SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
RESPIRO 25 mcg/250 mcg Aerosol Inhaler

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active substance:
Each single actuation contains;
36.3 microgram salmeterol xinafoate equivalent to 25 microgram salmeterol
250 microgram fluticasone propionate

Excipient(s):
For excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Pressurized inhalation, suspension

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
It is indicated for improvement and control of asthma symptoms. It is administered starting from the third step in stepwise treatment of asthma disease. It reduces symptoms and frequency of the attacks in moderate and severe COPD cases.

4.2 Posology and method of administration
Posology/frequency and duration of administration:
RESPIRO inhaler is for inhalation use only.
Patients should be made aware that RESPIRO must be used daily for optimum benefit, even when asymptomatic.

Patients should be regularly reassessed by a doctor, so that the strength of RESPIRO they are receiving remains optimal and is only changed on medical advice. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. Where the control of symptoms is maintained with the lowest strength of the combination given twice daily, then the next step should include a test of inhaled corticosteroid alone.

As an alternative, patients requiring a long acting beta 2 agonist can be titrated to RESPIRO given once daily if, in the opinion of the prescriber, it would be adequate to maintain disease control. In the event of once daily dosing when the patient has a history of nocturnal symptoms the dose should be given at night and when the patient has a history of mainly day-time symptoms the dose should be given in the morning.

Patients should be given the strength of RESPIRO containing the appropriate fluticasone propionate dosage for the severity of their disease.

Note: 25 microgram /50 microgram salmeterol/fluticasone propionate strength is not appropriate in adults and children with severe asthma. Prescribers should be aware that, in patients with asthma, fluticasone propionate is as effective as other inhaled steroids at approximately half the microgram daily dose. For example, 100 microgram of fluticasone propionate is approximately equivalent to 200 microgram of beclomethasone dipropionate (CFC containing) or budesonide. If an individual

patient should require dosages outside the recommended regimen, appropriate doses of beta-agonist and/or corticosteroid should be prescribed.

Recommended doses:

Asthma
Adults and adolescents 12 years and older:
Two inhalations of 25 microgram salmeterol and 50 microgram fluticasone propionate twice daily.
or
Two inhalations of 25 microgram salmeterol and 125 microgram fluticasone propionate twice daily.
or
Two inhalations of 25 microgram salmeterol and 250 microgram fluticasone propionate twice daily.

A short term trial of RESPIRO may be considered as initial therapy in adults or adolescents with moderate persistent asthma (defined as patients with daily symptoms, daily rescue use and moderate to severe airflow limitation) for whom rapid control of asthma is essential. In these cases, the recommended initial dose is two inhalations of 25 microgram salmeterol and 50 microgram fluticasone propionate twice daily. Once control of asthma is attained treatment should be reviewed and consideration given as to whether patients should be stepped down to an inhaled corticosteroid alone. Regular review of patients as treatment is stepped down is important.

A clear benefit has not been shown as compared to inhaled fluticasone propionate alone used as initial therapy when one or two of the criteria of severity are missing. In general inhaled corticosteroids remain the first line treatment for most patients. RESPIRO is not intended for the initial management of mild asthma. 25 microgram /50 microgram salmeterol/fluticasone propionate strength is not appropriate in adults and children with severe asthma; it is recommended to establish the appropriate dosage of inhaled corticosteroid before any fixed combination can be used in patients with severe asthma.

Chronic Obstructive Pulmonary Disease (COPD)
Adults:
For adult patients recommended dose is 2 inhalations of 25/125 microgram – 25/250 microgram salmeterol/ fluticasone propionate twice daily. The maximum salmeterol/fluticasone propionate dose of 50/500 microgram taken twice daily has been shown to reduce all-cause mortality (see section 5.1).

Administration:
Patients should be instructed in the proper use and care of their inhaler and their technique checked to ensure optimum delivery of the inhaled drug to the lungs. A spacer device may be used by patient who has difficulty using inhaler. Patients should continue to use the same type of spacer device as switching between spacer devices can result in changes in the dose delivered to the lungs.

Re-titration to the lowest effective dose should always follow the introduction or change of a spacer device.

Method of administration:
RESPIRO is for inhalation use only.
Patients should be instructed in the proper use of their inhaler. During inhalation, the patient should preferably upright sit or stand. The inhaler has been designed for use in a vertical position.

Additional information on special populations
Renal impairment:
There is no need to adjust the dose in patients with renal impairment.

Hepatic impairment:
There are no data available for use of RESPIRO in patients with hepatic impairment.

