New Zealand Data Sheet

1 PRODUCT NAME
Rexair Inhaler – with dose counter

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Fluticasone propionate/Salmeterol xinafoate (equivalent to 50mcg/25mcg, 125mcg/25mcg or 250mcg/25mcg per metered actuation).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Rexair Inhaler 50mcg/25mcg is a pressurised metered-dose inhaler that delivers 50 mcg of fluticasone propionate and 25 mcg of salmeterol (as salmeterol xinafoate) per actuation into a specifically designed actuator. Each canister supplies 120 actuations.

Rexair Inhaler 25mcg/125mcg is a pressurised metered-dose inhaler that delivers 125 mcg of fluticasone propionate and 25 mcg of salmeterol (as salmeterol xinafoate) per actuation into a specifically designed actuator. Each canister supplies 120 actuations.

Rexair Inhaler 25mcg/250mcg is a pressurised metered-dose inhaler that delivers 250 mcg of fluticasone propionate and 25 mcg of salmeterol (as salmeterol xinafoate) per actuation into a specifically designed actuator. Each canister supplies 120 actuations.

Rexair Inhaler consists of a pressurised aluminium canister filled with a suspension of salmeterol xinafoate and fluticasone propionate in a non-CFC propellant HFA-134a (norflurane). The aluminium canister has a metering valve within a plastic actuator incorporating an atomising orifice. The actuator is fitted with a plastic dust cap.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications

Reversible Obstructive Airways Disease (ROAD)
Rexair Inhaler is indicated for reversible obstructive airways disease (ROAD), or the regular therapy of asthma in children and adults, where a combination (inhaled corticosteroid and bronchodilator) is appropriate.

This could also include:

- Patients on successful inhaled corticosteroid maintenance treatment of and long-acting β (beta) agonists administered in separate inhalers.
- Patients whose current corticosteroid inhalation therapy is not well controlled.
- Patients who are inadequately controlled on "as required" short-acting beta-agonists (SABA's), as a substitute to the start of inhaled corticosteroid maintenance therapy at moderate or high doses offered individually.

In initial asthma management, Rexair Inhaler should not be administered unless symptoms are very poorly controlled. This is also the case where asthma can be controlled by the occasional use of SABA's (Small short acting beta-2 agonists).

Rexair Inhaler should not be administered to treat the acute symptoms of asthma.

Chronic Obstructive Pulmonary Disease (COPD)
Rexair Inhaler is indicated in patients for the symptomatic treatment of COPD which is moderate to severe (i.e. <60% of normal FEV_1 predicted prior to bronchodilator usage) and despite bronchodilator therapy, have significant symptoms.

4.2 Dose and method of administration

Rexair Inhaler is to be administered by oral inhalation only. In patients who find co-ordination of a pressurised metered-dose inhaler difficult, a spacer device may be used with Rexair Inhaler. Ask your doctor or pharmacist to explain how to use it or follow the instructions provided with the spacer.

Patients should be informed that Rexair Inhaler is a preventative asthma treatment and should be taken consistently for optimum benefit, irrespective of whether symptoms are present. Even if patients feel better, patients should be warned against stopping or reducing their treatment dosage without medical instruction.

Patients with asthma should have their diagnosis and treatment regularly reviewed, including reassessment of the dosage of their Rexair Inhaler. The inhaler dosage should only be adjusted on medical recommendation.

The dose of Rexair Inhaler should be carefully monitored and if possible reduced to the lowest dose where symptoms are effectively controlled and maintained. Where dosage is at the minimum level and patients are being effectively controlled and maintained i.e. 50mg fluticasone and 25mg salmeterol, then a possible next step could be the consideration of using an inhaled corticosteroid only.

Alternatively for those patients that require a LABA (Long Acting Beta Agonist) dosage could be titrated to a once daily dosage of Rexair Inhaler. This should only be done if the prescriber believes the disease would be adequately controlled. In the case of a patient having nocturnal symptoms the dose should be administered at night, or when predominantly symptoms occur during the day, then Rexair Inhaler should be administered in the morning.

On reducing dosage or titrating the dose down, regular medical review of the patient is essential.

Asthma
The strength of Rexair Inhaler that patients are prescribed should contain the suitable dosage of fluticasone propionate for their disease severity.

When patients need to treat additional symptoms they should be educated to use SABA's (short acting beta agonists) and not to take extra doses of Rexair Inhaler.

Adults and Adolescents older than 12 years:
The recommended dosage of Rexair Inhaler in adults or adolescents older than 12 years depends on the severity of their disease and includes:

- Rexair Inhaler 50mcg/25mcg (50mcg fluticasone/25mcg salmeterol), two inhalations twice a day.
- Rexair Inhaler 125mcg/25mcg (125mcg fluticasone/25mcg salmeterol), two inhalations twice a day.

