SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
ROLASTYM COMBI 12 mcg / 400 mcg Capsules with Inhalation Powder

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains:
Active substance:
Formoterol fumarate_____12 microgram (mcg)
Budesonide_____400 microgram (mcg)
Excipient(s) with known effect:
For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Capsule with inhalation powder
Transparent capsule containing white powder

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
It is indicated for the treatment and control of asthma symptoms. It is given from the 3rd step in stepwise management of asthma.

It reduces symptoms and frequency of attacks in moderate and severe COPD cases.

4.2 Posology and method of administration
Posology/frequency and duration of administration

Asthma

ROLASTYM COMBI should not be used to alleviate the acute symptoms of asthma attacks.

In the case of an acute attack, a short-acting β2-agonist should be used (see section 4.4)

Adults:
FORMOTEROL
Formoterol dose should be individualized to the patient's needs and should be at the lowest possible dose to fulfill the therapeutic objective. It should not be increased beyond the maximum recommended dose (see section 4.2).

For regular maintenance therapy, it is recommended to use 1 inhaler capsule twice daily (equivalent to 12 mcg formoterol). The maximum recommended maintenance dose is 48 mcg per day. In more severe cases, 2 inhaler capsules are given twice a day.

If required, an additional 1 to 2 capsules per day may be used for the relief of ordinary symptoms provided the recommended maximum daily dose of 48 mcg per day is not exceeded. However, if the need for additional doses is more than occasional (e.g. more frequent than 2 days per week) medical advice should be sought and therapy reassessed, as this may indicate a worsening of the underlying condition.

BUDESONIDE
The lowest dosage in a single capsule is 200 mcg. If a single dose of less than 200 mcg is required, this product cannot be used.

Treatment of adults with mild asthma may be initiated at the minimum effective dosage of 200 mcg once daily. The usual maintenance dosage is 200 to 400 mcg (1-2 capsules) twice daily (equivalent to 400-800 mcg budesonide per day).

The dosage may be increased up to 1.600 mcg daily in 2 to 4 doses during asthma exacerbations, when transferring the patient from oral corticosteroid therapy to budesonide inhalation therapy, or when reducing the dose of oral corticosteroid therapy.

The dosage should be adjusted individually to the lowest dose required for maintenance therapy. Budesonide should be taken regularly every day. The dose should be retitrated individually when transferring a patient from one inhalation device to another.

Children (aged 6 years and over)
FORMOTEROL
For regular maintenance therapy, 1 inhalation capsule (12 mcg) twice daily, in the morning and in the evening.

Formoterol should only be prescribed as an add-on to an inhaled corticosteroid. (e.g. budesonide).

BUDESONIDE
Due to the absence of clinical experience in children under 6 years of age, Budesonide should not be used in this age group.

Treatment of children with mild asthma may be initiated at 200 mcg once daily. The usual maintenance dosage is 200 mcg twice daily (equivalent to 400 mcg daily). The maximum daily dose is 800 mcg. Budesonide should be used under the supervision of adults. The use of the Inhaler should depend on the ability of the child to use the inhaler correctly.

Chronic obstructive pulmonary disease (COPD)
Adults:
FORMOTEROL
For regular maintenance therapy, 1 inhaler capsule twice daily (12 mcg).

The maximum daily dose is 48 mcg.

BUDESONIDE
Normal maintenance dose is 200-400 mcg budesonide twice daily (equivalent to 400-800 mcg budesonide daily).

The dosage may be increased up to 1,600 mcg daily in 2 to 4 doses during asthma exacerbations, when transferring the patient from oral corticosteroid therapy to budesonide inhalation therapy, or when reducing the dose of oral corticosteroid therapy.

The dosage should be adjusted individually to the lowest dose required for maintenance therapy. Budesonide should be taken regularly every day. The dose should be retitrated individually when transferring a patient from one inhalation device to another.

Method of administration
ROLASTYM COMBI capsules should only be used with their own device and by oral inhalation.

In order to reduce the risk of candida infection it is recommended to rinse the mouth well with water and subsequently spit out the rinsing water after each administration of ROLASTYM COMBI (see section 4.4 and Section 4.8). In addition, rinsing the mouth with water may possibly help to prevent throat irritation and reduce the risk of systemic effects.

To ensure proper administration of the drug, a physician or other health professional should:

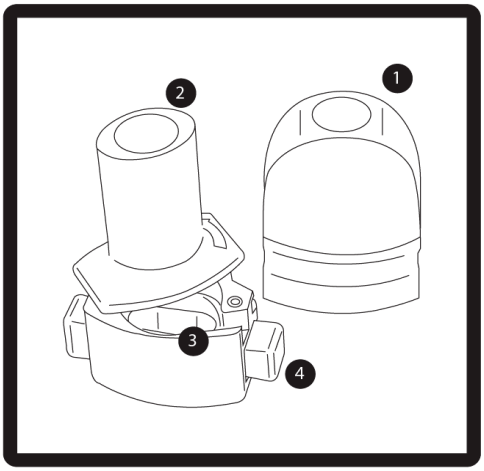
- Teach and show to the patients how to use the device in accordance with the package leaflet.
- Instruct patients that the capsules are only for inhalation and not swallowed (see section 4.4).