Pediatric population:
Children aged between 4 and 12 years:
Two inhalations of 25 microgram salmeterol and 50 microgram fluticasone propionate twice daily.
The maximum licensed dose of fluticasone propionate delivered by RESPIRO inhaler in children is 100 microgram twice daily.
There are no data available for use of RESPIRO inhaler in children under 4 years of age.

Geriatric population:
There is no need to adjust the dose in elderly patients.

4.3 Contraindications
RESPIRO is contraindicated in patients with hypersensitivity to any of the active substances or to the excipients.

4.4 Special warnings and precautions for use
- The management of asthma should normally follow a stepwise program, with patient response monitored clinically and by lung function tests.
- RESPIRO is not recommended for treatment of mild asthma.
- RESPIRO should not be used to treat acute asthma symptoms for which a fast and short acting bronchodilator is required. Patients should be advised to have their medicinal product to be used for relief in an acute asthma attack available at all times.
- Patients should not be initiated on RESPIRO treatment during an exacerbation, or if they have significantly worsening or acutely deteriorating asthma.
- Serious asthma-related adverse events and exacerbations may occur during treatment with RESPIRO. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation of the treatment with RESPIRO.
- Long-acting beta-agonists should be used for the shortest period of time required to achieve control of asthma symptoms and then discontinued, if possible, once asthma control is achieved. Patients should then be maintained on asthma controller medication.
- Increasing use of short-acting bronchodilators to relieve asthma symptoms indicates deterioration of asthma control and patients should be reviewed by a physician.
- Sudden and progressive deterioration in control of asthma is potentially life-threatening and the patient should undergo urgent medical assessment. Consideration should be given to increasing corticosteroid therapy. Also, where the current dosage of RESPIRO has failed to give adequate control of asthma, the patient should be reviewed by a physician. Consideration should be given to additional corticosteroid therapies.
- Patients should not be initiated on long-acting beta-agonists during an exacerbation, or in patients with significantly worsening asthma or acutely deteriorating asthma.
- Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of RESPIRO. Regular review of patients as treatment is stepped down is important. The lowest effective dose of RESPIRO should be used. Treatment with RESPIRO should not be

stopped abruptly.
- As with all inhaled medication containing corticosteroids, RESPIRO should be administered with caution in patients with pulmonary tuberculosis.
- Rarely, RESPIRO may cause cardiac arrhythmias (e.g. supraventricular tachycardia, extrasystoles and atrial fibrillation), and a mild transient reduction in serum potassium at high therapeutic doses. Therefore, RESPIRO should be used with caution in patients with severe cardiovascular disorders, heart rhythm abnormalities, diabetes mellitus, thyrotoxicosis, uncorrected hypokalemia or patients predisposed to low levels of serum potassium.
- There have been very rare reports of increases in blood glucose levels and this should be considered when prescribing to patients with a history of diabetes mellitus.
- As with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. RESPIRO should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.
- Care should be taken when transferring patients to RESPIRO therapy, particularly if there is any reason to suppose that adrenal function is impaired from previous systemic steroid therapy.
- Systemic effects may occur with any inhaled corticosteroids, particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. It is important, therefore, that the patient is reviewed regularly and the dose of inhaled corticosteroid is reduced to the lowest dose at which effective control of asthma is maintained.
- Prolonged treatment of patients with high doses of inhaled corticosteroids may result in adrenal suppression and acute adrenal crisis. Children and adolescents <16 years taking high doses of fluticasone (typically ≥1000 mcg/day) may be at particular risk. Very rare cases of adrenal suppression and acute adrenal crisis have also been described with doses of fluticasone propionate between 500 and less than 1000 mcg. Situations, which could potentially trigger acute adrenal crisis, include trauma, surgery, infection or any rapid reduction in dosage. Presenting symptoms are typically vague and may include anorexia, abdominal pain, weight loss, tiredness, headache, nausea, vomiting, hypotension, decreased level of consciousness, hypoglycemia, and seizures. Additional systemic corticosteroid use should be considered during periods of stress or elective surgery.
- Systemic absorption of salmeterol and fluticasone propionate is largely through the lungs. As the use of a spacer device with a metered dose inhaler may increase drug delivery to the lungs, it should be noted that this could potentially lead to an increase in the risk of systemic adverse effects.
- The benefits of inhaled fluticasone propionate therapy will minimize the need for oral steroids, but patients transferring from oral steroids may remain at risk of reduction of adrenal reserve for a considerable time. Patients who have required high dose emergency corticosteroid therapy in the past may also be at risk. This possibility of residual impairment should always be borne in mind in emergency and elective situations likely to produce stress, and appropriate corticosteroid treatment must be considered. The extent of the adrenal impairment may require specialist advice before elective procedures. Ritonavir can greatly increase the concentration of fluticasone propionate in plasma. Therefore, concomitant use should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side-effects. There is also an increased risk of systemic side effects when combining fluticasone propionate with other potent CYP3A inhibitors.
- There was an increased reporting of lower respiratory tract infections (particularly pneumonia and bronchitis) in a 3-year study in patients with Chronic Obstructive Pulmonary Disease

