal pain, inflammation, muscle pain, muscle stiffness, pain in joints, tightness, rigidity (1% to 3%).

Miscellaneous
Influenza (5%); oedema, fever, hyperglycaemia, localised aches and pains, pain, swelling (1% to 3%).

Reporting of suspected adverse reactions
Reporting 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 https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose
Signs and symptoms of salmeterol overdose are transient events consistent with adverse effects mediated by β_2 (beta-2) agonists, such as hypertension, tachycardia, headache, tremor, dizziness, hypokalaemia and blood glucose level increases.

A cardio selective β (beta) antagonist should be considered in patients presenting with cardiac symptoms following salmeterol overdosage; however, β (beta) antagonists should be used with caution in patients with a history of bronchospasm. Serum potassium levels should be monitored in patients who have taken Meterol Inhaler in dosages excessive to those approved. In patients with hypokalaemia, oral or intravenous potassium replacement may be necessary.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

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) β_2 (beta-2) adrenoceptor agonist. *In vitro* and *in vivo* pharmacologic studies demonstrate that salmeterol is selective for the β_2 (beta-2) adrenoceptor compared with isoproterenol, which has approximately equal agonist activity on β_1 (beta-1) and β_2 (beta-2) adrenoceptors. *In vitro* studies show salmeterol to be at least 50 times more selective for β_2 (beta-2) adrenoceptors than salbutamol.

The pharmacological effects of β_2 (beta-2) adrenoceptor agonist drugs, including salmeterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyses the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Salmeterol contains a long side chain, which attaches directly to the receptor exo-site. Compared with conventional short-acting β_2 (beta-2) agonists recommended doses, salmeterol induces bronchodilation over a longer duration (more than 12 hours) and more effectively protects against histamine-induced bronchoconstriction. In humans, the response to the inhaled allergen at the early and late phase is inhibited by salmeterol. The late phase

persists for over thirty hours after one dose when the effect of the bronchodilator is not evident.

A single dose of salmeterol reduces the effect of bronchial hyper-responsiveness. The significance of this clinical observation is not yet obvious but these properties suggest that salmeterol has supplementary non-bronchodilator activity. The method is unlike the corticosteroid anti-inflammatory effect, which should not be decreased or stopped when Meterol Inhaler is prescribed.

In vitro studies in human lung tissue have shown that salmeterol is a powerful and long-lasting inhibitor of leukotrienes, histamine, prostaglandin-D_2 and other mast cell mediators. Salmeterol inhibits histamine-induced plasma protein extravasation and inhibits platelet activating factor-induced eosinophil accumulation in the lungs of guinea pigs when administered by the inhaled route. In humans, single doses of inhaled salmeterol attenuate allergen-induced bronchial hyper-responsiveness.

By operating on the reversible component of the disease, Salmeterol improves symptoms, pulmonary function and quality of life in patients with COPD.

In patients with cystic fibrosis *in vitro* salmeterol has shown to decrease the acidiotoxic effect of Pseudomonas toxin on bronchial epithelium. Cilial beat frequency was increased in the bronchial epithelial cells.

5.2 Pharmacokinetic properties

Salmeterol xinafoate, an ionic salt, dissociates in solution so that the salmeterol and 1-hydroxy-2-naphthoic acid (xinafoate) moieties are absorbed, distributed, metabolised, and eliminated independently. Salmeterol acts locally in the tissues of the lung, and plasma levels are not predictive of therapeutic effect.

Only limited pharmacokinetic data is available on inhaled salmeterol due to the technical difficulties presented in assaying salmeterol in plasma (concentrations of approximately 200pg/ml or less after inhaled dosing). In subjects regularly dosed with salmeterol xinafoate, hydroxynaphthoic acid reaches steady state concentrations of approximately 100 ng/ml which is detected within the systemic circulation. Steady state concentrations in toxicity studies were up to 1,000 times higher than this. Furthermore, in individuals with airways obstruction receiving regular salmeterol xinafoate, no adverse effects associated with hydroxynaphthoic acid were observed.

Salmeterol plasma exposure is significantly increased (1.4 fold increase in maximum concentration and 15 fold increase is AUC) and was reported with co-administration of inhaled salmeterol 50 mcg twice a day and oral ketoconazole (a CYP3A4 inhibitor) 400 mg once a day for seven days in a crossover, placebo controlled, drug interaction study completed in 15 healthy subjects. Repeat dosing did not result in an increase in salmeterol accumulation. Palpitations or prolongation of QTc with sinus tachycardia led to three subjects being withdrawn from the study. Administration of both salmeterol and ketoconazole had no clinically significant effect on QTc duration, blood potassium or heart rate in the 12 remaining subjects (see section 4.4 and 4.5).