Detailed administration instructions are included in the package leaflet.

It is important for the patient to know that the gelatin capsule might fragment and small pieces of gelatin might reach the mouth or throat after inhalation. Patient should be informed that the gelatin is harmless, will get soft in the mouth, and can be swallowed. This can be minimized by not piercing the capsule more than once. Since the capsule is made from edible gelatin, digestion is not harmful.

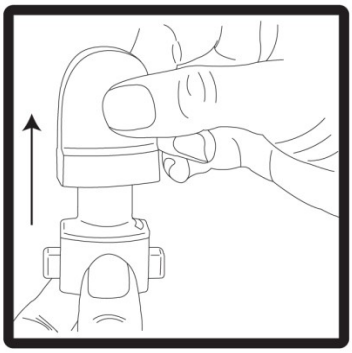
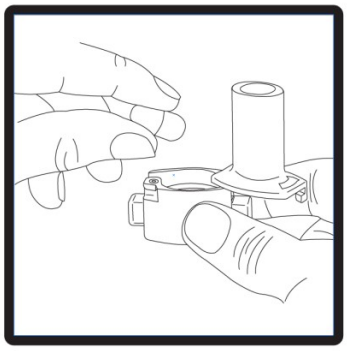
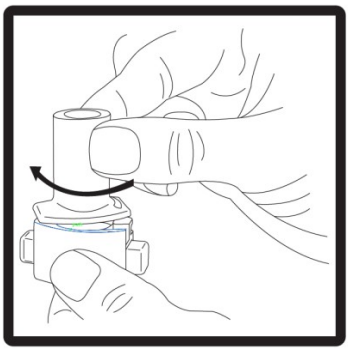
The capsules should be removed from the blister pack **only immediately** before use.

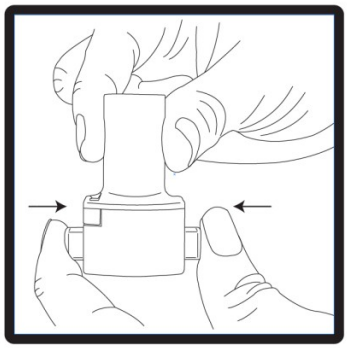
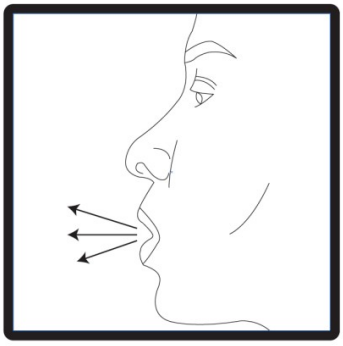
Parts of the Inhaler



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

Instructions for proper use

	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.
	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 mouthpiece. • 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 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.	

In order to reduce the risk of candida infection it is recommended to rinse the mouth well with water and subsequently spit out the rinsing water after each administration of ROLASTYM COMBI (see section 4.4 and Section 4.8).

Additional information on special populations

Renal/Hepatic impairment

There are no clinical studies in patients with renal impairment. Based on pharmacokinetic data with oral budesonide, it is unlikely that systemic exposure will be altered to clinically significant levels in such patients

There is no data, which indicates dose adjustment in patients with hepatic impairment. However, since budesonide is predominantly cleared by hepatic metabolism, caution should be exercised when using budesonide in patients with severe hepatic impairment. Based on pharmacokinetic data with oral budesonide, patients with mild to moderate hepatic impairment are unlikely to have clinically significant alteration in drug exposure.

No clinical studies have been done with the use of formoterol in patients with hepatic or renal impairment. In addition, there is no theoretical reason for Formoterol dosage adjustment in patients with hepatic or renal impairment.

Pediatric population

Children up to the age of 6 years should not be treated with Formoterol.

Due to the absence of clinical experience in children under 6 years of age, Budesonide should not be used in this age group.

Geriatric population

The available data from clinical trials performed in patients 65 years and older do not suggest that the dosage should be different from the dosage for other adults.

4.3 Contraindications

- Known hypersensitivity to formoterol, budesonide or any of its excipients.
- Patients with active pulmonary tuberculosis.

4.4 Special warnings and precautions for use

The risk of pneumonia is increased in elderly patients using combined inhaled steroids. There is insufficient clinical evidence regarding the advantage of high dose use in COPD.

Formoterol and budesonide should only be used in combination in asthmatic patients and according to the recommendation of the physician. The use of only one drug may be insufficient and ineffective for treatment.

Formoterol should not be used alone as monotherapy in asthmatic patients.

Formoterol, the active ingredient of ROLASTYM COMBI, belongs to the class of long-acting β2-adrenergic agonists (LABAs). In a study with salmeterol, a different long-acting β2-agonist, a higher rate of death due to asthma was observed in the patients treated with salmeterol (13/13,176) than in the placebo group (3/13,179). No study adequate to determine whether the rate of asthma-related death is increased with Formoterol has been conducted. Rarely, serious and sometimes fatal asthma related breathing problems might occur with the use of long-acting β-agonists.

Formoterol should not be used in conjunction with another long-acting β2-agonist (LABA).

Formoterol should not be used as the first treatment for asthma. ROLASTYM COMBI is not recommended as the initial treatment of mild asthma.