(COPD) receiving RESPIRO compared with placebo. In a 3 year COPD study, older patients, patients with a lower body mass index (<25 kg/m^2) and patients with very severe disease (FEV1<30% predicted) were at greatest risk of developing pneumonia regardless of treatment. Physicians should remain vigilant for the possible development of pneumonia and other lower respiratory tract infections in patients with COPD as the clinical features of such infections and exacerbation frequently overlap. If a patient with severe COPD has experienced pneumonia the treatment with RESPIRO should be re-evaluated.

- Pneumonia in patients with COPD
  An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, has been observed in patients with COPD receiving inhaled corticosteroids. There is some evidence of an increased risk of pneumonia with increasing steroid dose but this has not been demonstrated conclusively across all studies.
  There is no conclusive clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products.
  Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations.
  Risk factors for pneumonia in patients with COPD include current smoking, older age, low body mass index and severe COPD.
- Rarely, serious and sometimes fatal asthma-related breathing problems have occurred with the use of long-acting beta-agonist preparations.
- Data from a large clinical trial (the Salmeterol Multi-Center Asthma Research Trial, SMART) suggested African-American patients were at increased risk of serious respiratory-related events or deaths when using salmeterol compared with placebo. It is not known if this was due to pharmacogenetic or other factors. Patients of black African or Afro-Caribbean ancestry should therefore be asked to continue treatment but to seek doctor advice if asthma symptoms remained uncontrolled or worsen whilst using RESPIRO.
- Concomitant use of systemic ketoconazole significantly increases systemic exposure to salmeterol. This may lead to an increase in the incidence of systemic effects (e.g. prolongation in the QTC interval and palpitations). Concomitant treatment with ketoconazole or other potent CYP3A4 inhibitors should therefore be avoided unless the benefits outweigh the potentially increased risk of systemic side effects of salmeterol treatment.
- Pediatric and adolescent patients who require the addition of a long-acting beta agonist to an inhaled corticosteroid should use a combination product containing both an inhaled corticosteroid and a long-acting beta agonist to ensure compliance with both medications.

4.5 Interaction with other medicinal products and other forms of interaction

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

Concomitant use of other beta-adrenergic containing drugs can have a potentially additive effect.

Fluticasone Propionate

Under normal circumstances, low plasma concentrations of fluticasone propionate are achieved after inhaled dosing, due to extensive first pass metabolism and high systemic clearance mediated by cytochrome P450 3A4 in the gut and liver. Hence, clinically significant drug interactions mediated by fluticasone propionate are unlikely.

In an interaction study in healthy subjects with intranasal fluticasone propionate, ritonavir (a highly

potent cytochrome P450 3A4 inhibitor) 100 mg b.i.d. increased the fluticasone propionate plasma concentrations several hundred fold, resulting in markedly reduced serum cortisol concentrations. Information about this interaction is lacking for inhaled fluticasone propionate, but a marked increase in fluticasone propionate plasma levels is expected. Cases of Cushing's syndrome and adrenal suppression have been reported. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects.

In a small study in healthy volunteers, the slightly less potent CYP3A inhibitor ketoconazole increased the exposure of fluticasone propionate after a single inhalation by 150%. This resulted in a greater reduction of plasma cortisol as compared with fluticasone propionate alone. Co-treatment with other potent CYP3A inhibitors, such as itraconazole, is also expected to increase the systemic fluticasone propionate exposure and the risk of systemic side-effects. Caution is recommended and long-term treatment with such drugs should if possible be avoided.

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

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

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

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

Additional information on special populations
Pediatric population:
It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroid is regularly monitored. The dose of inhaled corticosteroid should be reduced to the lowest dose at which effective control of asthma is maintained.

4.6 Pregnancy and lactation
General recommendation
Pregnancy category: C

Women of childbirth potential/Birth control (Contraception)
There is not any information as to any effect of RESPIRO Inhaler on contraception methods.

Pregnancy
There are insufficient data on its use during pregnancy. Animal studies have shown reproductive toxicity (see section 5.3). Potential risk to human is unknown.

Reproductive toxicity studies in animals, either with single drug or in combination, revealed the fetal effects expected at excessive systemic exposure levels of a potent beta 2 adrenoceptor agonist and glucocorticosteroid.

