SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE HUMAN MEDICINAL PRODUCT
RESPIRO 25 mcg/50 mcg suspension for inhalation under pressure
RESPIRO 25 mcg/125 mcg suspension for inhalation under pressure
RESPIRO 25 mcg/250 mcg suspension for inhalation under pressure

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active substances:
Each single dose contains:
25 mcg of salmeterole (in form of salmeterole xinafoate) and 50 mcg, 125 mcg or 250 mcg of fluticasone propionate (exhausted from the valve).

Excipients:
For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Suspension for inhalation under pressure

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
ASTHMA (reversible obstructive airways disease)
RESPIRO is indicated in the regular treatment of asthma where use of a combination product (long-acting β_2 agonist and inhaled corticosteroid) is appropriate:
- In patients not adequately controlled with inhaled corticosteroids and „as needed" inhaled short-acting β_2 agonist or
- In patients already adequately controlled on both inhaled corticosteroid and long-acting β_2 agonist

Chronic Obstructive Pulmonary Disease (COPD)
RESPIRO is used in symptomatic treatment of patients with chronic obstructive pulmonary disease (COPD) which have FEV1 <60% of the predicted standard (prior to the application of bronchodilators) and frequent exacerbations that are not adequately controlled by regular treatment with bronchodilators.

4.2. Posology and method of administration
Posology
Route of administration: Inhalation use.

Patients should be made aware that RESPIRO must be used ordinarilly for optimum benefit, even when asymptomatic.
Patients should be regularly reassessed by a doctor, so that the therapeutic dose that they are receiving remains optimal and is only changed on medical advice.

ASTHMA - reversible obstructive airways diseases
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 RESPIRO given twice daily, then the next step could include a use of inhaled corticosteroid alone. As an alternative, patients requiring a long-acting beta-2-agonist could 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 daytime 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: RESPIRO 25 microgram/50 microgram strength is not appropriate for adults and children with severe asthma. If patients conditions require dosages outside the recommended regimen, appropriate doses of beta-2-agonist and/or corticosteroid should be prescribed.

Recommended Doses:

Adults and adolescents 12 years and older:

- Two inhalations (25 micrograms salmeterol and 50 micrograms fluticasone propionate) twice daily

or

- Two inhalations (25 micrograms salmeterol and 125 micrograms fluticasone propionate) twice daily

or

- Two inhalations (25 micrograms salmeterol and 250 micrograms fluticasone propionate) twice daily

A short-term usage of RESPIRO may be considered as initial maintenance therapy in adults or adolescents with moderate persistent asthma (in patients with daily symptoms, daily usage of short-acting bronchodilatators and moderate to severe airflow limitation) for whom rapid control of asthma is needed. In those cases, the recommended initial dose is two inhalations of 25 micrograms of salmeterol and 50 micrograms of fluticasone propionate twice daily. Once control of asthma is obtained, 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 maintenance therapy if one or two of the criteria for assessing the severity of asthma are missing. In general, inhaled corticosteroids remain the first line treatment for most patients. RESPIRO is not intended for the initial treatment of mild asthma. RESPIRO 25 micrograms/50 micrograms 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.

Paediatric population

Children 4 years and older:

- Two inhalations of 25 micrograms salmeterol and 50 micrograms 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 aged under 4 years.

Chronic Obstructive Pulmonary Disease (COPD)

Adults

For adults recommended dose is two inhalations (25 micrograms of salmeterol/250 micrograms of fluticasone propionate) twice daily.

Special patient groups:

There is no need to adjust the dose in elderly patients or in those with renal impairment. There are no data available for use of RESPIRO in patients with hepatic impairment.

Instructions for Use:

Patients should be instructed in the proper use of their suspension for inhalation under pressure (inhaler) (see patient information leaflet).

During inhalation, the patient should preferably sit or stand. The inhaler is designed for use in a vertical position.

Testing of 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 dose. 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 doses 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 container, a dose 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 start counting.