Long-acting β-agonists should be used for the shortest duration of time required to achieve control of asthma symptoms and discontinued, if possible, once asthma control is achieved. Patients should then be maintained on an asthma controller medication.

When treating patients with asthma, use Formoterol only as an add-on to an inhaled corticosteroid (ICS) for patients who are not adequately controlled on an ICS alone or whose disease severity clearly warrants initiation of treatment with both an ICS and a LABA.

For children of 5-12 years of age, treatment with a combination product containing an ICS and LABA is recommended; except in case where a separate ICS and LABA are required (see section 4.2 and 4.8). Pediatric and adolescent patients who require a LABA in addition to an inhaled corticosteroid should use a combination product containing both an inhaled corticosteroid and a LABA to ensure compliance with both medications.

When formoterol is prescribed, patients should be evaluated for the adequacy of the anti-inflammatory therapy they receive. Patients must be advised to continue taking anti-inflammatory therapy unchanged after the introduction of formoterol, even when their symptoms improve.

Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of formoterol. Regular monitoring of patients as treatment is stepped down is important. The lowest effective dose of formoterol should be used.

Anti-inflammatory treatment:
Patients should be made aware of the prophylactic nature of therapy with inhaled budesonide, and that it should be taken regularly even when they are asymptomatic.

Systemic effects:
Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include adrenal suppression, hyperadrenocorticism/Cushing's syndrome, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma, hypersensitivity reactions, and more rarely, a range of psychological or behavioral effects including psychomotor hyperactivity, sleep disorders, anxiety, depression, and aggression (particularly in children). Therefore, it is important that the dose of inhaled corticosteroid be titrated to the lowest dose at which effective control of asthma is maintained (see section 4.8).

Asthma exacerbations:
Clinical studies with formoterol suggested a higher incidence of serious asthma exacerbations in patients who received formoterol than in those who received placebo; particularly in patients 5-12 years of age (see section 4.8). These studies do not allow precise quantification of the differences in serious asthma exacerbation rates between treatment groups.

A physician should reassess asthma therapy if symptoms persist, or if the number of doses of formoterol required controlling symptoms increase, because this usually indicates a worsening of the underlying condition.

Patients should be advised to contact their doctor if their asthma deteriorates (increased frequency of short-acting inhaled bronchodilator treatment or persistent respiratory symptoms). The patient should be reassessed and the need for increased anti-inflammatory therapy, an increase in the dose of inhaled or oral corticosteroid, and/or additional treatment with antibiotics may be required if there is an infection.

Budesonide does not relieve acute bronchospasm, neither is it appropriate for the primary treatment of status asthmaticus or other acute asthmatic episodes.

Formoterol therapy must not be initiated nor the dose increased during an asthma exacerbation. Patients should not be initiated with long acting β-agonists during their exacerbation period, or if they have significantly worsening or acutely deteriorating asthma complaints.

Formoterol should not be used to relieve acute asthma symptoms. A short-acting β2-agonist should be used in acute attacks. Patients should be informed of getting medical treatment in case their asthma suddenly deteriorates.

Patients should always keep a short-acting inhaled bronchodilator available as rescue medication to alleviate acute asthma symptoms.

Concomitant conditions:
Special care and supervision, with particular emphasis on dosage limits, is required when formoterol is given in patients with the following conditions: Ischemic heart disease, cardiac arrhythmias (especially third-degree atrioventricular block), severe cardiac decompensation, idiopathic subvalvular aortic stenosis, severe hypertension, aneurysm, phaeocheomocytoma, hypertrophic obstructive cardiomyopathy, thyrotoxicosis, known or suspected prolongation of the QT interval (QTc >0.44 sec.; see section 4.5).

Caution should be exercised when co-administering theophylline and formoterol in patients with pre-existing cardiac conditions.

Due to the hyperglycemic effect of β2-stimulants, including formoterol, additional blood glucose monitoring is recommended in diabetic patients.

Special care is needed in patients with quiescent pulmonary tuberculosis, or fungal and viral airway infections.

Caution is necessary in treating patients with pulmonary disorders such as bronchiectasis and pneumoconiosis in view of the possibility of fungal infections.

Caution should be exercised if theophylline and formoterol are used simultaneously in patients with previously known heart problems.

Hypokalemia:
Potentially serious hypokalemia may result from β2-agonist therapy, including formoterol. Hypokalemia may increase susceptibility to cardiac arrhythmias. Particular caution is advised in severe asthma patients as this effect may be potentiated by concomitant treatment in hypoxia (see section 4.5). Serum potassium levels should be monitored in this condition.

Paradoxical bronchospasm:
As with other inhalation therapies, the potential for paradoxical bronchospasm should be kept in mind. If it occurs, ROLASTYM COMBI therapy should be discontinued immediately and alternative therapy should be started.

Effect on growth:
Data from long-term studies suggest that most children and adolescents treated with inhaled budesonide will ultimately achieve their adult target height.

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids be regularly monitored. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of inhaled corticosteroid, if possible, to the lowest dose at which effective control of asthma is maintained. In addition, consideration should be given to referring the patient to a pediatric respiratory specialist. The long-term effects of this reduction in growth velocity associated with inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for “catch-up” growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied.