- Rexair Inhaler 250mcg/25mcg (250mcg fluticasone/25mcg salmeterol), two inhalations twice a day.

Children to 12 Years of Age:
The recommended dosage of Rexair Inhaler in children over 4 years of age is 50mcg/25mcg (50mcg Fluticasone/25mcg Salmeterol), two inhalations twice a day.

Children Under 4 Years of Age:
Inhaled salmeterol/fluticasone propionate cannot be recommended in children under 4 years of age owing to insufficient clinical data.

Chronic Obstructive Pulmonary Disease
The recommended dosage of Rexair Inhaler in adults is 125mcg/25mcg (125mcg fluticasone/25mcg salmeterol), two inhalations twice a day. If additional symptomatic control is required, Rexair Inhaler 250mcg/25mcg (250mcg fluticasone/25mcg salmeterol), two inhalations twice a day can be given. The maximum recommended dose of Rexair Inhaler 250mcg/25mcg is two inhalations twice a day.

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

4.3 Contraindications
Hypersensitivity to salmeterol xinofoate, fluticasone propionate or the excipients (See section 6.1).

4.4 Special warnings and precautions for use
Where patients have acutely deteriorating asthma or are unstable, Rexair Inhaler should not be started during an exacerbation.

The treatment of asthma (Reversible Obstructive Airways Disease) should be managed in a stepwise manner, with pulmonary lung function tests and clinical judgement used to evaluate patient response.

Rexair Inhaler is indicated for routine long-term management of asthma, not for acute asthma exacerbations or for patients with acutely deteriorating or unstable asthma. Patients with acute symptoms should be advised to have a fast and short-acting inhaled bronchodilator (e.g. salbutamol) immediately available to resolve acute symptoms.

Even during treatment using Rexair Inhaler serious exacerbations and asthma related adverse events may occur. Individuals should be instructed to continue treatment and to seek medical advice as soon as possible - even if asthma symptoms worsen or continue to be uncontrolled after administrating Rexair Inhaler.

One of the features of worsening control of asthma is the increased use of inhaled short-acting β_2 (beta-2) agonists to alleviate symptoms. Patients should be instructed to request medical attention if they find that their short-acting bronchodilator appears less effective or they require more inhalations than usual. Increasing corticosteroid therapy should be considered in patients with progressive and rapid deterioration of asthma control, as this can be potentially life threatening.

Patients should be reviewed by a doctor if the disease is adequately controlled on Rexair Inhaler. Systemic corticosteroids should be considered to provide additional asthma or COPD control and antibiotics prescribed if an infection is present.

Rexair Inhaler treatment should not be suddenly withdrawn in patients with asthma due to risk of exacerbation. The Rexair Inhaler dosage should be titrated downwards under the supervision of a medical professional. Withdrawal of Rexair Inhaler may precipitate symptomatic decompensation in patients with COPD and should be supervised by a medical professional.

In studies of salmeterol/fluticasone propionate inhaler in patients with COPD, an increased incidence of pneumonia was reported (see section 4.8). Given that the clinical features of pneumonia and exacerbation often overlap, physicians should be vigilant for pneumonia in patients with COPD treated with Rexair Inhaler.

As with all inhaled corticosteroids, Rexair Inhaler recipients with active or quiescent pulmonary tuberculosis require special care and should be managed with caution.

Rexair Inhaler should be used with vigilance in patients who have been diagnosed with thyrotoxicosis.

Similar to that seen with other inhalation therapy, potentially life-threatening paradoxical bronchospasm may occur immediately after using inhaled fluticasone propionate. If this occurs, the patient should be administered a short-acting bronchodilator. Rexair Inhaler should be discontinued immediately and the patient should be treated with an alternative therapy. Side effects of β_2 (beta-2) agonist therapy such as headaches, palpitations and tremor have been reported but have been known to reduce with constant therapy.

An increase in heart rate, systolic blood pressure and other cardiovascular effects are occasionally observed with sympathomimetic drugs, particularly at dosages that are higher than those approved. Patients with pre-existing cardiovascular disease should exercise caution when using Rexair Inhaler. Cardiac arrhythmias such as atrial fibrillation, supraventricular tachycardia and extrasystoles have rarely been observed with the use of salmeterol xinafoate and fluticasone propionate.

All sympathomimetic drugs may cause transient decreases of serum potassium especially with higher than approved dosages. Patients predisposed to serum potassium at low levels should exercise caution when using Rexair Inhaler.

Rexair Inhaler contains fluticasone propionate which is an inhaled corticosteroid.

Any inhaled corticosteroid may be associated with systemic adverse effects including Cushingoid features, Cushing's syndrome, adrenal suppression, decrease in bone mineral density, disturbances in the behaviour of children and adolescents, growth retardation in children and adolescents, glaucoma and cataracts (see section 4.8). These effects are more common when the inhaled corticosteroid is administered at high doses for long periods of time, although the risk is much less than with oral corticosteroids (see section 4.9). Because of this, the inhaled corticosteroid should be titrated to the minimum effective dose in ROAD patients.

