SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

RESPIRO-D 50 mcg/100 mcg Capsules with Inhalation Powder
RESPIRO-D 50 mcg/250 mcg Capsules with Inhalation Powder
RESPIRO-D 50 mcg/500 mcg Capsules with Inhalation Powder

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains:
Active substance:
72.6 mcg salmeterol xinafoate equivalent to 50 mcg salmeterol
and
100 mcg or 250 mcg or 500 mcg fluticasone propionate

Excipient (s):
Each delivered dose contains up to 12.5 mg of lactose (as monohydrate).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules with Inhalation Powder
Transparent capsule containing white to off-white powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Asthma
RESPIRO-D is indicated in the regular treatment of asthma where use of a combination product (long- acting β2 agonist and inhaled corticosteroid) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting β2 agonist

or

- patients already adequately controlled on both inhaled corticosteroid and long-acting β2 agonist

Note: RESPIRO-D 50 mcg/100 mcg strength is not appropriate in adults and children with severe asthma.

Chronic Obstructive Pulmonary Disease (COPD)
RESPIRO-D is indicated for the symptomatic treatment of patients with COPD, with a FEV1 <60% predicted normal (pre-bronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy.

4.2. Posology and method of administration

Posology

Route of administration: Inhalation use.

Patients should be made aware that RESPIRO-D must be used daily for optimum benefit, even when asymptomatic.

Patients should be regularly reassessed by a doctor, so that the strength of RESPIRO-D 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 could include a test of inhaled corticosteroid alone.** As an alternative, patients requiring a long- acting β2 agonist could be titrated to RESPIRO-D 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-D containing the appropriate fluticasone propionate dosage for the severity of their disease. If an individual patient should require dosages outside the recommended regimen, appropriate doses of β2 agonist and/or corticosteroid should be prescribed.

Recommended Doses:

Asthma

Adults and adolescents 12 years and older:
- One inhalation of 50 mcg salmeterol and 100 mcg fluticasone propionate twice daily.
or
- One inhalation of 50 mcg salmeterol and 250 mcg fluticasone propionate twice daily.
or
- One inhalation of 50 mcg salmeterol and 500 mcg fluticasone propionate twice daily.

A short-term trial of RESPIRO-D may be considered as initial maintenance 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 one inhalation of 50 mcg salmeterol and 100 mcg 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 maintenance 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-D is not intended for the initial management of mild asthma. RESPIRO-D 50 mcg/100 mcg 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.

Pediatric population

Children 4 years and older:
- One inhalation of 50 mcg salmeterol and 100 mcg fluticasone propionate twice daily.

The maximum licensed dose of fluticasone propionate delivered by RESPIRO-D in children is 100 mcg twice daily.

There are no data available for use of RESPIRO-D in children aged under 4 years.

COPD

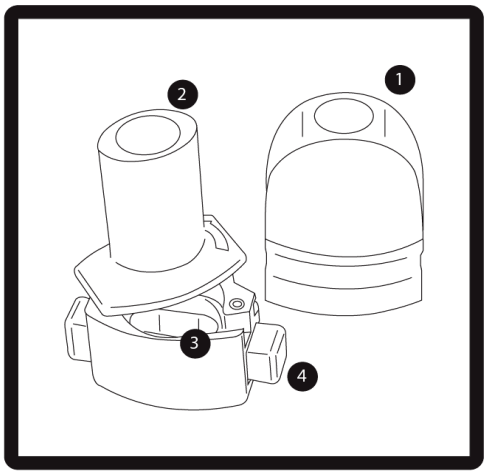
Adults:
- One inhalation of 50 mcg salmeterol and 500 mcg fluticasone propionate twice daily.

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-D in patients with hepatic impairment.

Method of administration:
RESPIRO-D is for inhalation use only.
Inhalation should be made every day, at the same time of day, with the use of the inhalation device.
Capsules are not for oral use.