Concomitant treatments:
Caution is advised in long-term concomitant administration of budesonide and a potent CYP3A4 inhibitor (e.g. itraconazole, ketoconazole, ritonavir, nelfinavir, amiodarone, clarithromycin) (see section 4.5).

Patients starting treatment with steroids:
A therapeutic effect is usually reached within 10 days. In patients with excessive mucus secretion in the bronchi, a short (about 2-week) additional oral corticosteroid regimen can be given initially.

Steroid-dependent patients:
When transfer from oral steroids to budesonide is started, the patient should be in a relatively stable phase. A high dose of budesonide is given in combination with the previously used oral steroid for about 10 days. The oral dose should then be gradually reduced (for example, by 2.5 mg prednisolone or the equivalent each month) to the lowest possible level. Treatment with supplementary systemic steroids or Budesonide should not be stopped abruptly but should take place slowly.

Particular caution is to be observed during the first months of switching from systemic corticosteroids to budesonide, to ensure that the patient's adrenocortical reserve is adequate to counter specific crisis situations, such as trauma, surgery, or severe infections. HPA (hypothalamic-pituitary-adrenal) axis function should be monitored regularly. Some patients need an extra supply of corticosteroids under these circumstances; they are advised to carry a warning card with them drawing attention to their potentially serious condition. Substitution of systemic corticosteroids by budesonide may reveal allergies previously suppressed by the systemic corticosteroids, such as allergic rhinitis or eczema, and patients may be troubled with lethargy, muscle or joint pain, and sometimes nausea and vomiting. Such allergies should be properly treated with locally applied antihistamines or corticosteroids.

Additional precautions:
To prevent oral candidiasis, patients should be advised to rinse the mouth with water after each administration of ROLASTYM COMBI. If this condition develops, it will respond in most cases to topical antifungal therapy without discontinuing treatment with budesonide therapy (see sections 4.2 and 4.8).

Dysphonia may occur but readily reverses after discontinuing treatment, reducing the dose, and/or resting the voice (see section 4.8).

Incorrect administration method:
There are reports of patients who accidentally swallowed the ROLASTYM COMBI capsules instead of placing the capsules in the inhalation device. The majority of these ingestions were not associated with side effects. Healthcare providers should instruct the patient on the correct use of ROLASTYM COMBI device (see section 4.2). If a patient who is prescribed ROLASTYM COMBI does not experience breathing improvement, the healthcare provider should ask how the patient is using the ROLASTYM COMBI device.

4.5 Interactions with other medicinal products and other forms of interaction
Interactions resulting from non-recommended concomitant use
Interactions affecting formoterol use:
β-adrenergic blockers may weaken or antagonize the effect of formoterol. Therefore ROLASTYM COMBI should not be given together with β-adrenergic blockers (including eye drops) unless absolutely necessary.

Possible interactions to be considered

Interactions affecting formoterol use:

Formoterol, like other β2-agonists, should be used with caution in patients being treated with drugs such as quinidine, disopyramide, procainamide, phenothiazines, antihistaminics, macrolides, monoamine oxidase inhibitors and tricyclic antidepressants or any drug known to prolong the QTc interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc-interval have an increased risk of ventricular arrhythmia (see section 4.4).

Concomitant administration of other sympathomimetic agents may potentiate the adverse effects of formoterol. Atomoxetine may increase the tachycardic effects of formoterol.

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate a possible hypokalemic effect of β2-agonists (see section 4.4).

There is an elevated risk of arrhythmia in patients receiving concomitant anesthesia with halogenated hydrocarbons.

Formoterol may diminish the bradycardic effect of β-blockers (β1-selective).

The bronchodilating effects of formoterol can be enhanced by anticholinergic drugs.

Interactions affecting budesonide use:

The main route of metabolism of budesonide is via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4). Concomitant administration of known CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, ritonavir, nelfinavir, amiodarone, clarithromycin) are known to inhibit the metabolism of budesonide and hence increases systemic exposure. If these products are administered together, adrenocortical function should be monitored and the dose of budesonide adjusted according to the response (see section 4.4 and Section 5.2).

Concomitant administration of strong inducers of CYP3A4 (e.g. rifampicin) may increase the metabolism of budesonide and hence decrease systemic exposure (see section 5.2).

Additional information on special populations

No interaction study has been conducted specific to special populations.

Pediatric population

No interaction study has been conducted specific to pediatric population.

4.6 Fertility, pregnancy and lactation

General principles

Pregnancy category “C”.

Women of childbearing potential/Contraception

There is no special requirement for women with childbearing potential in formoterol treatment. If pregnancy is determined, benefit/risk ratio of continued formoterol therapy against alternative therapies should be evaluated.

There is no specific advice in budesonide treatment for women with childbearing potential.

Pregnancy
There are no adequate data from the use of ROLASTYM COMBI in pregnant women. Studies on animals have shown that reproductive toxicity exists (see section 5.3). The potential risk for humans is unknown. Its use during pregnancy should be avoided unless there is no alternative.

If treatment with glucocorticosteroids during pregnancy is unavoidable, inhaled glucocorticosteroids should be preferred because of their lower systemic effect compared with equipotent anti-asthmatic doses of oral glucocorticosteroids.

Like other β2-adrenergic stimulants, formoterol may inhibit labor due to a relaxant effect on uterine smooth muscle.