Administration of drug should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus. Extensive clinical experience with drug in these classes has revealed no evidence that the effects are relevant to therapeutic doses. Neither salmeterol xinafoate nor fluticasone propionate has shown any potential for genetic toxicity. It should not be used during pregnancy unless necessary.

Breast-feeding
There are insufficient data on the use of salmeterol xinafoate and fluticasone propionate during pregnancy and lactation. Preferably, it should not be used during lactation.

Salmeterol is excreted into breast milk. Low plasma concentrations of salmeterol and fluticasone propionate are achieved after inhaled therapeutic doses and it is possible to excrete into breast milk with low concentrations. This was supported by the studies conducted with lactating animals having low concentrations of the drugs.

Fertility
There is no data.

4.7 Effects on ability to drive and use machines
No studies of the effect on the ability to drive and use machinery have been performed. But the pharmacology of both medicines does not indicate any effect.

4.8 Undesirable effects
As RESPIRO contains salmeterol and fluticasone propionate, the type and severity of adverse reactions associated with each of the compounds may be expected. There is no incidence of additional adverse events following concurrent administration of the two compounds. Adverse events that have been associated with salmeterol/fluticasone propionate are given below, listed by system organ class and frequency. Frequencies are defined as:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); unknown (cannot be estimated from the available data).

Very common, common and uncommon events were derived from clinical trial data. The incidence in placebo was not taken into account. Very rare events were derived from post-marketing spontaneous data.

Infections and infestations
Common : Candidiasis of the mouth and throat, pneumonia (in COPD patients), bronchitis

Immune system disorders

Uncommon : Cutaneous hypersensitivity reactions
Very rare : Angioedema (mainly facial and oropharyngeal edema), respiratory symptoms (dyspnea and/or bronchospasm), anaphylactic reactions including anaphylactic shock

Endocrine disorders
Very rare : Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decreased bone mineral density, cataract, glaucoma

Metabolism and nutrition disorders
Common : Hypokalemia
Very rare : Hyperglycemia

Psychiatric disorders
Very rare : Anxiety, sleep disorders and behavioral changes, including hyperactivity and irritability (predominantly in children)
Unknown : Depression, aggression (especially in children)

Nervous system disorders
Very common : Headache
Common : Tremor

Cardiac disorders
Common : Palpitations
Uncommon : Tachycardia
Very rare : Cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia and extrasystoles)

Respiratory, thoracic and mediastinal disorders
Very common : Nasopharyngitis
Common : Throat irritation, hoarseness/dysphonia, sinusitis
Very rare : Paradoxical bronchospasm

Skin and subcutaneous tissue disorders
Common : Contusions

Musculoskeletal and connective tissue and bone disorders
Common : Muscle cramps, traumatic fractures
Very rare : Arthralgia, myalgia

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 in accordance with local requirements.

4.9 Overdose
There are no data available from clinical trials on overdose with RESPIRO, however data on overdose with both drugs are given below:

The signs and symptoms of salmeterol overdose are tremor, headache and tachycardia. The preferred antidotes are cardioselective beta-blocking agents, which should be used with caution in patients with a history of bronchospasm. If RESPIRO therapy has to be withdrawn due to overdose of the beta agonist component of the drug, provision of appropriate replacement steroid therapy should be considered. Additionally, hypokalemia can occur and potassium replacement should be considered.

Acute: Acute inhalation of fluticasone propionate doses in excess of those recommended may lead to temporary suppression of adrenal function. This does not need emergency action as adrenal function is recovered in a few days, as verified by plasma cortisol measurements.
Chronic overdose of inhaled fluticasone propionate results in a risk of adrenal suppression.
Monitoring of adrenal reserve may be necessary. In cases of fluticasone propionate overdose RESPIRO therapy may still be continued at a suitable dosage for symptom control.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Selective Beta-2-adrenergic receptor agonists (inhaled)
Corticosteroids (inhaled)
ATC code: R03AK06

Salmeterol/fluticasone propionate asthma clinical trials
A 12 month study (Gaining Optimal Asthma Control, GOAL), in 3416 adult and adolescent patients with persistent asthma, compared the safety and efficacy of salmeterol/fluticasone propionate versus inhaled corticosteroid (Fluticasone Propionate) alone to determine whether the goals of asthma management were achievable. Treatment was stepped up every 12 weeks until **Total control was achieved or the highest dose of study drug was reached. GOAL showed more patients treated with salmeterol/fluticasone propionate achieved asthma control than patients treated with ICS alone and this control was attained at a lower corticosteroid dose.