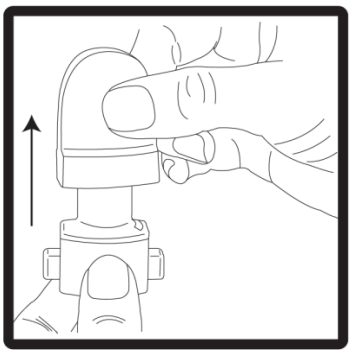
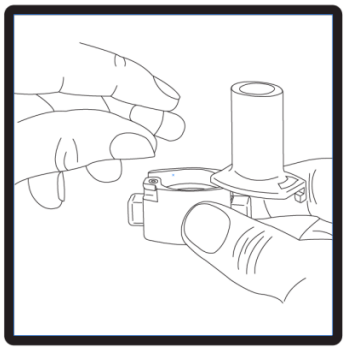
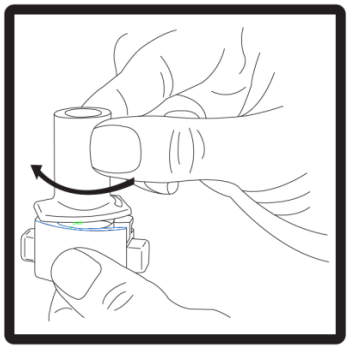
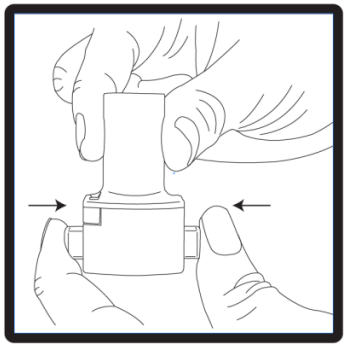
Capsules are not to be swallowed.
Patients should be instructed in the proper use and care of their inhaler and their technique checked to ensure optimum delivery of the inhaled drug to the lungs.

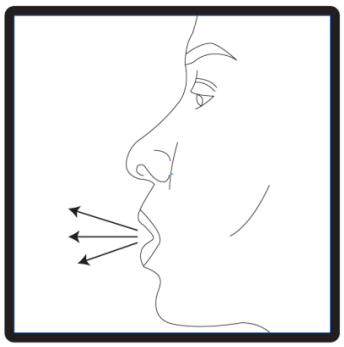
Parts of Inhaler



1. Cover
2. Mouthpiece
3. Capsule compartment
4. Punch button

Instructions for proper use
The inhaler device is a special configured device for the inhalation of RESPIRO-D capsules. It should not be used for any other medicine or purpose.

	1. Pull off the cap.
	2. Open the capsule compartment. Hold the base of the inhaler firmly and turn the mouthpiece in the arrow direction to open.
	3. Make sure your finger is completely dry. Take one capsule out of the blister strip. Place this capsule horizontally in the capsule compartment. It is important that you remove the capsule from the blister pack **only immediately** before you use it. **IMPORTANT: Do not put the capsule into the mouthpiece!**
	4. Close capsule compartment by turning the mouthpiece until you hear the "Click" sound.
	5. To release the powder from capsule: • Hold the device in the upright position with the mouthpiece facing upward. • Pierce the capsule by firmly pressing the two buttons on the edges **at the same time**. Do this **only once**. **Note:** The capsule might splinter at this step and small gelatin fragments might get into your mouth or throat. However, the gelatin is edible and therefore not harmful. Removing the capsule right before use and pressing the sides only once will decrease the splintering risk of the gelatin capsule (see step

	3).
	6. Breathe out fully.
	7. To inhale the medicine deeply into your airways: • Place the mouthpiece in your mouth and tilt your head slightly backwards. • Close your lips firmly around the mouth piece. • Inhale as strongly but steadily and as deeply as you can. **Note:** You should hear a whirring noise as the capsule spins around in the space above the capsule compartment. If you do not hear this whirring noise, open the capsule compartment and check if the capsule is stuck in the capsule compartment. Then, repeat step 7. DO NOT PRESS the buttons repeatedly to release the capsule if it is jammed.
8. After breathing in through the device, hold your breath for as long as you comfortably can and remove the device from your mouth. Then breathe out through your nose. Open the capsule compartment to see if there is any powder left in the capsule. If there is, repeat steps 6 to 8.	
9. After you have used up all the powder, open the capsule compartment (see step 2). Remove the empty capsule.	
10. Use a DRY and clean tissue or a soft brush to remove any powder left inside. Note: **DO NOT USE WATER** to clean the device. First close mouthpiece, then close the cap. Don't expose the capsules to high temperatures.	

RESPIRO-D capsules contain only a small amount of powder and therefore are only partially filled.

4.3. Contraindications

RESPIRO-D is contraindicated in patients with hypersensitivity to any of the active substances or to the excipients (see section 6.1).