Children treated with inhaled corticosteroids for long periods of time should have their height regularly monitored.

Some patients are more susceptible to the systemic effects of inhaled corticosteroids than others.

If patients are in an emergency or a potentially stress-induced elective situation, the potential of impaired adrenal response must be recognised and suitable corticosteroid therapy considered (see section 4.9).

Regular adrenocortical function monitoring and special care should be exercised in patients switching from oral corticosteroids to Rexair Inhaler because of the possibility of adrenal impairment. Systemic corticosteroids should be gradually tapered off after the initiation of Rexair Inhaler and patients advised to carry a warning card alerting to the possible requirement for additional corticosteroids in times of stress.

Rarely, elevations in blood glucose levels have been reported with salmeterol (as xinafoate) and fluticasone propionate (see section 4.8); this should be taken into consideration when prescribing Rexair Inhaler to patients with diabetes mellitus.

There are clinically significant post-marketing reports of drug interactions in individuals treated with fluticasone propionate and ritonavir, leading to adrenal suppression, Cushing's syndrome, and other systemic corticosteroid effects. For this reason, fluticasone propionate should not be used concomitantly with ritonavir, except if the potential advantage offsets the risk of systemic corticosteroid adverse effects (see section 4.5).

Rarely, Churg Strauss syndrome or other underlying eosinophilic conditions may be unmasked by inhaled corticosteroids. A direct causal relationship between inhaled corticosteroids and eosinophilic conditions has not been established and these cases are generally associated with oral corticosteroid reduction or withdrawal.

In a drug interaction study, ketoconazole increased exposure to salmeterol, which may lead to furtherance in the QTc interval. When co-administering salmeterol with strong CYP3A4 inhibitors (e.g. ketoconazole) caution should be used.

Visual disturbance
Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Other
SMART was a large study completed in the United States which compared the safety of salmeterol (50mcg taken twice a day) and a placebo which were both given as an additional asthma therapy to current treatment. The data from this study showed patients that were administering the salmeterol compared to patients on the placebo had an increase in asthma related deaths. This study also suggested that patients of African-American decent may have a higher risk of serious respiratory related illnesses or death when administering salmeterol instead of the placebo. It is unsure whether this was a result of other factors or pharmacogenetic. This study was not intended to establish whether synchronised use of inhaled corticosteroids changes the possibility of deaths related to asthma.

Spacer Devices
To obtain optimum delivery of fluticasone and salmeterol to the lungs, the inhaler technique of the patient should be monitored to make sure that the patient's inhalation is synchronised 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 fluticasone and salmeterol deposited in the mouth and throat will decrease with the use of a spacer (in turn this will decrease the incidence of hoarse voice and 'thrush' side effects).

In circumstances where the type of spacer device is changed, this may in turn cause a change in the amount of fluticasone and 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, Rexair Inhaler is to be actuated into the spacer and the patient is to then breathe in slowly and as 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 Rexair Inhaler. Delays between the actuation of Rexair Inhaler into the spacer and inhalation should be kept as short as possible. If this method is unsuccessful, the patient can be instructed to normally breathe via the spacer for approximately six breaths per inhaler actuation.

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

Individuals should avoid both non-selective and selective β (beta) antagonists, unless there is convincing rationale to use them.

In a study of drug interactions in healthy individuals, fluticasone propionate plasma concentrations were greatly increased with concomitant administration of ritonavir (a potent inhibitor of cytochrome P450 3A4), leading to markedly decreased serum cortisol concentrations. Clinically significant post-marketing reports of drug interactions within patients treated with fluticasone propionate and ritonavir, led to adrenal suppression, Cushing's syndrome, and other systemic corticosteroid effects. For this reason, fluticasone propionate should not be used concomitantly with ritonavir, unless the prospective benefit offsets the risk of the systemic corticosteroid adverse effects.

Other cytochrome P450 3A4 inhibitors have been administered concomitantly with fluticasone propionate in clinical studies: erythromycin produced negligible increases and ketoconazole produced minor increases after fluticasone propionate systemic exposure with no significant reductions in the concentration of serum cortisol. Notwithstanding, care should be taken when co-administering ketoconazole and other powerful cytochrome P450 3A4 inhibitors with Rexair Inhaler, fluticasone propionate can potentially arise with increased systemic exposure.