Well-controlled asthma was achieved more rapidly with Salmeterol/fluticasone propionate than with ICS alone. The time on treatment for 50% of subjects to achieve a first individual well-controlled week was 16 days for Salmeterol/fluticasone propionate compared to 37 days for the ICS group. In the subset of steroid naive asthmatics the time to an individual well-controlled week was 16 days in the Salmeterol/fluticasone propionate treatment compared to 23 days following treatment with ICS.

The overall study results showed below:

Percentage of Patients Attaining *Well Controlled (WC) and **Totally Controlled (TC) Asthma over 12 months				
Pre-Study Treatment	Salmeterol/FP		FP	
	WC	TC	WC	TC
No ICS (Short Acting Beta Agonist –SABA-alone)	78%	50%	70%	40%
Low dose ICS (≤500 mcg beclomethasone dipropionate (BDP) or equivalent/day)	75%	44%	60%	28%
Medium dose ICS (>500-1000 mcg beclomethasone dipropionate (BDP) or equivalent/day)	62%	29%	47%	16%
Pooled results across the 3 treatment levels	71%	41%	59%	28%

*Well controlled asthma; occasional symptoms or SABA use or less than 80% predicted lung function plus no night-time awakenings, no exacerbations and no side effects enforcing a change in therapy.
**Total control of asthma; no symptoms, no SABA use, ≥ 80% predicted lung function, no night-time

awakenings, no exacerbations and no side effects enforcing a change in therapy.

The results of this study suggest that Salmeterol/fluticasone 50/100 microgram b.i.d may be considered as initial maintenance therapy in patients with moderate persistent asthma for whom rapid control of asthma is deemed essential.

A double-blind, randomized, parallel group study in 318 patients with persistent asthma aged ≥ 18 years evaluated the safety and tolerability of administering two inhalations twice daily (double dose) of Salmeterol /fluticasone propionate for two weeks. The study showed that doubling the inhalations of each strength of salmeterol /fluticasone propionate for up to 14 days resulted in a small increase in beta-agonist-related adverse events (tremor; 1 patient [1%] vs. 0, palpitations; 6 [3%] vs. 1 [<1%], muscle cramps; 6[3%] vs. 1 [<1%]) and a similar incidence of inhaled corticosteroid related adverse events (e.g. oral candidiasis; 6 [6%] vs. 16 [8%], hoarseness; 2 [2%] vs. 4 [2%]) compared to one inhalation twice daily. The small increase in beta-agonist-related adverse events should be taken into account if doubling the dose of Salmeterol /fluticasone propionate is considered by the physician in adult patients requiring additional short-term (up to 14 days) inhaled corticosteroid therapy.

The Salmeterol Multi-center Asthma Research Trial (SMART)
SMART was a multi-centre, randomized, double-blind, placebo-controlled, parallel group 28-week study in the US which randomized 13,176 patients to salmeterol (50 mcg twice daily) and 13,179 patients to placebo in addition to the patients' usual asthma therapy. Patients were enrolled if ≥12 years of age, with asthma and if currently using asthma medication (but not a LABA). Baseline ICS use at study entry was recorded, but not required in the study. The primary endpoint in SMART was the combined number of respiratory-related deaths and respiratory-related life-threatening experiences.

Key Findings from SMART: Primary Endpoint

Patient group	Number of primary endpoint events/number of patients		Relative Risk (95% confidence intervals)
	Salmeterol	Placebo	
All patients	50/13,176	36/13,179	1.40 (0.91, 2.14)
Patients using inhaled steroids	23/6,127	19/6,138	1.21 (0.66, 2.23)
Patients not using inhaled steroids	27/7,049	17/7,041	1.60 (0.87, 2.93)
African-American patients	**20/2,366**	**5/2,319**	**4.10 (1.54, 10.90)**

(Risk in bold is statistically significant at the 95% level.)

Key Findings from SMART by Inhaled Steroid Use at Baseline: Secondary Endpoints

	Number of secondary endpoint events/number of patients		Relative Risk (95% confidence intervals)
	Salmeterol	Placebo	
Respiratory -related mortality			
Patients using inhaled steroids	10/6127	5/6138	2.01 (0.69, 5.86)
Patients not using inhaled steroids	14/7049	6/7041	2.28 (0.88, 5.94)
Combined asthma-related mortality or life-threatening experience			
Patients using inhaled steroids	16/6127	13/6138	1.24 (0.60, 2.58)
Patients not using inhaled steroids	**21/7049**	**9/7041**	**2.39 (1.10, 5.22)**
Asthma-related mortality			

Patients using inhaled steroids	4/6127	3/6138	1.35 (0.30, 6.04)
Patients not using inhaled steroids	9/7049	0/7041	*

(*=could not be calculated because of no events in placebo group. Risk in bold figures is statistically significant at the 95% level. The secondary endpoints in the table above reached statistical significance in the whole population.) The secondary endpoints of combined all-cause death or life-threatening experience, all cause death, or all cause hospitalization did not reach statistical significance in the whole population.