4.4. Special warnings and precautions for use

Deterioration of disease

RESPIRO-D 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-D 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-D. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on RESPIRO-D.
Increased requirements for use of reliever medication (short-acting bronchodilators), or decreased response to reliever medication indicate deterioration of 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.
Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of RESPIRO-D. Regular review of patients as treatment is stepped down is important. The lowest effective dose of RESPIRO-D should be used (see section 4.2).
For patients with COPD experiencing exacerbations, treatment with systemic corticosteroids is typically indicated, therefore patients should be instructed to seek medical attention if symptoms deteriorate with RESPIRO-D
Treatment with RESPIRO-D should not be stopped abruptly in patients with asthma due to risk of exacerbation. Therapy should be down-titrated under physician supervision. For patients with COPD cessation of therapy may also be associated with symptomatic decompensation and should be supervised by a physician.
As with all inhaled medication containing corticosteroids, RESPIRO-D should be administered with caution in patients with active or quiescent pulmonary tuberculosis and fungal, viral or other infections of the airway. Appropriate treatment should be promptly instituted, if indicated.

Cardiovascular effects
Rarely, RESPIRO-D may cause cardiac arrhythmias e.g. supraventricular tachycardia, extrasystoles and atrial fibrillation, and a mild transient reduction in serum potassium at high therapeutic doses. RESPIRO-D should be used with caution in patients with severe cardiovascular disorders or heart rhythm abnormalities and in patients with diabetes mellitus, thyrotoxicosis, uncorrected hypokalemia or patients predisposed to low levels of serum potassium.

Hyperglycemia
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.

Paradoxical bronchospasm
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-D should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.
The pharmacological side effects of β2 agonist treatment, such as tremor, palpitations and headache, have been reported, but tend to be transient and reduce with regular therapy.

Excipients
RESPIRO-D contains lactose monohydrate up to 12.5 mg/dose. This amount does not normally cause problems in lactose intolerant people. The excipient lactose contains small amounts of milk proteins, which may cause allergic reactions.

Systemic corticosteroid effects
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 behavioral effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children) (see Pediatric 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 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 cover should be considered during periods of stress or elective surgery.

The benefits of inhaled fluticasone propionate therapy should minimize 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
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 (BMI) and severe COPD.

Interactions with potent CYP3A4 inhibitors
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.

Pediatric Population
Children and adolescents <16 years taking high doses of fluticasone propionate (typically ≥ 1000 mcg/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 behavioral effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression. Consideration should be given to referring the child or adolescent to a pediatric 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 adrenergic blockers may weaken or antagonize the effect of salmeterol. Both non-selective and selective β blockers should be avoided unless there are compelling reasons for their use. Potentially serious hypokalemia 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 β 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 and cobicistat-containing products, and moderate CYP3A inhibitors, such as erythromycin, is also expected to increase the systemic fluticasone propionate exposure and the risk of systemic side effects. Combinations should be avoided unless the benefit outweighs the potential increased risk of systemic corticosteroid side-

effects, in which case patients should be monitored for systemic corticosteroid side-effects.

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 (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 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.

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 than 1000 pregnancy outcomes) indicates no malformative or feto/neonatal toxicity related to RESPIRO-D. Animal studies have shown reproductive toxicity after administration of β2 adrenoreceptor agonists and glucocorticosteroids (see section 5.3).
Administration of RESPIRO-D to 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-D 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 machinery
RESPIRO-D has no or negligible influence on the ability to drive and use machines.

4.8. Undesirable effects
As RESPIRO-D 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 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10.000 and <1/1.000), very rare (<1/10,000), unknown (not established by available data). Frequencies were derived from clinical trial data. The incidence in placebo was not taken into account.