In a drug interaction study, ketoconazole increased exposure to salmeterol (1.4 fold increase in maximum concentration and 15 fold increase in AUC), which may lead to prolongation in the QTc interval (see sections 4.4 and 5.2). The use of salmeterol alongside resilient CYP3A43 inhibitors (e.g. atazanavir, clarithromycin, intraconazole,

nelfinavir, ketoconazole, ritonavir, indinavir, nefazodone and saquinavir) is not advised due to the possibility of cardiovascular adverse events occurring (See sections 4.4 and 5.2).

During normal circumstances with the administration of fluticasone propionate, low plasma concentrations are achieved after inhalation. This occurs due to mediation by cytochrome P450 3A4 due to considerable first pass metabolism and a high systemic clearance within the liver and gut. Therefore, fluticasone propionate is unlikely to mediate clinically significant drug interactions.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

There is limited experience of human pregnancy with salmeterol xinafoate and fluticasone propionate.

Reproductive studies in animals prescribed fluticasone and salmeterol (either individually or combined), have shown foetal effects characteristic of β2 (beta-2) agonists and glucocorticoids at systemic exposures greatly exceeding the recommended inhaled therapeutic dosage.

Lactation

Rexair Inhaler should only be considered during lactation if the potential benefit to the mother exceeds any possible risk to the breast-feeding child.

There is limited experience of human lactation with salmeterol xinafoate and fluticasone propionate.

Animal studies suggest that salmeterol xinafoate and fluticasone propionate are only likely to be excreted into breast milk in small amounts. No data is available for human studies.

Plasma levels of salmeterol and fluticasone propionate are very low in patients receiving the recommended dosages of the inhaled medicine and therefore excretion of salmeterol or fluticasone propionate into breast milk is likely to also be low.

Fertility

There are no data in humans. However, animal studies showed no effects of salmeterol or fluticasone propionate on fertility.

4.7 Effects on ability to drive and use machines

No studies have specifically evaluated the effect of inhaled salmeterol/fluticasone propionate on the ability to drive and use machines; however, the pharmacology of each agent suggests that any effects are unlikely.

4.8 Undesirable effects

Rexair Inhaler contains salmeterol and fluticasone propionate; therefore, the type and severity of adverse reactions associated with each of the compounds individually may be expected in the combination product. Additional adverse events associated with concurrent administration of the two compounds have not been reported.

Similar to that seen with other inhalation therapy, paradoxical bronchospasm with an increase in wheezing may occur immediately after inhalation. The patient should be treated immediately with a fast and short-acting inhaled bronchodilator and Rexair Inhaler should be discontinued. The patient should then be assessed and an alternative therapy initiated as required.

Adverse reactions associated with salmeterol or fluticasone propionate are given below:

Salmeterol
Tremor, subjective palpitations and headache (all pharmacological side effects of β_2 (beta-2) agonists) have been reported with salmeterol; however, these tend to be transient and reduce with regular therapy.

Atrial fibrillation, supraventricular tachycardia, extrasystoles and other cardiac arrhythmias may occur with salmeterol, particularly in susceptible patients.

Arthralgia has been reported with salmeterol.

Rarely, hypersensitivity reactions such as oedema, angio-oedema, bronchospasm, anaphylactic shock and other analphylactic reactions have been reported with salmeterol. Rash can occur with salmeterol; however, the incidence of this is uncommon.

Oropharyngeal irritation has been reported with salmeterol.

Rarely, muscle cramps have been reported with salmeterol.

Very rarely, hyperglycaemia has been reported with salmeterol and fluticasone propionate

Some patients have experienced hoarseness and candidiasis (thrush) of the mouth and throat with inhaled fluticasone propionate. It may be helpful for patients to gargle with water immediately after inhalation to prevent candidiasis. Symptomatic candidiasis can be treated with a topical anti-fungal without discontinuing Rexair Inhaler.

Cutaneous hypersensitivity reactions have been uncommonly reported with fluticasone propionate. Rarely, hypersensitivity reactions manifesting as angioedema (mainly facial and oropharyngeal oedema) and respiratory symptoms (dyspnoea and/or bronchospasm) have been reported with inhaled fluticasone propionate. Anaphylactic reactions have been very rarely reported.

Possible adverse effects of fluticasone propionate include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents; decrease in bone mineral density; cataract and glaucoma (see section 4.4).

Rarely, hyperglycaemia has been reported with fluticasone propionate.

Very rarely, anxiety, sleep disorders and behavioural changes (including hyperactivity and irritability) have been reported, mainly in children.

Clinical trials of salmeterol/fluticasone propionate
Adverse reactions commonly reported in clinical trials include: hoarseness/dysphonia, throat irritation, headache, candidiasis of the throat and mouth and palpitations. Pneumonia was also reported in COPD patients.

Contusions were also reported in clinical trials; however, the incidence of this effect was uncommon.