COPD
Symptomatic COPD patients without restriction to 10% reversibility to a short-acting beta2-agonist: Placebo-controlled clinical trials, over 6 months, have shown that regular use of both salmeterol/fluticasone propionate 50/250 microgram and 50/500 microgram rapidly and significantly improves lung function, significantly reduced breathlessness and the use of relief medication. There were also significant improvements in health status.

Symptomatic COPD patients who demonstrated less than 10% reversibility to a short-acting beta2-agonist:
Placebo-controlled clinical trials, over 6 and 12 months, have shown that regular use of Salmeterol/fluticasone propionate 50/500 microgram rapidly and significantly improves lung function, significantly reduced breathlessness and the use of relief medication. Over a 12-month period the risk of COPD exacerbations and the need for additional courses of oral corticosteroids was significantly reduced. There were also significant improvements in health status.

Salmeterol/fluticasone propionate 50/500 microgram was effective in improving lung function, health status and reducing the risk of COPD exacerbations, in both current and ex-smokers.

TORCH study (Towards a Revolution in COPD Health):
TORCH was a 3-year study to assess the effect of treatment with Salmeterol/fluticasone propionate Discus/inhaler 50/500 microgram twice daily, salmeterol Discus/inhaler 50 microgram twice daily, FP (fluticasone propionate) Discus/inhaler 500 microgram twice daily or placebo on all-cause mortality in patients with COPD. Patients with moderate to severe COPD with a baseline (pre bronchodilator) FEV1 <60% of predicted normal were randomized to double-blind medication. During the study, patients were permitted usual COPD therapy with the exception of other inhaled corticosteroids, long acting bronchodilators, and long-term systemic corticosteroids. Survival status at 3 years was determined for all patients regardless of withdrawal from study medication. The primary endpoint was reduction in all-cause mortality at 3 years for Salmeterol/fluticasone propionate vs. placebo (Table 1).

Table 1

	Placebo N= 1524	Salmeterol 50 N= 1521	FP 500 N= 1534	Salmeterol/ fluticasone propionate 50/500 N= 1553
All-cause mortality at 3 years				
Number of deaths (%)	231 (15.2%)	205 (13.5%)	246 (16.0%)	193 (12.6%)
Hazard ratio vs. placebo (Cls) p value	Not applicable	0.879 (0.73, 1.06) 0.180	1.060 (0.89, 1.27) 0.525	0.825 (0.68, 1.00) 0.0521
Hazard ratio, Salmeterol/ fluticasone propionate 50/500	Not applicable	0.932 (0.77, 1.13)	0.774 (0.64, 0.93)	Not applicable

vs. components (Cls) p value		0.481	0.007	

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

Salmeterol/fluticasone propionate reduced risk of dying at any time during the 3 years by 17.5% compared to placebo (Hazard ratio 0.825 (95% CI 0.68, 1.00, p= 0.052); all adjusted for interim analyses). There was a 12% reduction in the risk of dying any time within three years from any cause for salmeterol compared with placebo (p= 0.18) and a 6% increase for FP compared with placebo (p= 0.525) (Table 1).

A supporting analysis using Cox's Proportional Hazards model gave a hazard ratio of 0.811 (95% CI 0.670, 0.982, p=0.031) for Salmeterol/fluticasone propionate vs. placebo which represented a 19% reduction in the risk of dying at any time within 3 years. The model adjusted for important factors (smoking status, age, sex, region, baseline FEV1 and Body Mass Index). There was no evidence that treatment effects varied for these factors (Table 1).

The percentage of patients who died within three years due to COPD-related causes was 6.0% for placebo, 6.1% for salmeterol, 6.9% for FP and 4.7% for Salmeterol/fluticasone propionate (Table 1).

Salmeterol/fluticasone propionate reduced the rate of moderate to severe exacerbations by 25% (95% CI: 19% to 31%; p<0.001) compared with placebo. Salmeterol/fluticasone propionate reduced the exacerbation rate by 12% compared with salmeterol (95% CI: 5% to 19%, p=0.002) and 9% compared with FP (95% CI: 1% to 16%, p=0.024). Salmeterol and FP significantly reduced exacerbation rates compared with placebo by 15% (95% CI: 7% to 22%; p<0.001) and 18% (95% CI: 11% to 24%; p<0.001) respectively.