System Organ Class	Adverse Event	Frequency
Infections & Infestations	Candidiasis of the mouth and throat	Common
	Pneumonia (in COPD patients)	Common[1, 3, 5]
	Bronchitis	Common[1, 3]
	Esophageal candidiasis	Rare
Immune System Disorders	Hypersensitivity reactions with the following manifestations:	
	Cutaneous hypersensitivity reactions	Uncommon
	Angioedema (mainly facial and oropharyngeal edema)	Rare
	Respiratory symptoms (dyspnea)	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	Hypokalemia	Common[3]
	Hyperglycemia	Uncommon[4]
Psychiatric Disorders	Anxiety	Uncommon
	Sleep disorders	Uncommon
	Behavioral changes, including psychomotor hyperactivity and irritability (predominantly in children)	Rare
	Depression, aggression (predominantly in children)	Not Known
Nervous System Disorders	Headache	Very Common[1]
	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	Contusions	Common[1, 3]

subcutaneous tissue disorders		
Musculoskeletal & Connective Tissue Disorders	Muscle cramps Traumatic fractures Arthralgia Myalgia	Common Common[1, 3] Common Common

1. Reported commonly in placebo
2. Reported very commonly in placebo
3. Reported over 3 years in a COPD study
4. See section 4.4
5. See section 5.1.

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-D 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 esophagus can occur in some patients. Both hoarseness and incidence of candidiasis may be relieved 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-D.

Pediatric 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 behavioral changes, including hyperactivity and irritability.

Reporting of suspected adverse reactions
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 RESPIRO-D, however data on overdose with both drugs are given below:

Salmeterol
The signs and symptoms of salmeterol overdose are dizziness, increases in systolic blood pressure, tremor, headache and tachycardia.
If RESPIRO-D therapy has to be withdrawn due to overdose of the β agonist component of the drug, provision of appropriate replacement steroid therapy should be considered. Additionally, hypokalemia can occur and therefore serum potassium levels should be monitored. Potassium replacement should be considered.

Fluticasone propionate
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 stabilized, 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-D 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, excl. Anticholinergics.
ATC Code: R03AK06

Mechanism of action and pharmacodynamic effects:
Salmeterol/Fluticasone propionate contains salmeterol and fluticasone propionate which 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) β_2 adrenoceptor agonist with a long side chain which binds to the exo-site of the receptor.
Salmeterol produces a longer duration of bronchodilation, lasting for at least 12 hours, than recommended doses of conventional short-acting β_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.

Clinical efficacy and safety

Salmeterol/Fluticasone propionate Asthma clinical trials
A twelve 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:

Percentage of Patients Attaining *Well Controlled (WC) and **Totally Controlled (TC) Asthma over 12 months				
Pre-Study Treatment	Salmeterol/FP		FP[a]	
	WC	TC	WC	TC
No ICS (Short Acting Beta Agonist –SABA-alone)	78%	50%	70%	40%
Low dose ICS (≤500 microgram BDP[b] or equivalent/day)	75%	44%	60%	28%
Medium dose ICS (>500-1000 microgram BDP[b] 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 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] Fluticasone propionate
[b] Beclomethasone Dipropionate

The results of this study suggest that Salmeterol/Fluticasone propionate 50/100 mcg 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.

Salmeterol/Fluticasone propionate COPD clinical trials
TORCH (TOwards a Revolution in COPD Health) was a 3-year study to assess the effect of treatment with Salmeterol/Fluticasone propionate 50/500 mcg bd, salmeterol 50 mcg bd, fluticasone propionate (FP) 500 mcg bd or placebo on all-cause mortality in patients with COPD. COPD

patients with a baseline (pre-bronchodilator) FEV_1 <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.

	Placebo N=1524	**Salmeterol 50 N=1521**	**FP[1] 500 N = 1534**	**Salmeterol/Fluticasone propionate 50/500 N = 1533**
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 (CIs) p value	N/A	0.879 (0.73, 1.06) 0.180	1.060 (0.89, 1.27) 0.525	0.825 (0.68, 1.00) 0.052[1]
Hazard Ratio Salmeterol/ Fluticasone propionate 50/500 vs components (CIs) p value	N/A	0.932 (0.77, 1.13) 0.481	0.774 (0.64, 0.93) 0.007	N/A
1. Non-significant P value after adjustment for 2 interim analyses on the primary efficacy comparison from a log-rank analysis stratified by smoking status				

[1] Fluticasone propionate

There was a trend towards improved survival in subjects treated with Salmeterol/Fluticasone propionate compared with placebo over 3 years however this did not achieve the statistical significance level.

The percentage of patients who died within 3 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.