Post-marketing data with salmeterol/fluticasone propionate
In post-marketing analyses, cutaneous hypersensitivity reactions have been reported infrequently. Rarely, hypersensitivity reactions manifesting as angioedema (mainly facial and oropharyngeal oedema), Cushingoid features, growth retardation in young people, Cushing's syndrome, adrenal suppression, bone mineral density decreased, mediastinal disorders, thoracic and respiratory symptoms (dyspnoea and/or bronchospasm) have been reported. Also rarely reported is paradoxical bronchospasm. Anaphylactic reactions have been very rarely reported.

Very rarely, anxiety, sleep disorders and behavioural changes (including hyperactivity and irritability) have been reported, mainly in children.

There have been rare reports of hyperglycaemia.

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
Symptoms and signs of salmeterol overdose are transient events consistent with adverse effects mediated by β_2 (beta-2) agonists, which includes headache, tremor, increase in systolic blood pressure, tachycardia, raised blood glucose levels and hypokalaemia.

Patients who have taken Rexair Inhaler at dosages that exceed those approved may require appropriate symptomatic treatment (e.g. a cardioselective β (beta) antagonist); however, β (beta) antagonists should be used with caution in patients with a history of bronchospasm. If Rexair Inhaler is withdrawn because of overdose of the salmeterol component, appropriate replacement corticosteroid treatment should be considered.

Short-term inhibition of the hypothalamic-pituitary-adrenal axis may occur in the case of fluticasone propionate acutely inhaled in dosages excessive to those approved. However, normal adrenal function generally recovers within several days and emergency action is not unusually necessary.

Significant adrenocortical inhibition is possible if fluticasone propionate dosages are greater than approved and are continued over a prolonged time. Very rarely, acute adrenal crisis has been reported in children exposed to elevated doses larger than the approved (typically at least 1000 mcg daily over several months or years); these individuals exhibit features including hypoglycaemia and sequelae of decreased consciousness and/or convulsions. Surgery, infection, any rapid reduction in corticosteroid dosage or trauma, can trigger acute adrenal crisis.

It is not recommended that Rexair Inhaler is prescribed at dosages that are higher than those approved. Treatment should be regularly reviewed, with Rexair Inhaler titrated to the lowest effective dose that allows disease control to be maintained (see section 4.2).

In the event of salmeterol and fluticasone propionate overdose the individual should be monitored appropriately and supportively treated as necessary. There is no detailed treatment in this circumstance.

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: Drugs for obstructive airway diseases; adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics, ATC code: R03AK06

The two components of the salmeterol/fluticasone propionate inhaler have different modes of action. Salmeterol protects against asthma and COPD symptoms, while fluticasone propionate improves pulmonary function and prevents exacerbations. A salmeterol/fluticasone propionate inhaler can provide an easier and simpler regimen than separate inhalers for patients on concurrent β (beta) agonist and inhaled corticosteroid therapy. The mechanisms of action of both components are discussed further below:

Salmeterol

Salmeterol is a selective long-acting (12 hour) β_2 (beta-2) adrenoceptor agonist that contains a long side-chain that connects directly to the receptor exo-site.

Compared with recommended doses of conventional short-acting β_2 (beta-2) agonists, salmeterol induces bronchodilation over a longer duration (more than 12 hours) and more effectively protects against histamine-induced bronchoconstriction.

In vitro studies in human lung tissue have shown that salmeterol is a powerful and long-lasting inhibitor of leukotrienes, histamine, prostaglandin D2 and other mast cell mediators. Clinical studies have demonstrated that the early and late phase reaction to inhaled allergens is inhibited by salmeterol, with effects on the late-phase response enduring beyond the bronchodilatory effect (more than 30 hours after a single dose). Because bronchial hyper-responsiveness is attenuated with a single dose of salmeterol, it is suggested that it has additional non-bronchodilator activity; however, the full clinical significance of this observation has not yet been established. The mechanism of action of salmeterol on bronchial hyper-responsiveness is different from that of corticosteroids.

Fluticasone propionate

Fluticasone propionate is a potent glucocorticoid with anti-inflammatory activity. When inhaled at approved dosages, fluticasone propionate reduces asthma symptoms and exacerbations, without the adverse effects typically observed with systemic corticosteroids.

Even at the highest recommended dose of inhaled fluticasone propionate during chronic treatment, the daily output of adrenocortical hormones typically remains within

the standard range. In patients who have switched from oral corticosteroids, the daily output of adrenocortical hormones typically returns to normal with inhaled fluticasone propionate. Normal increment of adrenal function on a stimulation test indicates that the adrenal reserve also remains normal during chronic treatment. However, for some time residual impairment of adrenal reserve from prior treatment may continue and should be remembered (see section 4.4).

