SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ROLASTYM 80 mcg/4.5 mcg Inhalation Aerosol

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Each actuation delivers
Budesonide……80 micrograms/inhalation
Formoterol fumarate dihydrate…….4.5 micrograms/inhalation

Excipient(s) with known effect:
For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Aerosol inhaler, suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Asthma
ROLASTYM is indicated in the treatment and control of asthma symptoms. ROLASTYM is not suitable for patients with severe asthma.

ROLASTYM is suitable for children aged 6-12 years.

4.2 Posology and method of administration

Posology/frequency and duration of administration
Asthma
The dose of the components of ROLASTYM is individual and should be adjusted to the severity of the disease. This should be considered not only when treatment with combination products is initiated but also when the maintenance dose is adjusted. If the patient requires a combination of doses other than the doses in the combination preparation, appropriate doses of $beta_2$ agonists and corticosteroids or preparations containing corticosteroid alone should be given.

The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. Patients should be regularly reassessed by their prescribers so that the dosage of ROLASTYM remains optimal. When long-term control of symptoms is maintained with the lowest recommended dosage, then the next step could include a test of inhaled corticosteroid alone.

For ROLASTYM, there are two treatment approaches:

A. ROLASTYM maintenance therapy: ROLASTYM is taken as regular maintenance treatment with a separate rapid-acting bronchodilator as rescue.

B. ROLASTYM maintenance and reliever therapy: ROLASTYM is taken as regular maintenance treatment and as needed in response to symptoms.

A. ROLASTYM maintenance therapy

Patients should be advised to have their separate rapid-acting bronchodilator available for rescue use at all times.

Recommended doses:
Adults (18 years and older): 1-2 inhalations twice daily. Some patients may require up to a maximum of 4 inhalations twice daily.

Adolescents (12-17 years): 1-2 inhalations twice daily.

In usual practice, when control of symptoms is achieved with the twice daily regimen, titration to the lowest effective dose could include ROLASTYM given once daily, when in the opinion of the prescriber, a long-acting bronchodilator in combination with an inhaled corticosteroid would be required to maintain control.

Increasing use of a separate rapid-acting bronchodilator indicates a worsening of the underlying condition and warrants a reassessment of the asthma therapy.

Children under 6 years: ROLASTYM is not recommended for children younger than 6 years of age, as limited data is available.

B. ROLASTYM maintenance and reliever therapy

Rolastym is taken as regular maintenance therapy and as needed in response to symptoms. Patients should be advised to always have ROLASTYM available for rescue use.

ROLASTYM maintenance and reliever therapy should especially be considered for patients with:
- inadequate asthma control and in frequent need of reliever medication
- asthma exacerbations in the past requiring medical intervention

Close monitoring for dose-related adverse effects is needed in patients who frequently take high numbers of ROLASTYM as-needed actuations.

Recommended doses:
Adults (18 years and older): The recommended maintenance dose is 2 inhalations per day, given either as 1 actuation in the morning and evening or as 2 inhalations in either the morning or evening. Patients should take 1 additional actuation as needed in response to symptoms. If symptoms persist after a few minutes, 1 additional actuation should be taken. Not more than 6 actuations should be taken on any single occasion.

A total daily dose of more than 8 actuations is not normally needed; however, a total daily dose of up to 12 actuations could be used for a limited period. Patients using more than 8 actuations daily should be strongly recommended to seek medical advice. They should be reassessed and their maintenance therapy should be reconsidered.

Children under 12 years: ROLASTYM maintenance and reliever therapy is not recommended for children under 12 years of age.

Method of administration
Precautions for the correct use of ROLASTYM:
ROLASTYM is in form of aerosol and the drug reaches the respiratory tract when breathing deeply through the mouthpiece of ROLASTYM.

Note: It is important to inform the patient about:
- The information regarding the use of ROLASTYM in the patient leaflet provided with each inhaler should be read carefully.
- In order for a sufficient dose to reach the lungs, the patient should breathe strongly and deeply through the mouthpiece of ROLASTYM L.
- The patient should never exhale while the inhaler is still in the mouth.
- The cover of ROLASTYM must be closed after use.
- To minimize the risk of oropharyngeal candida infection, the patient should be instructed to rinse their mouth out with water after inhaling the maintenance dose. If oropharyngeal thrush occurs, patients should also rinse their mouth out with water after the as-needed inhalations.

The patient may not feel any taste in the mouth after inhalation, since the amount of medication in a dose is very small.

There is a counter on the front of ROLASTYM which tells you how many doses are left. Each time you press the canister, a puff of medicine is released and the counter will count down a little bit. The counter measures interval of 20 doses. Take care not to drop the inhaler as this may cause the counter to count down.