The mean number of moderate to severe exacerbations per year was significantly reduced with Salmeterol/Fluticasone propionate as compared with treatment with salmeterol, FP and placebo (mean rate in the Salmeterol/Fluticasone propionate group 0.85 compared with 0.97 in the salmeterol group, 0.93 in the FP group and 1.13 in the placebo). This translates to a reduction in the rate of moderate to severe exacerbations of 25% (95% CI: 19% to 31%; p<0.001) compared with placebo, 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). A 4-unit decrease is considered clinically relevant.

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/Fluticasone propionate (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.

Placebo-controlled clinical trials, over 6 and 12 months, have shown that regular use of Salmeterol/Fluticasone propionate 50/500 mcg improves lung function and reduces breathlessness and the use of relief medication.

Studies SCO40043 and SCO100250 were randomized, double blind, parallel group, replicate studies comparing the effect of Salmeterol/Fluticasone propionate 50/250 mcg bd (a dose not licensed for COPD treatment in the European Union) with salmeterol 50 mcg bd on the annual rate of moderate/severe exacerbations in subjects with COPD with FEV_1 less than 50% predicted and a history of exacerbations. Moderate/ severe exacerbations were defined as worsening symptoms that required treatment with oral corticosteroids and/or antibiotics or in-patient hospitalization.

The trials had a 4 week run-in period during which all subjects received open-label salmeterol/ FP 50/250 to standardize COPD pharmacotherapy and stabilize disease prior to randomization to blinded study medication for 52 weeks. Subjects were randomized 1:1 to salmeterol/ FP 50/250 (total ITT n=776) or salmeterol (total ITT n=778). Prior to run-in, subjects discontinued use of previous COPD medications except short-acting bronchodilators. The use of concurrent inhaled long-acting bronchodilators (β_2 agonist and anticholinergic), ipratropium/salbutamol combination products, oral β_2 agonists, and theophylline preparations were not allowed during the treatment period. Oral corticosteroids and antibiotics were allowed for the acute treatment of COPD exacerbations with specific guidelines for use. Subjects used salbutamol on an as-needed basis throughout the studies.

The results of both studies showed that treatment with Salmeterol/Fluticasone propionate 50/250 resulted in a significantly lower annual rate of moderate/severe COPD exacerbations compared with salmeterol (SCO40043: 1.06 and 1.53 per subject per year, respectively, rate ratio of 0.70, 95% CI: 0.58 to 0.83, p<0.001; SCO100250: 1.10 and 1.59 per subject per year, respectively, rate ratio of 0.70, 95% CI: 0.58 to 0.83, p<0.001). Findings for the secondary efficacy measures (time to first moderate/severe exacerbation, the annual rate of exacerbations requiring oral corticosteroids, and pre-dose morning (AM) FEV_1) significantly favored Salmeterol/Fluticasone propionate 50/250 mcg bd over salmeterol. Adverse event profiles were similar with the exception of a higher incidence of pneumonias and known local side effects (candidiasis and dysphonia) in the Salmeterol/Fluticasone propionate 50/250 mcg bd group compared with salmeterol. Pneumonia-related events were reported for 55 (7%) subjects in the Salmeterol/Fluticasone propionate 50/250 mcg bd group and 25 (3%) in the salmeterol group. The increased incidence of reported pneumonia with Salmeterol/Fluticasone propionate 50/250 mcg bd appears to be of similar magnitude to the incidence reported following treatment with Salmeterol/Fluticasone propionate 50/500 mcg bd in TORCH.

Asthma

The Salmeterol Multi-center Asthma Research Trial (SMART)

The Salmeterol Multi-center Asthma Research Trial (SMART) was a 28-week US study that evaluated the safety of salmeterol compared to placebo added to usual therapy in adult and adolescent subjects. Although there were no significant differences in the primary endpoint of the

combined number of respiratory-related deaths and respiratory-related life-threatening experiences, the study showed a significant increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated with salmeterol versus 3 deaths out of 13,179 patients on placebo). The study was not designed to assess the impact of concurrent inhaled corticosteroid use, and only 47% of subjects reported ICS use at baseline.