Breastfeeding
Formoterol has been detected in the milk of lactating rats. Plasma concentrations achieved in infants would be expected to reach around 1/600 of the concentrations in maternal plasma (see section 5). Mothers who use ROLASTYM COMBI should not breastfeed.

Fertility
There is no data on the effect of formoterol on human fertility. Studies on male and female rats show no deterioration in fertility. There is an adverse effect on fertility in budesonide in rats with subcutaneous administration.

There is no evidence that budesonide shows any teratogenicity or reproductive toxicity in humans (see section 5.3)

4.7. Effects on ability to drive and use machines
Patients with dizziness or other similar side effects should be advised not to drive or use machines.

4.8. Undesirable effects

FORMOTEROL

Adverse reactions are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), unknown (it cannot be estimated from the available data).

Immune system disorders
Very rare: Hypersensitivity (including hypotension, urticaria, angioedema, pruritus, rash))

Psychiatric disorders
Uncommon: Agitation, anxiety, nervousness, restlessness, sleep disturbances

Nervous system disorders
Common: Headache, tremor
Uncommon: Dizziness
Very rare: Dysgeusia

Cardiac disorders
Common: Palpitations
Uncommon: Tachycardia
Very rare: Peripheral edema

Respiratory, thoracic and mediastinal disorders
Uncommon: Bronchospasm, including paradoxical bronchospasm, throat irritation, exacerbation of acute asthma.

Gastrointestinal disorders
Uncommon: Dry mouth
Very rare: Nausea

Musculoskeletal disorders, connective tissue and bone disorders
Uncommon: Muscle cramps, myalgia

BUDESONIDE
Adverse drug reactions are listed according to system organ classes in MedDRA. Adverse drug reactions are listed as the most common adverse reaction, according to their frequency, to be first. In each frequency group, adverse reactions are listed in order of decreasing seriousness. In addition, each adverse drug reaction is based on the following conversion (CIOMS III) in the relevant frequency category: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), unknown (it cannot be estimated from the available data).

Infections and infestations
Common: Oropharyngeal Candida infection.

Immune system disorders
Rare: Hypersensitivity reactions (dermatitis, erythema), rash, urticaria, angioedema, pruritus, anaphylactic reactions.

Endocrine disorders
Rare: Adrenal suppression, Cushing's syndrome, hyperadrenocorticism, hypocorticism, growth retardation in children and adolescents

Psychiatric disorders
Rare: Depression, unrest
Very rare: Irritability

Eye disorders
Rare: Cataract, glaucoma

Respiratory, thoracic and mediastinal disorders
Common: Cough
Rare: Paradoxical bronchospasm, dysphonia, throat irritation.

Musculoskeletal disorders, connective tissue and bone disorders
Rare: Decrease in bone mineral density

Systemic effects may occur with inhaled corticosteroids, especially in high-dose long-term use. Some possible systemic effects include adrenal suppression, hypercorticism/Cushing's syndrome, growth suppression in children and adolescents, decrease in bone mineral density, cataract, glaucoma and hypersensitivity reactions (see section 4.4).
In published literature, long-term clinical trials have reported the following undesirable effects with budesonide formulations in COPD patients: skin bruises and pneumonia.

Adverse drug reactions from post-marketing spontaneous notifications (The frequencies are unknown)
The following adverse drug reactions have been derived from post-marketing experience with formoterol. Because these restrictions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency, which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Adverse drug reactions are listed as the most common adverse reaction, according to their frequency, to be first.

Metabolism and nutrition disorders
Unknown: Hypokalemia, hyperglycemia

Cardiac disorders
Unknown: QT prolongation in electrocardiogram, angina pectoris, cardiac arrhythmias such as atrial fibrillation, ventricular extrasystoles, tachyarrhythmia

Respiratory tract, thoracic and mediastinal disorders
Unknown: Cough

Skin and subcutaneous tissue disorders
Unknown: Skin rash

Investigations
Unknown: Increased blood pressure (including hypertension)

Identification of selected undesirable effects
Severe asthma attacks:
Placebo-controlled clinical studies of at least 4 weeks treatment duration with formoterol suggested a higher incidence of serious asthma exacerbations in patients who received formoterol (0.9% for 10-12 mcg twice daily, 1.9% for 24 mcg twice daily) than in those who received placebo (0.3%) (Particularly in patients 5-12 years of age).

Experiences in adolescent and adult patients with asthma:
In two pivotal 12-week controlled trials conducted in US for registration with combined enrolment of 1095 patients 12 years of age and older, serious asthma exacerbations (acute worsening of asthma resulting in hospitalization) occurred more commonly with formoterol 24 mcg twice daily (9/271, 3.3%) than with formoterol 12 mcg twice daily (1/275, 0.4%), placebo (2/277, 0.7%) or albuterol (2/272, 0.7%).
A subsequent clinical trial to address this observation enrolled 2085 patients to compare asthma-related serious adverse events in the higher and lower dose groups. The results from this 16 week trial did not show an apparent dose-relationship for formoterol. The percent of patients with serious asthma exacerbations in this study was somewhat higher for formoterol than for placebo (for the three double-blind treatment groups: formoterol 24 mcg twice daily (2/527, 0.4%), formoterol 12 mcg twice daily (3/527, 0.6%), and placebo (1/514, 0.2%) and for the open-label treatment group: formoterol 12 mcg twice daily plus up to two additional doses per day (1/517, 0.2%).