Instructions for the use of RESPIRO suspension for inhalation under pressure

Patients should remove the mouthpiece cover by gently squeezing both sides of the cover.
Patients should check inside and outside of the inhaler including the mouthpiece for the presence of foreign objects.
Patients should shake the inhaler well to ensure that any foreign objects are removed and that the contents of the inhaler are evenly mixed.
Patients should hold the inhaler upright between fingers and thumb with their thumb on the base, below the mouthpiece.
Patients should breathe out to the limit of discomfort 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.
Just before starting to breathe in through their mouth, patients should press firmly down on the top of the inhaler to release RESPIRO, while still breathing steadily and deeply.
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 to the limit of discomfort.
To take a second inhalation, patients should keep the inhaler upright and wait about 30 seconds before repeating steps 3 to 7.
Patients should immediately return 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 right position.

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

Patients should rinse their mouth out with water and spit out, and/or brush their teeth after each dose of medicine, in order to minimise the risk of oropharyngeal candidiasis and hoarseness.

The dose counter is getting red when 40 doses are left. The counter is getting totally red when 20 doses are left, which tells you that there is a 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 in inhaler contains inadequate dose for you. You should not change number on counter or you should not try to remove the counter.

Cleaning (also described in Instructions for Use)
You should clean your inhaler at least once a week.
Remove the mouthpiece cover.
Do not remove the metal container 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 right position.

DO NOT PUT THE METAL CONTAINER IN WATER.

4.3. Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4. Special warnings and precautions for use
RESPIRO suspension for inhalation under pressure 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 inhaler to be used for relief in an acute asthma attack available at all times.
Patients should not be initiated on RESPIRO 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 salmeterole/fluticasone propionate. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on salmeterole/fluticasone propionate treatment.

Increased requirements for use of reliever medication (short-acting bronchodilators), or decreased response to this medication indicate 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.
In patients with COPD experiencing exacerbation of the disease, usually indicate systemic corticosteroid therapy, therefore patients should be advised to seek medical assistance in the event of an exacerbation of symptoms in RESPIRO therapy.
Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of RESPIRO. Regular patient control is important during the gradual reduction of the dose of the medicinal product. The lowest effective dose of RESPIRO should be used (see section 4.2).
Treatment with RESPIRO should not be stopped abruptly due to risk of exacerbation. Therapy should be down-titrated under physician supervision. For patients with COPD, termination of treatment may be associated with worsening of the symptoms of the disease and should be performed under the supervision of a physician.
As with all inhaled medication containing corticosteroids, RESPIRO should be administered with caution in patients with active or inactive (latent) pulmonary tuberculosis and fungal, viral or other infections of the airway. Appropriate treatment should be promptly instituted, if indicated.
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 or heart rhythm abnormalities and in patients with diabetes mellitus, thyrotoxicosis, uncorrected hypokalaemia or patients predisposed to low levels of serum potassium.
There have been very rare reports of increases in blood glucose levels (see section 4.8) 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 and shortness of breath after dosing. Paradoxical bronchospasm responds to a fast-acting bronchodilator and should be treated straightaway. RESPIRO suspension for inhalation under pressure should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.
The pharmacological side effects of β_2 agonist treatment, such as tremor, palpitations and headache, have been reported, but tend to be transient and reduce with regular therapy.
Systemic effects may occur with any inhaled corticosteroid, 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, decrease in bone mineral density, cataract and glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children) (see Paediatric population sub-heading below for information on the systemic effects of inhaled corticosteroids in children and adolescents). **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. 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 micrograms. 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, hypoglycaemia, and seizures. Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.
Systemic absorption of salmeterol and fluticasone propionate is mostly through the lungs.
The treatment with inhaled fluticasone propionate therapy should minimise the need for oral steroids, but patients transferring from oral steroids may remain at risk of impaired adrenal reserve for a considerable time. Therefore, these patients should be treated with special care and adrenocortical function regularly monitored. 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 (see section 4.5).