The dose counter will start turning red when 40 doses are left. When there are 20 doses left, the counter will be completely red; this indicates that the drug level in the device is low. In this case, please consult your doctor. When the meter shows 0, do not use the medicine remaining in the device as it will not provide you with the full dose. Do not try to change the numbers on the counter or remove the counter.

Additional information on special populations
Renal/Hepatic impairment
There are no data available for use of ROLASTYM in patients with hepatic or renal impairment. As budesonide and formoterol are primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe liver cirrhosis.

Geriatric population
There are no special dosing requirements for elderly patients.

Pediatric population
ROLASTYM maintenance and reliever therapy is not recommended for children under 12 years of age.

4.3 Contraindications

It should not be used in patients with hypersensitivity to the active substances or any excipients listed in Section 6.1.

4.4 Special warnings and precautions for use

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

Rarely, serious and sometimes fatal asthma related breathing problems may occur with the use of long-acting β-agonists.

ROLASTYM should not be used as the first treatment for asthma.

Long-acting beta-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.

Pediatric and adolescent patients who require a long-acting beta-agonist in addition to an inhaled corticosteroid should use a combination product containing both an inhaled corticosteroid and a long-acting beta-agonist to ensure compliance with both medications.

Treatment with long-acting beta-agonists should not be initiated if patients are in exacerbations or if you have severe or acutely worsening asthma.

When discontinuing treatment, it is recommended that the dose be tapered off and not abruptly discontinued.

If patients find the treatment ineffective or exceed the highest recommended dose of ROLASTYM, medical attention must be sought (see section 4.2). Sudden and progressive worsening of asthma and COPD is a life-threatening condition, and the patient should undergo urgent medical assessment. In this situation, consideration should be given to the need for increased therapy with corticosteroids, e.g. a course of oral corticosteroids, or antibiotic treatment if an infection is present.

Patients should be advised to have their rescue inhaler available at all times, either ROLASTYM (for patients using ROLASTYM as maintenance and reliever therapy) or a separate rapid-acting bronchodilator (for patients using ROLASTYM as maintenance therapy only).

Patients should be reminded to take their ROLASTYM maintenance dose as prescribed, even when asymptomatic. The prophylactic use of budesonide/formoterol, e.g. before exercise, has not been studied. The reliever inhalations of ROLASTYM should be taken in response to asthma symptoms but are not intended for regular prophylactic use, e.g. before exercise. For such use, a separate rapid-acting bronchodilator should be considered.

It is recommended that the dose is tapered when the treatment is discontinued and should not be stopped abruptly. Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of ROLASTYM. Regular review of patients as treatment is stepped down is important. The lowest effective dose of ROLASTYM should be used (see section 4.2).

Patients should not be initiated on ROLASTYM 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 ROLASTYM. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation of ROLASTYM.

There are no clinical study data on budesonide/formoterol combination products available in COPD patients with a pre-bronchodilator FEV_1 >50% predicted normal and with a post-bronchodilator FEV_1 <70% predicted normal (see section 5.1).

As with other inhalation therapy, paradoxical bronchospasm may occur, with an immediate increase in wheezing and shortness of breath, after dosing. In this case, ROLASTYM should be discontinued immediately, the patient should be assessed and an alternative therapy instituted, if necessary. Paradoxical bronchospasm responds to a rapid-acting inhaled bronchodilator and should be treated straightaway (see section 4.8).

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur with inhalation treatment than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma, and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).

Potential effects on bone density should be considered particularly in patients on high doses for prolonged periods that have coexisting risk factors for osteoporosis. Long-term studies with inhaled budesonide in children at mean daily doses of 400 mcg (metered dose) or in adults at daily doses of 800 mcg (metered dose) have not shown any significant effects on bone mineral density. No information regarding the effect of ROLASTYM at higher doses is available.

If there is any reason to suppose that adrenal function is impaired from previous systemic steroid therapy, care should be taken when transferring patients to ROLASTYM therapy.

The benefits of inhaled budesonide therapy would normally minimize the need for oral steroids, but patients transferring from oral steroids may remain at risk of impaired adrenal reserve for a considerable time. Recovery may take a considerable amount of time after cessation of oral steroid therapy and hence oral steroid-dependent patients transferred to inhaled budesonide may remain at risk from impaired adrenal function for some considerable time. In such circumstances, HPA axis function should be monitored regularly.

The prolonged treatment with high doses of inhaled corticosteroids, particularly higher than recommended doses, may also result in clinically significant adrenal suppression. Therefore, additional systemic corticosteroid cover should be considered during periods of stress such as severe infections or elective surgery. Rapid reduction in the dose of steroids can induce acute adrenal crisis. Symptoms and signs which might be seen in acute adrenal crisis may be somewhat vague but may include anorexia, abdominal pain, weight loss, tiredness, headache, nausea, vomiting, decreased level of consciousness, seizures, hypotension and hypoglycemia.