Experiences in children aged 5-12 years with asthma:
The safety of formoterol 12 mcg twice daily compared to formoterol 24 mcg twice daily and placebo was investigated in one large, multicenter, randomized, double-blind, 52-week clinical trial in 518 children with asthma (ages 5-12) in need of daily bronchodilators and anti-inflammatory treatment. More children who received formoterol 24 mcg twice daily (11/171, 6.4%) or formoterol 12 mcg twice daily (8/171, 4.7%) than children who received placebo (0/176, 0.0%) experienced serious asthma exacerbations.
For treatment recommendations, see section 4.2 Posology and method of administration and Section 4.4 Special warnings and precautions for use.
The following post-marketing adverse drug reactions have been reported in patients treated with budesonide. Because of these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably determine their frequency, which is therefore categorized as 'not known'. Adverse drug reactions are listed according to system organ classes in MedDRA. In each frequency group, adverse reactions are listed in order of decreasing seriousness.

Immune system disorders
Unknown: Contact dermatitis (Type IV [delayed] hypersensitivity reaction).

Psychiatric disorders
Unknown: Psychomotor hyperactivity, sleep disturbances, behavioral changes (predominantly in children).

In the published literature, long-term clinical trials have reported the following undesirable effects with budesonide formulations in COPD patients: skin bruises and pneumonia.

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose
Symptoms
An overdose of formoterol is likely to lead to effects that are typical of β2-adrenergic stimulants: nausea, vomiting, headache, tremor, drowsiness, palpitations, tachycardia, ventricular arrhythmias, metabolic acidosis, hypokalemia, hyperglycemia and hypertension.
Acute toxicity of budesonide is low. Largely harmful effect that follows inhalation of large amounts of the drug over a short period is suppression of hypothalamic pituitary-adrenal (HPA) function.

Treatment
FORMOTEROL
Supportive and symptomatic treatment is indicated. In serious cases, patients should be hospitalized. Use of cardioselective β-blockers may be considered, but only under the supervision of a physician and with extreme caution since the use of beta-adrenergic blocker medication may provoke bronchospasm.

BUDESONIDE
No special emergency action needs to be taken. Budesonide therapy should be continued at the recommended dose to control asthma.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

FORMOTEROL

Pharmacotherapeutic group: Selective beta2-adrenoceptor agonist
ATC code: R03AC13

Formoterol is a potent selective β2-adrenergic stimulant. It exerts a bronchodilator effect in patients with reversible airways obstruction. The effect sets in rapidly (within 1 to 3 minutes) and is still significant 12 hours after inhalation. At therapeutic doses, cardiovascular effects are minor and occur occasionally.
Formoterol inhibits the release of histamine and leukotrienes from passively sensitized human lung. In animal experiments, some anti-inflammatory properties, such as inhibition of edema and inflammatory cell accumulation, have been observed.
In vitro studies on guinea pig trachea have indicated that racemic formoterol and its (R,R) - and (S,S) -enantiomers are highly selective β2-adrenoceptor agonists. The (S,S) - enantiomer was 800 to 1,000 times less potent than the (R,R)-enantiomer and did not affect the activity of the (R,R)-enantiomer on tracheal smooth muscle. No pharmacological basis for the use of one of the two enantiomers in preference to the racemic mixture was demonstrated.
In human, formoterol has been shown to be effective in preventing bronchospasm induced by inhaled allergens, exercise, cold air, histamine or methacholine.
Inhale formoterol administered by the inhaler device at doses of 12 mcg twice daily and 24 mcg twice daily was shown objectively to provide rapid onset of bronchodilation in patients with stable chronic obstructive pulmonary disease (COPD) that was maintained over at least 12 hours, and which was accompanied by subjective improvement in Quality of Life using the 'Saint George's Respiratory Questionnaire'.

BUDESONIDE

Pharmacotherapeutic group: Other drugs for obstructive airway diseases, Inhalants; Glucocorticoids
ATC code: R03BA02

Budesonide is a corticosteroid that has a significant topical effect in humans but it has no significant systemic effect. As with other inhale glucocorticoids, budesonide also shows pharmacological effects by interacting with intracellular glucocorticoid receptors. The production of many different cytokines, chemokines, enzymes and cell adhesion molecules are inhibited. When patients who benefit from treatment with corticosteroids are used as inhalation powder, they can usually control asthma within 10 days of treatment. Budesonide reduces chronic inflammation in asthmatic lungs when used regularly. Budesonide also increases lung functions and reduces asthma symptoms and bronchial hyperresponsiveness and prevents asthma attacks.

5.2 Pharmacokinetic properties

General properties

Formoterol has a therapeutic dose range of 12 to 24 mcg twice daily. Data on the plasma pharmacokinetics of formoterol was collected in healthy volunteers after inhalation of doses higher than the recommended range and in COPD patients after inhalation of therapeutic doses. Urinary excretion of unchanged formoterol, used as an indirect measure of systemic exposure, correlates with drug pharmacokinetic data in plasma. The elimination half-lives calculated for urine and plasma are similar.