Absorption

Systemic levels of salmeterol are low or undetectable at therapeutic doses. Following chronic administration of an inhaled dose of salmeterol 50 micrograms twice daily in seven patients with asthma, salmeterol was detected in plasma within 5 to 45 minutes; plasma concentrations were very low, with mean peak concentrations of 167 pg/mL at 20 minutes; and no accumulation was reported with repeated doses.

Distribution
In *in vitro* studies, the percentage of salmeterol bound to human plasma proteins averages 96% over the concentration range of 8 to 7,722 ng/mL, much higher concentrations than those achieved following therapeutic doses of salmeterol.

Metabolism
Salmeterol base is extensively metabolised by hydroxylation, with subsequent elimination predominantly in the faeces. No significant amount of unchanged salmeterol base has been detected in either urine or faeces.

It was evident from an *in vitro* study using human liver microsomes that salmeterol is significantly metabolised by cytochrome P450 3A4 (CYP3A4) to (alpha)-hydroxysalmeterol (aliphatic oxidation). Ketoconazole, a strong inhibitor of CYP3A4, completely inhibited the formation of (alpha)-hydroxysalmeterol *in vitro*.

A study that was repeated in healthy volunteers using erythromycin and salmeterol showed no significant clinical changes in pharmacodynamics with erythromycin 500mg given three times a day.

Elimination
In two healthy subjects who received 1 mg of radiolabeled salmeterol (as salmeterol xinafoate) orally, approximately 25% and 60% of the radiolabeled salmeterol was eliminated in urine and faeces, respectively, over a period of 7 days. The terminal elimination half-life was about 5.5 hours (1 volunteer only).

The xinafoate moiety has no apparent pharmacologic activity. The xinafoate moiety is highly protein bound (>99%) and has a long elimination half-life of 11 days.

5.3 Preclinical safety data
Rabbit foetuses exposed in utero to salmeterol at doses far exceeding normal therapeutic doses exhibited a profile of effects characteristic of excessive β_2 (beta-2) adrenoceptor stimulation, including sternebral fusion, premature open eyelids and cleft palate.

In *in vitro* studies, salmeterol did not produce any detectable or reproducible increases in gene mutations. In addition, there was no effect on chromosomes or any delay in erythrocyte maturation in an *in vivo* study in the rat.

High doses of salmeterol were associated with an increased incidence of smooth muscle hyperplasia and benign smooth muscle tumours (leiomyomas) of the mesovarium in the rat and of the uterus in the mouse.

Very high vapour concentrations of the non-CFC propellant HFA-134a have not shown any toxic effects in a wide range of animal species exposed daily for two years. These concentrations greatly exceeded any likely to be experienced by individuals treated with Meterol Inhaler.

Carcinogenicity
Salmeterol xinafoate that was orally administered in mice for 18 months at 0.2 mg/kg/day, 1.4 mg/kg/day and 10 mg/kg/day resulted in smooth muscle tumour development in the uterus (possibly leiomyosarcomas or leiomyomas). Combined oral/inhalational administration in rats at the following dose levels 0.2 mg/kg/day, 0.7 mg/kg/day and 2.6 mg/kg/day for 24 months resulted in a greater occurrence of benign pituitary tumours and leiomyomas in the suspensory ligament of the ovaries. In both mice and rats, the smooth

muscle tumours are thought to be due from the beta-adrenoceptors being chronically stimulated while the methodology in regard to the pituitary tumour development is not known.

Propellant
Fluorocarbon propellants in large doses can result in cardiac arrhythmia in animals along with the effect of sensitising their hearts to arrhythmia induced by adrenaline (see section 4.5). Meterol contains fluorocarbon propellants as does many other pressurised aerosol formulations.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
HFA-134a, ethanol, soy lecithin.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
Shelf life is 24 months (2 years) from manufacture.

6.4 Special precautions for storage
When Meterol Inhaler is not in use, the plastic dust cap should be securely placed back on the mouthpiece of the actuator.

Store Meterol Inhaler below 25°C.

The shelf-life of Meterol Inhaler is 24 months.

Avoid direct sunlight or heat and protect from frost. As the canister is pressurised, no attempt should be made to puncture or dispose of it by burning.