Clinical trials
Asthma
A twelve month large study of 3,416 patients who had asthma (GOAL, Gaining Optimal Asthma Control) was completed to compare the safety and effectiveness of salmeterol and fluticasone propionate in relation to an individually inhaled corticosteroid in managing pre-defined asthma control levels. Every twelve weeks, treatment was increased until total control** was managed or the maximum dosage was achieved. Control of asthma had to be continuous for at least seven weeks out of the eight treatment weeks. The GOAL study demonstrated:

1) 71% of salmeterol and fluticasone propionate treated patients attained ‘well controlled*’ asthma in comparison with only 59% of single inhaled corticosteroid treated patients.

2) 41% of salmeterol and fluticasone propionate treated patients’ attained ‘total control**’ asthma in comparison with only 28% of single inhaled corticosteroid treated patients.

Observations of these effects were shown at earlier stages with salmeterol and fluticasone propionate in comparison with an individually inhaled corticosteroid and at a decreased level of an inhaled corticosteroid dose.

The GOAL study in addition demonstrated:

1) Salmeterol and fluticasone propionate had a lower rate of exacerbations of 29% in comparison to managing the individual treatment of inhaled corticosteroids.

2) Asthma that was considered ‘Well controlled*’ and 'Totally controlled**’ improved Quality of Life (QoL). Negligible or no impairment on QoL was recorded in 61% of the patients, which was measured in an asthma specific quality of life questionnaire after the treatment with salmeterol and fluticasone propionate. This was in comparison to only 8% of patients at baseline.

***Well controlled asthma** is described as having a symptom score that is greater than one (a symptom score of one is defined as experiencing symptoms over a short period of the day), and occurring over two days or less, the use of a short acting beta agonist on two day or less, or four occasions per week, no awakenings during the night, no side effects or exacerbations forcing a change in treatment and 80% or greater predicted morning expiratory peak flow.

****Total controlled asthma** is described as having no symptoms, short acting beta agonists are not used, no awakenings during the night, no side effects or exacerbations forcing a change in treatments and 80% or greater predicted morning expiratory peak flow.

Improvements in the function of the lung, reduction is medication rescue use, and the symptom free days percentage have been shown in two additional studies. The results

showed an improvement of 60% less inhaled corticosteroid dosage with salmeterol and fluticasone propionate in comparison to therapy with inhaled corticosteroids alone. Maintenance of underlying inflammation of the airway was controlled and measured by bronchoalveolar lavage and bronchial biopsy.

Asthma symptoms and lung function are significantly improved with the treatment of salmeterol and fluticasone propionate as shown by further studies. The treatment of asthma symptoms also decreased the need for rescue medication in comparison to treatment with components individually or a placebo. The results from the GOAL study show that over the minimum of twelve months, improvements are seen and maintained with the treatment of salmeterol and fluticasone propionate.

Symptomatic COPD patients who demonstrated less than 10% reversibility to a short-acting β_2 (beta-2) agonist
In placebo-controlled clinical trials, regular use of inhaled salmeterol xinafoate and fluticasone propionate 50 mcg/500 mcg over regular 6 to 12 months usage produced rapid and significant improvements in pulmonary function, breathlessness and requirement for relief medication. The risk of COPD exacerbations and added oral corticosteroids courses were reduced at 12 months in inhaled salmeterol/fluticasone propionate recipients compared with placebo recipients. Health status also improved significantly with inhaled salmeterol/fluticasone propionate. Current and ex-smokers showed an improvement in health status, lung function, and COPD exacerbations with inhaled salmeterol xinafoate and fluticasone propionate compared with placebo.

Symptomatic COPD patients without restriction to 10% reversibility to a short-acting β_2 (beta-2) agonist
In placebo-controlled clinical trials, inhaled salmeterol/fluticasone propionate 50 mcg/250 mcg and 50 mcg/500 mcg over 6 months produced rapid and significant improvements in pulmonary function, breathlessness and requirement for relief medication. Health status also improved significantly with inhaled salmeterol/fluticasone propionate.

TORCH study (Towards a Revolution in COPD Health):
The TORCH study was a randomised, double-blind trial comparing salmeterol/fluticasone propionate inhaler 50/500 mcg twice a day with placebo, salmeterol 50 mcg twice a day alone and fluticasone propionate 500 mcg twice a day alone in patients that had moderate to severe COPD (baseline pre-bronchodilator FEV_1 <60% of predicted normal). All patients were allowed usual COPD background treatment with the exclusion of long-term systemic corticosteroids other long-acting bronchodilators, and inhaled corticosteroids. The primary endpoint of the study was all-cause mortality at 3 years, regardless of withdrawal from the study medication.