Pneumonia in patients with COPD
Patients with COPD treated with inhaled corticosteroids reported increased incidence of pneumonia, including pneumonia requiring hospitalization.
There are some indicators of increased risk of pneumonia with increasing steroid doses, but this has not been conclusively proven in all trials.
There is no convincing clinical evidence of differences in the risk of pneumonia among individual inhaled corticosteroids within that group.
Physicians should carefully monitor the possible development of pneumonia in patients with COPD since the clinical manifestations of these infections coincide with symptoms of exacerbation of COPD.
Patient risk factors for COPD patients include active smokers, older age, low body mass index (BMI), and severe COPD.
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 (see section 4.5).

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.

Paediatric Population
Children and adolescents < 16 years taking high doses of fluticasone propionate (typically ≥1000 micrograms/day) may be at particular risk. Systemic effects may occur, particularly at high doses prescribed for long periods. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, acute adrenal crisis and growth retardation in children and adolescents and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression. Consideration should be given to referring the child or adolescent to a paediatric respiratory specialist.
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.**

4.5. Interaction with other medicinal products and other forms of interaction
β_2 adrenergic blockers may weaken or antagonise the effect of salmeterol. Both non-selective and selective beta blockers should be avoided, unless there are compelling reasons for their use.
Potentially serious hypokalaemia may result from β_2 agonist therapy. Particular caution is advised in acute severe asthma as this effect may be potentiated by concomitant treatment with xanthine derivatives, steroids and diuretics.
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 in the liver and high systemic clearance mediated by cytochrome CYP3A4 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 CYP3A4 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 glucocorticoid 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-administration with other potent CYP3A inhibitors, such as itraconazole and medicinal products containing cobicistat and moderate CYP3A inhibitors, such as erythromycin, is also expected to increase the systemic fluticasone propionate exposure and the risk of systemic side effects. Combination should be avoided unless the benefit outweighs the increased risk of systemic undesirable effects of corticosteroids and in that case the patients need to be monitored to detect systemic undesirable effects of corticosteroids.

Salmeterol

Potent CYP3A4 inhibitors

Co-administration of ketoconazole (400 mg orally once daily) and salmeterol (50 micrograms inhaled twice daily) in 15 healthy subjects for 7 days, resulted in a significant increase in salmeterol exposure in plasma (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 (see section 4.4).

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 repeated 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 three times a day) and salmeterol (50 micrograms inhaled twice daily) in 15 healthy subjects for 6 days, resulted in a small but nonstatistically 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.

4.6. Fertility, pregnancy and lactation

Fertility

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

Pregnancy

A large amount of data on pregnant women (more then 1000 pregnancy outcomes) indicates no malformative or feto/neonatal toxicity related to salmeterol and fluticasone. Animal studies have shown reproductive toxicity after administration of beta-2-adrenoreceptor agonists and glucocorticosteroids (see section 5.3).

Administration of RESPIRO in pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus.

The lowest effective dose of fluticasone propionate needed to maintain adequate asthma control should be used in the treatment of pregnant women.

Breastfeeding

It is unknown whether salmeterol and fluticasone propionate/metabolites are excreted in human milk.

Studies have shown that salmeterol and fluticasone propionate, and their metabolites, are excreted into the milk of lactating rats.

A risk to breastfed newborns/infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue RESPIRO therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

4.7. Effects on ability to drive and use machines

RESPIRO suspension for inhalation under pressure has no or negligible influence on the ability to drive and use machines

4.8. Undesirable effects

As medicinal product contains combination of 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 which 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 (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000) and not

known (cannot be estimated from the available data). Frequencies were derived from clinical trial data. The incidence in placebo was not taken into account.