As for other medications that are inhaled from aerosol canisters, the effect of the medication may be reduced if the canister is very cold. If this is the case, warm the inhaler in your hands for a few minutes before use. Do not use anything else to assist with warming up the inhaler.

6.5 Nature and contents of container
Meterol Inhaler is available at a strength equivalent of 25 micrograms of salmeterol per actuation, with 120 actuations per inhaler.

6.6 Special precautions for disposal and other handling
Instructions for Handling and Use
Usage instructions can be found in the package insert.

Correct operation of the Meterol Inhaler is essential for successful therapy.

Prior to using the Meterol Inhaler for the first time, remove the plastic dust cap from the mouthpiece of the inhaler, shake the inhaler well and depress the canister twice (into the air) to prime the inhaler. If the inhaler has not been used for more than one week, remove the plastic dust cap from the mouthpiece of the inhaler, shake the inhaler well and depress the canister once (into the air) to prime the inhaler.

Technique for proper administration of Meterol Inhaler is described in the following steps:

1. Remove the plastic dust cap from the mouthpiece of the inhaler and check the mouthpiece is clean. Shake inhaler well and prime if necessary as described above.
2. Hold the inhaler, using either one or two fingers on the top of the canister and your thumb on the base. Breathe out deeply through your mouth. Place the mouthpiece of the actuator in your mouth taking care to not bite it and close your lips over the mouthpiece.
3. Start breathing in through your mouth. Then depress the canister to release one dose while continuing to breathe in deeply and steadily.
4. Remove the inhaler from your mouth and hold your breath for 10 seconds or as long as comfortable. Breathe out slowly.
5. If another dose is required, wait for at least one minute with the inhaler in an upright position, and then repeat steps 2 to 4.
6. After use, replace the mouthpiece cover making sure the dust cap is secure.

Do not rush steps 2, 3 and 4. It is essential that just before depressing the canister that you begin breathing in as slowly as possible.

It is useful to complete this exercise using a mirror for the initial few actuations. If you see “mist or vapour” coming from the sides of your mouth or top of the inhaler, start again from stage 2.

Provide feedback to your doctor if you have any concerns or issues when using your Meterol Inhaler. If different directions have been provided by your doctor, please follow these instructions with care.

Children:
An adult may need to assist young children with operating their inhaler. The child should be instructed to breathe out then breathe in again slowly with the actuator in their mouth. As the child begins to breathe in, the adult should depress the canister. This technique may require practice. Older children or individuals with weak hands should use both hands to hold the inhaler, with two forefingers on top of the inhaler and two thumbs on the base below the mouthpiece.

Built-in dose counter
The Meterol Inhaler has a built-in dose counter or indicator to see how many actuations are left in the inhaler.

After Meterol Inhaler is primed for the first time, the dose counter should read 120. This means that there are 120 doses or actuations of medicine left in the inhaler. Each time the inhaler is used, the dose counter will count down by one number.

When there are 40 doses of medicine remaining in the Meterol Inhaler, the colour on the dose counter will change from green to red. When the dose counter on the Meterol Inhaler is red, the patient should ask their doctor for a new inhaler.

The dose counter will stop counting when it reaches 0. This means that there is no medication left in the inhaler and it should be discarded. The Meterol Inhaler may not feel empty and may continue to operate; however, the right amount of medicine may not be dispensed if the inhaler is continued to be used once the dose counter has reached 0. The dose counter will continue to show 0 even if the inhaler is used again.

The dose counter cannot be reset and is permanently attached to the plastic actuator. Never try to change the numbers on the dose counter.

Cleaning

The mouthpiece of the Meterol Inhaler should always be kept clean to ensure that the inhaler works properly.

The Meterol Inhaler plastic actuator must be cleaned at least once a week using the following method:

1. Remove the plastic dust cap from the mouthpiece of the inhaler. The metal canister should NOT be removed from the plastic actuator.
2. The plastic mouthpiece and the dust cap are to be wiped inside and outside with a clean dry cloth.
3. Replace the plastic dust cap on to the mouthpiece of the inhaler.

NEVER wash or soak any part of the inhaler in water.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

REX Medical Ltd
PO Box 18-119
Glen Innes 1743
AUCKLAND.

Ph (09) 574 6060
Fax (09) 574 6070

9 DATE OF FIRST APPROVAL

26 January 2012

10 DATE OF REVISION OF THE TEXT

14 September 2018

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.6	Fertility section added
4.7	Section added
4.8	Reporting of adverse events added
4.9	Poison information centre contact added
5.3	Section added