Absorption-Formoterol:
Following inhalation of a single 120 mcg dose of formoterol fumarate by healthy volunteers, formoterol was rapidly absorbed into plasma, reaching a maximum concentration of 266 pmol/l within 5 min of inhalation. In COPD patients treated for 12 weeks with 12 or 24 mcg formoterol fumarate twice daily, the mean plasma concentrations of formoterol ranged between 11.5-25.7 pmol/l and 23.3-50.3 pmol/l, respectively, 10 min, 2 hours and 6 hours after inhalation.
Studies investigating the cumulative urinary excretion of formoterol and/or its (R, R) - and (S, S) - enantiomers showed the amount of formoterol available in the circulation to increase in proportion to the inhaled dose (12 to 96 mcg).
After inhalation of 12 mcg or 24 mcg twice daily for 12 weeks, urinary excretion of unchanged formoterol increased by between 63% and 73% (When the first dose compared to the last dose) in patients with asthma and by between 19% and 38% in COPD patients. This suggests some limited accumulation of formoterol in plasma with repeated dosing. There was no relative accumulation of one enantiomer over the other after repeated dosing.
As reported for other inhaled drugs, it is likely that most of the formoterol administered from an inhaler will be swallowed and then absorbed from the gastrointestinal tract. When 80 mcg of ^{3}H-labeled formoterol fumarate was orally administered to two healthy volunteers, at least 65% of the dose was absorbed.

Absorption-Budesonide:
The amount of budesonide deposited in the lungs is rapidly and completely absorbed. Peak plasma concentrations are reached immediately after administration. After correction for the dose deposited in the oropharynx absolute bioavailability is 73%. Only 10 to 13% of the swallowed fraction of an inhaled dose is bioavailable due to significant presystemic metabolism in the liver.

Distribution-Formoterol:
Plasma protein binding of formoterol was 61-64%, and binding to human serum albumin was 34%. There is no saturation of binding sites in the concentration range reached with therapeutic doses.

Distribution-Budesonide:
The plasma protein binding of budesonide is 85 to 90% over the concentration range 1 to 100 nmoL. Budesonide is widely distributed into tissues, with a volume of distribution of 183 to 301 L at steady state. Animal studies have shown high concentrations in spleen, lymph glands, thymus, adrenal cortex, reproductive organs, and bronchi. Budesonide crosses the placental barrier in mice. It also passes into breast milk, with a milk to plasma concentration ratio of around 0.46. The estimated daily infant dose is 0.3% of the daily maternal dose, and the estimated average plasma concentration in infants is 1/600th of the maternal plasma concentration, even after assuming complete infant oral bioavailability.

Biotransformation-Formoterol:
Formoterol is eliminated primarily by metabolism, with direct glucuronidation being the major pathway of biotransformation. O-demethylation followed by glucuronidation is another pathway. Minor pathways involve sulphate conjugation of formoterol and deformylation followed by sulphate conjugation. Multiple isoenzymes catalyze the glucuronidation (UGT1A1, 1A3, 1A6, 1A7, 1A8, 1A9, 1A10, 2B7 and 2B15) and O-demethylation (CYP2D6, 2C19, 2C9 and 2A6) of formoterol, suggesting a low potential for drug-drug interactions though inhibition of a specific isoenzyme involved in formoterol metabolism. Formoterol did not inhibit or induce cytochrome P450 isoenzymes at therapeutically relevant concentrations.

Biotransformation-Budesonide:
Budesonide is not metabolized in the lungs. After absorption it is broken down in the liver to yield a number of inactive metabolites, including 6-β-hydroxybudesonide and 16-alphahydroxyprednisolone.
The main route of metabolism of budesonide is via CYP3A4 and may be affected by known inhibitors or inducers of this enzyme (see section 4.5).

Elimination-Formoterol:
In asthmatic and COPD patients treated for 12 weeks with 12 or 24 mcg formoterol fumarate twice daily, approximately 10% and 7% of the dose, respectively, were recovered in the urine as unchanged formoterol. The (R,R) and (S,S)-enantiomers accounted, respectively, for 40% and 60% of urinary recovery of unchanged formoterol, after single doses, (12 to 120 mcg) in healthy volunteers, and after single and repeated doses in asthma patients.
The drug and its metabolites were completely eliminated from the body with about 2/3 of an oral dose being excreted in the urine, and 1/3 in the feces. Renal clearance of formoterol in the blood was 150 ml/min.
In healthy volunteers, the elimination half-life of formoterol fumarate in plasma after inhalation of a single 120 mcg dose of formoterol fumarate was 10 hours and the elimination half-life of the (R,R)- and (S,S)-enantiomers, as derived from the urinary excretion rates, were 13.9 and 12.3 hours, respectively.

Elimination- Budesonide:
In human volunteers inhaling radiolabeled budesonide (via metered dose inhaler) approximately 32% of the discharged dose was recovered in the urine and 15% in the feces.
Following inhalation, 16-alpha-hydroxyprednisolone, but not budesonide, was detected in the urine.
Budesonide shows high plasma clearance (84 L/h) following intravenous dosing. The elimination half-life was around 2.8 to 5 h.

Linearity/non-linearity:
There is no adequate study that is available on linearity/non-linearity of formoterol and budesonide.