System Organ Class	Adverse events	Frequency
Infections & Infestations	Candidiasis of the mouth and throat	common
	Pneumonia (in COPD patients)	common[1,3]
	Bronchitis	common[1,3]
	Oesophageal candidiasis	rare
Immune System Disorders	Hypersensitivity reactions with the following manifestations:	
	Cutaneous hypersensitivity reactions	uncommon
	Angioedema (mainly facial and oropharyngeal oedema)	rare
	Respiratory symptoms (dyspnoea)	uncommon
	Respiratory symptoms (bronchospasm)	rare
	Anaphylactic reactions including anaphylactic shock	rare
Endocrine Disorders	Cushing's syndrome, Cushingoid features, Adrenal suppression, Growth retardation in children and adolescents, Decreased bone mineral density	rare[4]
Metabolism & Nutrition Disorders	Hypokalaemia	common[3]
	Hyperglycaemia	uncommon[4]
Psychiatric Disorders	Anxiety	uncommon
	Sleep disorders	uncommon
	Behavioural changes, including psychomotor hyperactivity and irritability (predominantly in children)	rare
	Depression, aggression (predominantly in children)	Not known
Nervous System Disorders	Headache	very common[1]
	Chills/tremor	uncommon
Eye Disorders	Cataract	uncommon
	Glaucoma	rare[4]
	Vision, blurred	Not known[4]
Cardiac Disorders	Palpitations	uncommon
	Tachycardia	uncommon
	Cardiac arrhythmias (including supraventricular tachycardia and extrasystoles).	rare
	Atrial fibrillation	uncommon
	Angina pectoris	uncommon
Respiratory, Thoracic & Mediastinal Disorders	Nasopharyngitis	very common[2,3]
	Throat irritation	common
	Hoarseness/dysphonia	common
	Sinusitis	common[1,3]
	Paradoxical bronchospasm	rare[4]

Skin and subcutaneous tissue disorders	Contusions	common[1,3]
Musculoskeletal & Connective Tissue Disorders	Muscle cramps	common
	Traumatic fractures	common[1,3]
	Arthralgia	common
	Myalgia	common

[1] Reported commonly in placebo group of patients
[2] Reported very commonly in placebo group of patients
[3] Reported over 3 years in a COPD study
[4] See section 4.4

Description of selected adverse reactions
The pharmacological side effects of β_2 agonist treatment, such as tremor, palpitations and headache, have been reported, but tend to be transient and reduce with regular therapy.
As with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid-acting bronchodilator and should be treated straightaway. RESPIRO suspension for inhalation under pressure should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

Due to the fluticasone propionate component, hoarseness and candidiasis (thrush) of the mouth and throat and, rarely, of the oesophagus can occur in some patients. Both hoarseness and incidence of mouth and throat candidiasis can be avoided by rinsing the mouth with water and/or brushing the teeth after using the product. Symptomatic mouth and throat candidiasis can be treated with topical anti-fungal therapy whilst still continuing with the RESPIRO suspension for inhalation under pressure.

Paediatric population
Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression and growth retardation in children and adolescents (see section 4.4). Children may also experience anxiety, sleep disorders and behavioural changes, including hyperactivity and irritability.

Reporting suspected AE
Reporting suspected AE for the medicines after obtaining MA is of high relevance for forming more complete picture of safety profile of the product, respectively for making better evaluation of risk-benefit ratio in therapeutic use of product.
Process of reporting suspected AE improves continued monitoring of benefit-risk ratio and adequate evaluation of safety profile of the product. Healthcare professionals are required to report every suspect adverse event for Medicinal Product directly to ALMBIH. Report can be submitted:

- Within software application for reporting AE for Human Medicinal products (IS Farmakovigilansa) of which you can get more information in Main Office for pharmacovigilance in Mostar or
- Via appropriate application form for reporting AE, which can be found at the internet address of Bosnian Agency www.almbih.gov.ba. Filled application form can be submitted to ALMBIH via post, at the address of Bosnian Agency: Veljka Mlađenovica bb, Banja Luka, or via e-mail (e-mail address: ndl@almbih.gov.ba)

4.9. Overdose
There are no data available from clinical trials on overdose with salmeterol/fluticasone propionate, however data on overdose with both drugs are given below:
The signs and symptoms of salmeterol overdose are dizziness, increases in systolic blood pressure, tremor, headache and tachycardia.
If RESPIRO therapy has to be withdrawn due to overdose of salmeterol, provision of appropriate replacement steroid therapy should be considered. Additionally, hypokalaemia can occur and therefore serum potassium levels should be monitored. 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: Adrenal reserve should be monitored and treatment with a systemic corticosteroid may be necessary. When stabilised, treatment should be continued with an inhaled corticosteroid at the recommended dose. Refer to section 4.4: Risk of adrenal suppression.