Safety and efficacy of salmeterol-FP versus FP alone in asthma

Two multi-centre 26-week studies were conducted to compare the safety and efficacy of salmeterol-FP versus FP alone, one in adult and adolescent subjects (AUSTRI trial), and the other in paediatric subjects 4-11 years of age (VESTRI trial). For both studies, enrolled subjects had moderate to severe persistent asthma with history of asthma-related hospitalization or asthma exacerbation in the previous year. The primary objective of each study was to determine whether the addition of LABA to ICS therapy (salmeterol-FP) was non-inferior to ICS (FP) alone in terms of the risk of serious asthma related events (asthma-related hospitalization, endotracheal intubation, and death). A secondary efficacy objective of these studies was to evaluate whether ICS/LABA (salmeterol-FP) was superior to ICS therapy alone (FP) in terms of severe asthma exacerbation (defined as deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroids).

A total of 11,679 and 6,208 subjects were randomized and received treatment in the AUSTRI and VESTRI trials, respectively. For the primary safety endpoint, non-inferiority was achieved for both trials (see Table below).

Serious Asthma-Related Events in the 26-Week AUSTRI and VESTRI Trials

	AUSTRI		VESTRI	
	Salmeterol-FP (n = 5,834)	FP Alone (n = 5,845)	Salmeterol-FP (n = 3,107)	FP Alone (n = 3,101)
Composite endpoint (Asthma-related hospitalization, endotracheal intubation, or death)	34 (0.6%)	33 (0.6%)	27 (0.9%)	21 (0.7%)
Salmeterol-FP/FP Hazard ratio (95% CI)	1.029 (0.638-1.662)[a]		1.285 (0.726-2.272)[b]	
Death	0	0	0	0
Asthma-related hospitalization	34	33	27	21
Endotracheal intubation	0	2	0	0

[a] If the resulting upper 95% CI estimate for the relative risk was less than 2.0, then non-inferiority was concluded.

[b] If the resulting upper 95% CI estimate for the relative risk was less than 2.675, then non-inferiority was concluded.

For the secondary efficacy endpoint, reduction in time to first asthma exacerbation for salmeterol-FP relative to FP was seen in both studies, however only AUSTRI met statistical significance:

	AUSTRI		VESTRI	
	Salmeterol-FP (n = 5,834)	FP Alone (n = 5,845)	Salmeterol-FP (n = 3,107)	FP Alone (n = 3,101)
Number of subjects with an asthma exacerbation	480 (8%)	597 (10%)	265 (9%)	309 (10%)
Salmeterol-FP/FP Hazard ratio (95% CI)	0.787 (0.698, 0.888)		0.859 (0.729, 1.012)	

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 to doubling the dose of fluticasone propionate regarding symptom control and lung function. This study was not designed to investigate the effect on exacerbations.
In a 12 week trial of children aged 4 to 11 years [n=257] treated with either salmeterol/fluticasone propionate 50/100 or salmeterol 50 mcg + fluticasone propionate 100 mcg both twice daily, both treatment arms experienced a 14% increase in peak expiratory flow rate as well as improvements in symptom score and rescue salbutamol use. There were no differences between the 2 treatment arms. There were no differences in safety parameters between the 2 treatment arms.
In a 12 week trial of children 4 to 11 years of age [n=203] randomized in a parallel-group study with persistent asthma and who were symptomatic on inhaled corticosteroid, safety was the primary objective. Children received either salmeterol/fluticasone propionate (50/100 mcg) or fluticasone propionate (100 mcg) alone twice daily. Two children on salmeterol/fluticasone propionate and 5 children on fluticasone propionate withdrew because of worsening asthma. After 12 weeks no children in either treatment arm had abnormally low 24 hour urinary cortisol excretion. There were no other differences in safety profile between the treatment arms.

Fluticasone propionate containing medications in asthma during pregnancy
An observational retrospective epidemiological cohort study utilizing electronic health records from the United Kingdom was conducted to evaluate the risk of MCMs following first trimester exposure to inhaled FP alone and salmeterol-FP relative to non-FP containing ICS. No placebo comparator was included in this study.
Within the asthma cohort of 5362 first trimester ICS-exposed pregnancies, 131 diagnosed MCMs were identified; 1612 (30%) were exposed to FP or salmeterol-FP of which 42 diagnosed MCMs were identified. The adjusted odds ratio for MCMs diagnosed by 1 year was 1.1 (95%CI: 0.5 – 2.3) for FP exposed vs non-FP ICS exposed women with moderate asthma and 1.2 (95%CI: 0.7 – 2.0) for women with considerable to severe asthma. No difference in the risk of MCMs was identified following first trimester exposure to FP alone versus salmeterol-FP. Absolute risks of MCM across the asthma severity strata ranged from 2.0 to 2.9 per 100 FP-exposed pregnancies which is comparable to results from a study of 15,840 pregnancies unexposed to asthma therapies in the General Practice Research Database (2.8 MCM events per 100 pregnancies).