A total of 6,112 patients were included in the efficacy population: of these, 875 died within 3 years of the start of the study. All-cause mortality rates were: 193/1,533 (12.6%) with salmeterol/fluticasone propionate; 205/1521 (13.5%) with salmeterol alone; 246/1,534 (16.0%) with fluticasone propionate alone; and 231/1,524 (15.2%) with placebo. Compared with placebo, the hazard ratio for death with salmeterol/fluticasone propionate was 0.825 (95% CI 0.68–1.00; p=0.052), salmeterol was 0.879 (95% CI 0.73–1.06; p=0.180) and fluticasone propionate was 1.060 (95% CI 0.89–1.27; p=0.525). Salmeterol/fluticasone propionate showed an overall survival advantage over fluticasone propionate alone (hazard ratio 0.774; 95% CI 0.64–0.93; p=0.007) but not salmeterol alone (hazard ratio 0.932; 95% CI 0.77–1.13; p=0.481).

COPD-related mortality at 3 years was 4.7%, 6.1%, 6.9% and 6.0% with salmeterol/fluticasone propionate, salmeterol alone, fluticasone propionate alone and placebo, respectively.

Salmeterol/fluticasone propionate inhaler decreased the rate of moderate to severe COPD exacerbations by 12% (p=0.002), 9% (p=0.024) and 25% (p<0.001), compared with salmeterol alone, fluticasone propionate alone and placebo, respectively.

All active treatments produced significant improvements compared with the placebo in Health Related Quality of Life, as measured by the St George's Respiratory Questionnaire (SGRQ). Over 3 years, salmeterol/fluticasone propionate inhaler improved SGRQ by 2.2 units (p<0.001), 1.2 units (p=0.017) and 3.1 units (p<0.001), compared with salmeterol alone, fluticasone propionate alone and placebo, respectively. The likelihood of salmeterol/fluticasone propionate inhaler recipients attaining health status that was a clinically significant improvement (i.e. ≥ 4 point reduction in SGRQ) was 86% (p<0.001), 40% (p<0.001) and 24% (p=0.006) greater than placebo recipients, salmeterol recipients and fluticasone propionate recipients respectively.

FEV_1 values were increased in salmeterol/fluticasone propionate recipients than placebo recipients (average difference: 92 ml, p<0.001) over the treatment period of 3 years. Salmeterol/fluticasone propionate was also more effective than salmeterol or fluticasone propionate alone in enhancing FEV_1 (average difference 50 ml; p<0.001 and 44 ml; p<0.001, respectively).

The estimated probability of obtaining pneumonia as a reported adverse event was 12.3%, 13.3%, 18.3% and 19.6% for placebo, salmeterol alone, fluticasone propionate alone and salmeterol/fluticasone propionate inhaler, respectively over the three year treatment period. The hazard ratio for pneumonia was 1.64 with salmeterol/fluticasone propionate inhaler vs placebo (p<0.001). No between-treatment differences in pneumonia-related deaths were reported: eight patients died from pneumonia while on salmeterol/fluticasone propionate inhaler compared with seven patients on placebo, nine patients on salmeterol alone and 13 patients on fluticasone propionate alone.

No between-treatment difference was reported in bone fracture incidence. The incidence of bone disorders, HPA axis disorders and eye disorders, were minimal and there was no variation observed between treatments. No increases in cardiac adverse events were reported in the receiving salmeterol treatment groups

Another randomised, double-blind study (INSPIRE) supports the all-cause mortality findings from TORCH. This 2-year study compared salmeterol/fluticasone propionate inhaler 50 mcg/500 mcg twice daily with tiotropium 18mcg once daily in 1,323 COPD patients with post-bronchodilator FEV_1 <50% predicted normal. All-cause mortality was the safety endpoint. In this study, salmeterol/fluticasone propionate inhaler reduced the risk of dying on therapy by 52% compared with tiotropium (p=0.012).

5.2 Pharmacokinetic properties

Co-administration of inhaled salmeterol and fluticasone propionate has not been shown to influence the pharmacokinetics of either compound in animal or human studies. Each compound can therefore be considered separately for the purposes of pharmacokinetic analyses.

Plasma levels of salmeterol and fluticasone propionate are considered very low after the administration of Rexair Inhaler, however, possible interactions with inhibitors of CYP 3A4 and other substrates cannot be excluded.

Salmeterol
Only limited pharmacokinetic data is available on inhaled salmeterol because of the technical difficulties presented in assaying the drug in plasma (concentrations of approximately 200 pg/ml or less after inhaled dosing). Because salmeterol acts locally in the pulmonary tissues, plasma levels are not predictive of therapeutic effect.

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 1000 times higher than this. Furthermore, in patients with airways obstruction receiving regular salmeterol xinafoate period over twelve months, no adverse effects associated with hydroxynaphthoic acid were observed.

Exposure in plasma salmeterol is significantly increased (1.4-fold increase in maximum concentration and 15-fold increase in AUC) was reported with co-administration of inhaled salmeterol 50 mcg twice daily and oral ketoconazole (a CYP 3A4 inhibitor) 400 mg once daily for 7 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. QTc prolongation or palpitations with sinus tachycardia led to three subjects being withdrawn from the study. Administration of both salmeterol and ketoconazole had no clinically significant effect on blood potassium, heart rate or QTc duration in the remaining 12 subjects (see Warnings and Precautions, and Interactions).