In cases of both acute and chronic fluticasone propionate overdose RESPIRO therapy should be continued at a suitable dosage for symptom control.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Adrenergics in combination with corticosteroids or other drugs, excluding anticholinergics.
ATC code: R03AK06

Mechanism of action and pharmacodynamic effects:
RESPIRO contains salmeterol and fluticasone propionate which have different 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-agonist with a long side chain which binds to the exo-site of the β_2 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 antiinflammatory effect in the lungs, resulting in reduced symptoms and exacerbations of asthma, with less adverse effects than when corticosteroids are administered systemically.

Clinical efficacy and safety
Salmeterol/fluticasone propionate Asthma clinical trials
A twelve month study GOAL (Gaining Optimal Asthma ControL), 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. Dose was increases every 12 weeks until ***total control* was achieved or the highest dose of study drug was reached. GOAL study showed that total control of asthma was achieved in more patients treated with salmeterol/fluticasone propionate 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 patients in salmeterol/fluticasone propionate group 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 group compared to 23 days in group on treatment with ICS.

The overall study results showed:

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

*Well controlled asthma; less than or equal to 2 days with results of symptoms (symptom score) greater than 1 („symptom score“ 1 defined as ‘symptoms for one short period during the day’), SABA use on less than or equal to 2 days and less than or equal to 4 occasions/week, greater than or equal to 80% predicted morning peak expiratory flow, no night-time awakenings, no exacerbations and no side effects enforcing a change in therapy.
**Total control of asthma; no symptoms, no SABA use, greater than or equal to 80% predicted morning peak expiratory flow, no night-time awakenings, no exacerbations and no side effects enforcing a change in therapy.
A double blind, randomised, 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-2-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-2-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.

Asthma
The Salmeterol Multi-center Asthma Research Trial (SMART)
Multi-Center Salmeterol Asthma Research Trial (SMART) conducted in the United States for 28 weeks evaluating salmeterol safety compared with placebo added to the usual therapy in adults and adolescents. Although there were no significant differences in the primary outcome of the combination of deaths due to respiratory events and the number of life-threatening respiratory events, the study showed a significant increase in asthma-related deaths in patients receiving salmeterol (13 deaths from 13176 patients treated with salmeterol compared to 3 deaths from 13179 patients on placebo). The study was not intended to evaluate concurrent administration of inhaled corticosteroids, and only 47% of examinees used the inhaled corticosteroid at the beginning.

Safety and efficacy of combination salmeterol-FP versus FP monotherapy in asthma
Two 26-week multicenter trials comparing the safety and efficacy of salmeterol-FP combination versus FP alone, one in adults and adolescents (AUSTRI trial), and another in pediatric subjects aged 4-11 (VESTRI trial) were performed.
In both studies, included patients had moderate to severe persistent asthma, who had previously been hospitalized for asthma or had exacerbation of asthma in the previous year.
The primary objective of each study was to determine if the addition of LABA to ICS therapy (salmeterol-FP) was non-inferior compared to the ICS (FP) alone in terms of the risk of occurrence of asthma-related serious events (hospitalization due to asthma, endotracheal intubation and death).
The secondary efficacy goal of these trials was to evaluate whether the combination of ICS/LABA (salmeterol-FP) was superior to ICS (FP) monotherapy with respect to exacerbation of severe asthma (defined as worsening of asthma that requires the use of systemic corticosteroids for at least 3 days or hospitalization of patients or visits to the emergency department due to asthma requiring application of systemic corticosteroids).
Total 11679 and 6208 subjects were randomized and received therapy in AUSTRI or VESTRI trials. For the primary measure outcome of drug safety, noninferiority was achieved in both studies (see table below).