Characteristics in patients
Renal/Hepatic Impairment
The pharmacokinetics of formoterol and budesonide has not been studied in patients with hepatic or renal impairment.
However, after oral administration the systemic availability of budesonide was reported to be 2.5 times higher in patients with cirrhosis than in healthy controls. Mild hepatic impairment is reported to have little effect on systemic exposure of oral budesonide.
Although renal impairment has been reported not expected to have any effect on oral budesonide pharmacokinetics, budesonide metabolites are excreted in the urine an increased risk of adverse events due to metabolite accumulation cannot be excluded in severe renal impairment.

Pediatric population
In a study in 5 to 12 year old children with asthma who were given 12 or 24 mcg formoterol fumarate twice daily by inhalation for 12 weeks, urinary excretion of unchanged formoterol increased by between 18% and 84% as compared to the amounts measured after the first dose. Accumulation in children was not more from adult patients and the increase was between 63% and 73% (see Absorption). In the studied children, about 6% of the formoterol dose was recovered in the urine as unchanged formoterol.

The pharmacokinetics of budesonide has not been studied in the pediatric population. However, data with other inhalational budesonide products suggest that body weight-normalized clearance in children above 3 years of age is around 50% higher than in adults.

Geriatric population:
The pharmacokinetics of formoterol and budesonide has not been studied in geriatric patients.

Gender:
After correction for body weight, formoterol pharmacokinetics did not differ significantly between males and females.

5.3 Preclinical safety data

Mutagenicity

Formoterol

Mutagenicity tests covering a broad range of experimental endpoints have been conducted and no genotoxic effects were found in any of the *in vitro* or *in vivo* tests performed.

Budesonide

Budesonide was shown to have no mutagenic potential in a battery of *in vitro* and *in vivo* mutagenicity tests.

Carcinogenicity

Formoterol

Two-year studies in rats and mice did not show any carcinogenic potential.
Male mice treated at very high dose levels showed a slightly higher incidence of benign adrenal subcapsular cell tumors. However, this finding was not seen in a second mouse study, in which pathological changes at high doses consisted of an increased incidence both of benign smooth muscle tumors in the female genital tract, and of liver tumors in both sexes. Smooth muscle tumors are a known effect of β-agonists at high doses in rats.
Two studies in rats, covering different dose ranges, showed an increase in mesovarial leiomyomas. These benign neoplasms are typically associated with long-term treatment of rats at high doses of β 2-adrenergic drugs. Increased incidences of ovarian cysts and benign granulosa/thecal cell tumors were also seen; β-agonists are known to have effects on the ovary in rats, which are very likely specific to rodents. A few other tumor types noted in the first study using the higher doses were within the incidences of the control group, and were not seen in the lower dose experiments.
None of the tumor incidences was increased to a statistically significant extent at the lowest dose of the second study (a dose leading to a systemic exposure 10 times higher than that expected from the maximum recommended dose of formoterol in humans).
Based on these findings and the absence of a mutagenic potential, it is concluded that use of formoterol at therapeutic doses does not present a carcinogenic risk.

Budesonide

Orally administered budesonide was shown to increase the incidence of liver tumors in mala rats starting at dose levels of 25 mcg/kg/day. These effects were also observed in a follow-up study including other steroids (prednisolone and triamcinolone acetonide) and are considered a class effect of corticosteroid administration.

Reproduction toxicity

Formoterol

Animal tests have shown no teratogenic effects. Formoterol was evaluated for its effects on fertility and general reproductive performance in sexually mature male and female rats. No impairment of fertility or effect on early embryonic development was observed at doses up to 60 mg/kg/day

administered orally to rats (approximately 12,000 times the maximum recommended daily inhalation powder dose in human on a mg/m^2 basis). After oral administration, formoterol was excreted in the milk of lactating rats.

Budesonide
Inhale budesonide has been shown to cause decrease in body weight of rat pups, but there is no reported teratogenic effect. The effects of subcutaneously administered budesonide on decreased viability of pups and maternal toxicity of budesonide in rats and its teratogenic potential and effects on growth retardation and fetal death in rabbits are consistent with the known teratogenic potential of glucocorticoids in animals. There is no evidence that budesonide has any teratogenicity or reproductive toxicity in humans (see section 4.6). Subcutaneously administered budesonide did not have an adverse effect on fertility in rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate (from bovine milk)
Clear hard gelatin capsule (from bovine bone)

6.2 Incompatibilities
There is no known incompatibility.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Store at room temperature below 25°C and keep always in blisters.
Blisters must be opened only immediately before use.

6.5 Nature and contents of container
ROLASTYM COMBI capsules are packaged in Alu/Alu blisters. Each cardboard box contains 60 capsules. ROLASTYM COMBI, blister containing inhaler capsule and an inhalation device with package leaflet are replaced in a cardboard box.

6.6 Special precautions for disposal and other handling
Any unused product or waste material should be disposed of in accordance with local disposal regulations.

7. MARKETING AUTHORIZATION HOLDER
DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece – İSTANBUL / TÜRKİYE

8. MARKETING AUTHORIZATION NUMBER
241/98

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
Date of first authorization : 26.04.2012
Date of last renewal :

10. DATE OF REVISION OF THE TEXT