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

Over the three-year treatment period, FEV1 values were higher in subjects treated with Salmeterol/fluticasone propionate than for those treated with placebo (average difference over 3 years 92 ml, 95% CI: 75 to 108 ml; p<0.001). Salmeterol/fluticasone propionate was also more effective than salmeterol or FP in improving FEV1 (average difference 50 ml, p<0.001 for salmeterol and 44 ml, p<0.001 for FP).

The estimated 3 year probability of having pneumonia reported as an adverse event was 12.3% for placebo, 13.3% for salmeterol, 18.3% for FP and 19.6% for salmeterol-FP (Hazard ratio for Salmeterol/fluticasone propionate vs. placebo: 1.64, 95% CI: 1.33 to 2.01, p<0.001). There was no increase in pneumonia related deaths; deaths while on treatment that were adjudicated as primarily due to pneumonia were 7 for placebo, 9 for salmeterol, 13 for FP and 8 for Salmeterol/fluticasone propionate. There was no significant difference in probability of bone fracture (5.1% placebo, 5.1% salmeterol, 5.4% FP and 6.3% Salmeterol/fluticasone propionate; Hazard ratio for Salmeterol/ fluticasone propionate vs. placebo: 1.22, 95% CI: 0.87 to 1.72, p=0.248). The incidence of adverse events of eye disorders, bone disorders, and hypothalamus-pituitary-adrenal axis disorders was low and there was no difference observed between treatments. There was no evidence of an increase in cardiac adverse events in the treatment groups receiving salmeterol.

Mechanism of action:
RESPIRO contains salmeterol and fluticasone propionate that have differing modes of action. The respective mechanisms of action of both drugs are discussed below.

Salmeterol:
Salmeterol is a selective long-acting (12-hour) beta 2 adrenoceptor agonist with a long side chain which binds to secondary binding side of the receptor. Salmeterol produces a longer duration of bronchodilation, lasting for at least 12 hours, than recommended doses of conventional short-acting beta 2 agonists.

Fluticasone propionate:
Fluticasone propionate given by inhalation at recommended doses has a glucocorticoid anti-inflammatory action within the lungs, resulting in reduced symptoms and exacerbations of asthma, with less adverse effects than when corticosteroids are administered systemically.

5.2 Pharmacokinetic properties
General properties
When salmeterol and fluticasone propionate were administered in combination by the inhaled route, the pharmacokinetics of each component were similar to those observed when the drugs were administered separately. For pharmacokinetic purposes, therefore each component can be considered separately.

Salmeterol:
Absorption:
Salmeterol acts locally in the lung therefore plasma levels are not an indication of therapeutic effects. In addition, there are only limited data available on the pharmacokinetics of salmeterol because of the technical difficulty of assaying the drug in plasma due to the low plasma concentrations at therapeutic doses (approximately 200 pg/ml or less) achieved after inhaled dosing. After regular dosing with salmeterol xinafoate, hydroxynaphthoic acid can be detected in the systemic circulation, reaching steady-state concentrations of approximately 100 ng/ml. These concentrations are up to 1000 fold lower than steady-state concentrations observed in toxicity studies. No detrimental effects have been seen following long-term regular dosing (more than 12 months) in patients with airway obstruction.

Distribution:
Plasma protein binding rate of salmeterol is 96%.

Biotransformation:
An in-vitro study showed that salmeterol is extensively metabolized to α-hydroxysalmeterol (aliphatic oxidation) by cytochrome P450 (CYP3A4).

Elimination:
Elimination half-life is 5.5 hours. Salmeterol is excreted in feces by 60% and in urine by 25%.

Linearity/Nonlinearity status:
There is no data.

Fluticasone propionate:

Absorption:
The absolute bioavailability of a single dose of inhaled fluticasone propionate in healthy subjects varies between approximately 5-11% of the nominal dose depending on the inhalation device used. In patients with asthma, a lesser degree of systemic exposure to inhaled fluticasone propionate has been observed. Systemic absorption occurs mainly through the lungs and is initially rapid then prolonged. The remainder of the inhaled dose may be swallowed but contributes minimally to systemic exposure due to the low aqueous solubility and pre-systemic metabolism, resulting in oral availability of less than 1%.

Distribution:
The kinetics of fluticasone propionate is characterized by high plasma clearance (1150 ml/min), a large volume of distribution at steady state (approximately 300 L) and a terminal half-life of approximately 8 hours.
Plasma protein binding rate is 91%.

Biotransformation:
Fluticasone propionate is cleared very rapidly from the systemic circulation. The main pathway is metabolism to an inactive carboxylic acid metabolite, by the cytochrome P450 enzyme CYP3A4. Other unidentified metabolites are also determined in the feces.

Elimination:
The renal clearance of fluticasone propionate is negligible. Less than 5% of the dose is excreted in urine, mainly as metabolites. The main part of the dose is excreted as feces as metabolites and unchanged drug.