Serious events associated with asthma in the 26th week of AUSTRI and VESTRI trials

	AUSTRI		VESTRI	
	Salmeterol-FP (n = 5834)	FP monotherapy (n = 5845)	Salmeterol-FP (n = 3107)	FP monotherapy (n = 3101)
Summary measure outcome (Hospitalization due to asthma, endotracheal intubation, or death)	34 (0,6%)	33 (0,6%)	27 (0,9%)	21 (0,7%)
Salmeterol-FP/FP	1,029		1,285	

risk ratio (95% CI)	(0,638-1,662)[a]		(0,726-2,272)[b]	
Death	0	0	0	0
Hospitalization due to asthma	34	33	27	21
Endotracheal intubation	0	2	0	0

[a] If the upper confidence interval 95% (CI) estimate for relative risk was less than 2.0; then a non-inferiority is concluded.
[b] If the upper confidence interval 95% (CI) estimate for relative risk was less than 2.675; then a non-inferiority is concluded.
For secondary efficacy outcomes, shortening of time to the first exacerbation of asthma for salmeterol-FP versus FP was observed in both studies, however only in AUSTRI statistical significance was achieved:

	AUSTRI		VESTRI	
	Salmeterol-FP (n = 5834)	FP monotherapy (n = 5845)	Salmeterol-FP (n = 3107)	FP monotherapy (n = 3101)
Number of subjects with asthma exacerbation	480 (8%)	597 (10%)	265 (9%)	309 (10%)
Salmeterol-FP/FP risk ratio (95% CI)	0,787 (0,698, 0,888)		0,859 (0,729, 1,012)	

Data from clinical trials of salmeterol/fluticasone propionate in COPD
Patients with COPD symptoms without restrictions on 10% reversibility on short-acting beta$_2$ -agonists
Placebo controlled studies, within a period of 6 months, showed that regular administration of salmeterol/fluticasone propionate 50/250 mcg rapidly and significantly improves the lung function, significantly reducing the loss of breath and the need for the use of medicinal products for the relief of symptoms. Significant improvement of the overall health status was also noted.

Pediatric population:
In trial SAM101667, in 158 children aged 6 to 16 years with symptomatic asthma, the combination of salmeterol/fluticasone propionate is equally efficacious as doubling the dose of fluticasone propionate regarding symptom control and lung function. This study was not designed to investigate the effect on exacerbations.
Salmeterol/fluticasone propionate Diskus 50/100 (one inhalation twice daily) and Salmeterol/Fluticasone Propionate Inhaler (25/50 microgram two inhalations, twice a day) efficacy of treatment was compared in the 12-week study in children ages 4-11 (n = 428).
The adjusted mean change in relation to the initial value of the mean maximum morning peak expiratory flow for 1-12 weeks was 37.7 l/min in the group of patients using Diskus and 38.6 l/min in the group of patients who received inhaler. In both groups, improvement was observed in the sense of days without using a symptomatic drug and days without day and night symptoms.

The use of medicines containing fluticasone propionate in asthma therapy during pregnancy
It was conducted observational, retrospective, epidemiological study of cohorts by using electronic medical data in the United Kingdom to assess the risk of major congenital malformations (MCM) after exposure to only inhaled fluticasone propionate and a combination of salmeterol-FP versus ICS without fluticasone propionate in the first trimester of pregnancy. No placebo was included as a comparator in this study.
In the cohort with asthma, from 5362 pregnancies exposed to ICS in the first trimester, 131 diagnosed MCM were identified; 1612 (30%) was exposed to fluticasone propionate or a combination of salmeterol-FP of which 42 MCM diagnoses were identified.
The adjusted MCM-like appearance ratio during 1 year was 1.1 (95% CI: 0.5-2.3) for women with moderate asthma exposed to fluticasone propionate versus ICS without fluticasone propionate and 1.2 (95 % CI: 0.7 - 2.0) for women with moderate to severe asthma. There was no difference in MCM risk after exposure to fluticasone propionate versus salmeterol-FP combination in the first trimester of pregnancy. Absolute risk for MCM in all asthma severity ranges was from 2.0 to 2.9 on 100 fluticasone propionate exposed pregnancies, which was comparable to the studies results of the 15840 pregnancy

that were not exposed to asthma treatments in the research database of family medicine (*General Practice Research Database*) (2.8 MCM events per 100 pregnancies).