5.2. Pharmacokinetic properties

For pharmacokinetic purposes 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 picograms/ml or less) achieved after inhaled dosing.

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 or COPD 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 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 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 is 91%.
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 found in the feces.
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 feces as metabolites and unchanged drug.

Pediatric population:
In a population pharmacokinetic analysis utilizing data from 9 controlled clinical trials with different devices (dry powder metered dose inhaler) that included 350 patients with asthma aged 4 to 77 years (174 patients 4 to 11 years of age) higher fluticasone propionate systemic exposure following treatment with Salmeterol/Fluticasone propionate dry powder inhaler 50/100 compared to fluticasone propionate dry powder inhaler 100 were seen.
Geometric Mean Ratio [90% CI] for the Salmeterol/fluticasone propionate vs. fluticasone propionate dry powder Inhaler Comparison in Children and Adolescent/Adult Populations

Treatment (test vs. ref)	***Population***	***AUC***	***C_{max}***
Salmeterol+fluticasone propionate 50/100 Fluticasone propionate (100) dry powder Inhaler	Children (4–11 yr)	1.20 [1.06 – 1.37]	1.25 [1.11 – 1.41]
Salmeterol/+fluticasone propionate 50/100 Fluticasone propionate (100) dry powder Inhaler	Adolescent/Adult (≥12 yr)	1.52 [1.08 – 2.13]	1.52 [1.08 – 2.16]

The effect of 21 days of treatment with Salmeterol/Fluticasone propionate Inhaler 25/50 mcg (2 inhalations twice daily with or without a spacer) or Salmeterol/Fluticasone propionate dry powder Inhaler 50/100 mcg (1 inhalation twice daily) was evaluated in 31 children aged 4 to 11 years with mild asthma. Systemic exposure to salmeterol was similar for Salmeterol/ Fluticasone propionate Inhaler, Salmeterol/Fluticasone propionate Inhaler with spacer, and Salmeterol/Fluticasone propionate dry powder Inhaler (126 pg hr/ml [95% CI: 70, 225], 103 pg hr/ml [95% CI: 54, 200], and 110 pg hr/ml [95% CI: 55, 219], respectively). Systemic exposure to fluticasone propionate was similar for Salmeterol/Fluticasone propionate Inhaler with spacer (107 pg hr/ml [95% CI: 45.7, 252.2]) and Salmeterol/Fluticasone propionate dry powder Inhaler (138 pg hr/ml [95% CI: 69.3, 273.2]), but lower for Salmeterol/Fluticasone propionate Inhaler (24 pg hr/ml [95% CI: 9.6, 60.2]).

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. Neither salmeterol

xinafoate or fluticasone propionate have shown any potential for genetic toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate (Inhalac 230) (which contains milk proteins)
Lactose monohydrate (Inhalac 400) (which contains milk proteins)
Capsule no:3
Hypromellose

6.2. Incompatibilities
NA.

6.3 Shelf life
24 months

6.4 Special precautions for storage
Keep at room temperature below 25°C and protect from moisture.

6.5 Nature and contents of container
RESPIRO-D is packed into OPA-Alu-PVC and Aluminum foil blister. Blisters are supplied in carton boxes with monodose dry powder inhaler and package leaflet.
Each box contains 60 capsules and 1 device (monodose dry powder inhaler).

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

7. NAME AND ADDRESS OF THE MANUFACTURER (administrative site)
DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece – ISTANBUL
TURKEY

MANUFACTURER OF THE FINISHED PRODUCT (Batch Release Site)
DEVA Holding A.Ş.
Çerkezköy Organize Sanayi Bölgesi,
Karaağaç Mah.Atatürk Cad. No: 32
Kapakli /TEKIRDAG
TURKEY

NAME AND ADDRESS OF MARKETING AUTHORIZATION HOLDER
Unifarm d.o.o.
Novo Naselje Bistarac bb
75300 Lukavac
Bosna i Hercegovina

8. MARKETING AUTHORIZATION NUMBER

9. DATE OF REVISION OF SUMMARY OF PRODUCT CHARACTERISTICS
23.03.2020