Linearity/Nonlinearity status:
There is a linear increase in systemic exposure with increasing inhaled dose.

5.3. Preclinical safety data
The only safety concerns for human use derived from animal studies of salmeterol and fluticasone propionate given separately were effects associated with exaggerated pharmacological actions. In animal reproduction studies, glucocorticosteroids have been shown to induce malformations (cleft palate, skeletal malformations). However, these animal experimental results do not seem to be relevant for man given recommended doses. Animal studies with salmeterol have shown embryofetal toxicity only at high exposure levels. Following co-administration, increased incidences of transposed umbilical artery and incomplete ossification of occipital bone were found in rats at doses associated with known glucocorticoid-induced abnormalities. The non-chlorofluorocarbon (CFC) propellant, norflurane, has been shown to have no toxic effect at very high vapor concentrations, far in excess of those likely to be experienced by patients, in a wide range of animal species exposed daily for periods of two years.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
HFA 134a

6.2 Incompatibilities
None.

6.3 Shelf life

36 months

6.4 Special precautions for storage
Keep at room temperature below 25°C.
Do not freeze. Protect from direct sunlight.
As with most inhaled medicinal products in pressurised containers, the therapeutic effect of this medicinal product may decrease when the container is cold. The container should not be punctured, broken or burnt even when apparently empty.

6.5 Nature and contents of container
120-dosage, concave based metal tube with a metering valve containing Salmeterol/Fluticasone 25 mcg/250 mcg aerosol.

6.6 Special precautions for disposal and other handling
Any unused material should be disposed according to local disposal regulations.

Testing the inhaler:
Before using for the first time patients should remove the mouthpiece cover by gently squeezing the sides of the cover, shake the inhaler well, hold the inhaler between the fingers and thumb with thumb at the base, below the mouthpiece and release puffs into the air. The inhaler should be shaken immediately after releasing each puff. If the inhaler has not been used for a week or more remove the mouthpiece cover, the patients should shake the inhaler well and release two puffs into the air.
There is a counter on the front of RESPIRO which tells you how many doses are left. Each time you press the canister, a puff of medicine is released and the counter will count down a little bit. The counter measures interval of 20 doses. Take care not to drop the inhaler as this may cause the counter to count down.

Instructions for the use of RESPIRO Aerosol Inhaler
1. Patients should remove the mouthpiece cover by gently squeezing the sides of the cover.
2. Patients should check inside and outside of the inhaler including the mouthpiece for the presence of loose objects.
3. Patients should shake the inhaler well to ensure that any lose objects are removed and that the contents of the inhaler are evenly mixed.
4. Patients should hold the inhaler upright between fingers and thumb with their thumb on the base, below the mouthpiece.
5. Patients should breathe out as far as is possible and then place the mouthpiece in their mouth between their teeth and close their lips around it. Patients should be instructed not to bite the mouthpiece.
6. Just after starting to breathe in through their mouth, patients should press firmly down on the top of the inhaler to release RESPIRO, while still breathing in steadily and deeply.
7. While holding their breath, patients should take the inhaler from their mouth and take their finger from the top of the inhaler. Patients should continue holding their breath for as long as is possible.
8. To take a second inhalation, patients should keep the inhaler upright and wait about 30 seconds before repeating steps 3 to 7.
9. Patients should immediately replace the mouthpiece cover in the correct orientation by firmly pushing and snapping the cap into position. The cover does not require excessive force and it will click into position.

Patients should not rush stages 5, 6 and 7. It is important that patients start to breathe in as slowly as

possible just before operating their inhaler. Patients should practice in front of a mirror for the first few times. If they see "mist" coming from the top of their inhaler or the sides of their mouth they should start again from stage 2.

The dose counter is getting red when 40 doses are left. The counter is getting totally red when 20 doses are left to which tells decreased level of medicine. In this case you should consult your doctor. When the counter reaches 0, you should not use it as remaining medicine contains inadequate dose for you. You should not change number of counter or you should not try to remove the counter.

Cleaning
You should clean your inhaler at least once a week. Remove the mouthpiece cover. Do not remove the tube from the plastic casing. Wipe the inside and outside of the mouthpiece and the plastic casing with a dry cloth or tissue. Replace the mouthpiece cover in the correct orientation. The cover does not require excessive force and it will click into position.
DO NOT PUT THE METAL CONTAINER IN WATER.

7. MARKETING AUTHORIZATION HOLDER
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8. MARKETING AUTHORIZATION NUMBER(S)
232/5

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
Date of first authorization : 12.05.2011
Date of last renewal :

10. DATE OF REVISION OF THE TEXT