5.2. Pharmacokinetic 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:

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 picogram/mL or less) achieved after inhalation.

Fluticasone propionate:

The absolute bioavailability of a single dose of inhaled fluticasone propionate in healthy subjects varies between approximately 5 to 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 of fluticasone propionate occurs mainly through the lungs and is initially rapid then prolonged. The remain of the inhaled dose may be swallowed but contributes minimally to systemic exposure due to the low water solubility and presystemic metabolism, resulting in oral availability of less than 1%. There is a linear increase in systemic exposure with increasing inhaled dose.

The disposition of fluticasone propionate is characterised 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 is 91%.

Fluticasone propionate is removed 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 found in the faeces.

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 in faeces as metabolites and unchanged drug.

Pediatric population

Effects of treatment during 21 days with Salmeterol/fluticasone propionate Inhaler 25/50 micrograms (2 inhalations per day with or without auxiliary inhalation chambers) or salmeterol/fluticasone propionate Diskus 50/100 micrograms (1 inhalation twice a day) were evaluated on 31 children aged from 4 to 11 years with moderate asthma. Systemic exposure to fluticasone propionate was similar for salmeterol/fluticasone propionate Inhaler with auxiliary chamber (107 pg hr mL [95% CI: 45.7; 252.2]) and salmeterol/fluticasone propionate Diskus (138 pg h/mL [95% CI : 69.3; 273.2]) but lower than salmeterol/fluticasone propionate Inhaler (24 pg h/mL [95% CI: 9.6, 60.2]). Salmeterol systemic exposure was similar to salmeterol/fluticasone propionate Inhaler, salmeterol/fluticasone propionate Inhaler with inhalation chamber and salmeterol/fluticasone propionate Diskus (126 pg h/mL [95% CI: 70, 225], 103 pg h/mL [95% CI: 54, 200] and 110 pg h/mL [95% CI: 55, 219]).

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 human 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.

Salmeterol xinafoate and fluticasone propionate didn't showed any potential for genetic toxicity.

The non-CFC propellant, norflurane, has not shown any toxic effects applied at very high concentrations on a large number of animal species every day for two years. These concentrations are far greater than those inhaled by the patients.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Norfluran (HFA 134a)

6.2. Incompatibilities

Not applicable

6.3. Shelf life

24 months.

6.4. Special precautions for storage

Keep at room temperature below 25°C, protected from light.
Do not freeze.

6.5. Nature and contents of container

120 doses, concave metallic container with measured vent, aerosol salmeterol/fluticasone 25/50 micrograms with 10.22 g suspension for inhalaration, pressurized.
120 doses, concave metallic container with measured vent, aerosol salmeterol/fluticasone 25/125 micrograms with 10.22 g suspension for inhalaration, pressurized
120 doses, concave metallic container with measured vent, aerosol salmeterol/fluticasone 25/250 micrograms with 10.22 g suspension for inhalaration, pressurized

6.6. Special precautions for disposal and other handling

Any unused material should be disposed according to local disposal regulations.
The container should not be punctured, broken or burnt even when apparently empty.
As with most inhaled medicinal products in pressurised containers, the therapeutic effect of this medicinal product may decrease when the container is cold.

6.7. Dispensing regimen

Medicinal product is given under medicinal prescript.

7. NAME AND ADDRESS OF THE MANUFACTURER (administrative site)

Deva Holding A.Ş.
Halkalı Merkez Mah. Basın Ekpres Cad. No:1
34303 Küçükçekmece/İSTANBUL
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NAME AND ADDRESS OF THE MANUFACTURER (batch release site)

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MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER(S)

RESPIRO 25 mcg-50 mcg	number: 04-07.9-1-1300/14 dtd 23.10.2014.
RESPIRO 25 mcg-125 mcg	number: 04-07.9-1-1301/14 dtd 23.10.2014.
RESPIRO 25 mcg-250 mcg	number: 04-07.9-6204/13 dtd 18.06.2014.