Fluticasone propionate
For fluticasone propionate administered via a metered-dose inhaler, the absolute bioavailability has been estimated from studies comparing the pharmacokinetic parameters of inhaled and intravenous formulations. In healthy adults, the absolute bioavailability is estimated at 10.9%, with a lesser degree of systemic exposure reported in patients with ROAD or COPD. Inhaled fluticasone propionate is mainly absorbed into the systemic circulation through the lungs in a rapid then prolonged manner. The rest of the inhaled dose may be swallowed; however, oral availability is less than 1% as fluticasone propionate has a low aqueous solubility and extensively metabolised before entering the systemic circulation. Systemic exposure increases with increased inhaled dose in a linear fashion. Fluticasone propionate has a terminal half-life of an estimated 8 hours, a high plasma clearance of 1150 ml/min, and a considerable volume of distribution at the steady-state (approximately 300 L). Approximately 91% of fluticasone propionate is bound to plasma proteins. Fluticasone propionate is metabolised to an inactive carboxylic acid metabolism by cytochrome P450 3A4 and is rapidly cleared from the systemic circulation. The renal clearance of fluticasone propionate is small (<0.2%), with <5% as the metabolite. There is potential for improved systemic exposure to fluticasone propionate when administered concomitantly with cytochrome P450 3A4 inhibitors; therefore, care should be taken in this situation.

5.3 Preclinical safety data
Only class effects typical of potent β_2 (beta-2) agonists and corticosteroids have been seen with salmeterol and fluticasone propionate in animal toxicology studies; these were only reported at dosages greatly exceeding those recommended therapeutically.

Class-related benign tumours in the smooth muscle of the uterus of mice and the mesovarium of rats have been observed with long-term salmeterol xinafoate exposure. Please note that regardless of rodents which are sensitive to these pharmacologically-induced tumours, salmeterol is not considered to be an oncogenic hazard in humans.

Some cardiovascular interactions were reported with co-administration of salmeterol and fluticasone propionate at high doses in animal models. In rats, focal coronary arteritis and transient mild atrial myocarditis were reported, which resolved with regular dosing. Salmeterol plus fluticasone propionate caused greater heart rate increases in dogs compared with salmeterol alone. No serious adverse cardiac events that are clinically relevant have been observed in clinical studies.

In animals, class related toxicities were not modified in the administration of both salbutamol and fluticasone propionate.

In extensive clinical experience β_2 (beta-2) agonists and corticosteroids have not shown any evidence that the effects seen in animals are relevant at therapeutic doses. No potential genetic toxicity has been observed in either salmeterol xinafoate or fluticasone propionate.

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 Rexair Inhaler.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lecithin, Ethanol, HFA-134a

6.2 Incompatibilities

None reported.

6.3 Shelf life

The shelf-life of Rexair Inhaler is 24 months.

6.4 Special precautions for storage

When the Rexair Inhaler is not in use, the plastic dust cap should be securely placed back on the mouthpiece of the actuator.

Store Rexair Inhaler below 25°C.

Avoid direct sunlight or heat and do not refrigerate or freeze. 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.

Instructions for Handling and Use

Usage instructions can also be found in the package insert.

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

Prior to using the Rexair Inhaler for the first time, remove the plastic dust cap from the mouthpiece of the inhaler, shake 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 Rexair 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. Rinse mouth with water after inhalation and spit it out.
7. After use, replace the mouthpiece cover making sure the dust cap is secure.

IMPORTANT:
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" appearing from the sides of your mouth or top of the inhaler, start again from step 2.

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

Children
An adult may be required 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 Rexair Inhaler has a built-in dose counter to see how many actuations are left in the inhaler.

After Rexair Inhaler is primed for the first time, the dose counter should read 120. This means that there are 120 doses 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 Rexair Inhaler, the colour on the dose counter will change from green to red. When the dose counter on the Rexair 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 Rexair 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 Rexair Inhaler plastic actuator should be cleaned at least once a week to ensure that it functions correctly.

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

6.5 Nature and contents of container
Rexair Inhaler is available in three strengths: 50 mcg fluticasone propionate/25 mcg salmeterol, 125 mcg fluticasone propionate/25 mcg salmeterol or 250 mcg fluticasone propionate/25 mcg salmeterol per actuation, with 120 actuations per inhaler.

6.6 Special precautions for disposal
No special requirements

7 MEDICINE SCHEDULE
Prescription Medicine

8 SPONSOR
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9 DATE OF FIRST APPROVAL
17 May 2012

10 DATE OF REVISION OF THE TEXT
14 May 2018

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.8	Addition of warning for visual disturbances