Treatment with supplementary systemic steroids should not be stopped abruptly.

During transfer from oral therapy to ROLASTYM, a generally lower systemic steroid action will be experienced which may result in the appearance of allergic or arthritic symptoms such as rhinitis, eczema and muscle and joint pain. Specific treatment should be initiated for these conditions. A general insufficient glucocorticosteroid effect should be suspected if, in rare cases, symptoms such as tiredness, headache, nausea and vomiting should occur. In these cases, a temporary increase in the dose of oral glucocorticosteroids is sometimes necessary.

Patients should be advised to rinse their mouth with water after each inhalation of the maintenance dose to reduce the risk of developing thrush in the mouth and throat area. In case of thrush, they should rinse their mouth with water after as-needed inhalation.

Concomitant treatment with itraconazole, ritonavir or other potent CYP3A4 inhibitors should be avoided (see section 4.5). If this is not possible, the time interval between administrations of the interacting drugs should be as long as possible. In patients taking potent CYP3A4 inhibitors, maintenance and reliever therapy is not recommended.

ROLASTYM should be administered with caution in patients with thyrotoxicosis, pheochromocytoma, diabetes mellitus, untreated hypokalemia, hypertrophic obstructive cardiomyopathy, idiopathic subvalvular aortic stenosis, severe hypertension, aneurysm or other severe cardiovascular disorders, such as ischemic heart disease, tachyarrhythmias or severe heart failure.

Caution should be observed when treating patients with prolongation of the QTc-interval. Formoterol itself may induce prolongation of the QTc-interval.

The need for inhaled corticosteroids should be re-evaluated in patients with active or quiescent pulmonary tuberculosis, fungal and viral infections in the airways.

Potentially serious hypokalemia may result from high doses of beta$_2$-agonists. Concomitant treatment of beta$_2$-agonists with drugs which can induce hypokalemia or potentiate a hypokalemic effect, e.g. xanthine derivatives, steroids and diuretics, may enhance the possible hypokalemic effect of beta$_2$-agonists. Particular caution is recommended in unstable asthma with variable use of rescue bronchodilators, in acute severe asthma as the associated risk may be augmented by hypoxia and in other conditions when the likelihood for hypokalemia is increased. It is recommended that serum potassium levels are monitored during these circumstances.

As with all beta$_2$-agonists, blood glucose levels should be monitored more frequently in diabetic patients.

Pediatric population
It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be re-evaluated with the aim of reducing the dose of inhaled corticosteroid to the lowest dose at which effective control of asthma is maintained, if possible. The benefits of the corticosteroid therapy and the possible risks of growth suppression must be carefully weighed. In addition, consideration should be given to referring the patient to a pediatric respiratory specialist.

Limited data from long-term studies suggest that most children and adolescents treated with inhaled budesonide will ultimately achieve their adult target height. However, an initial small but transient reduction in growth (approximately 1 cm) has been observed. This generally occurs within the first year of treatment.

Pneumonia in patients with COPD
An increase in the incidence of pneumonia, including pneumonia requiring hospitalization, 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 patient with COPD include current smoking, older age, low body mass index and severe COPD.

4.5 Interactions with other medicinal products and other forms of interaction

Pharmacokinetic interactions
Potent inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, nefazodone and HIV protease inhibitors) are likely to markedly increase plasma levels of budesonide and concomitant use should be avoided. If this is not possible the time interval between administration of the inhibitor and budesonide should be as long as possible. In patients using potent CYP3A4 inhibitors, ROLASTYM maintenance and reliever therapy is not recommended.

The potent CYP3A4 inhibitor ketoconazole, 200 mg once daily, increased plasma levels of concomitantly orally administered budesonide (single dose of 3 mg), on average, 6-fold. When ketoconazole was administered 12 hours after budesonide, the concentration was, on average, increased only 3-fold showing that separation of the administration times can reduce the increase in plasma levels. Limited data about this interaction for high-dose inhaled budesonide indicates that marked increase in plasma levels (on average, 4 fold) may occur if itraconazole, 200 mg once daily, is administered concomitantly with inhaled budesonide (single dose of 1000 mcg).

Pharmacodynamic interactions
Beta-adrenergic blockers can weaken or inhibit the effect of formoterol. ROLASTYM should therefore not be given together with beta-adrenergic blockers (including eye drops) unless there are compelling reasons.

Concomitant treatment with quinidine, disopyramide, procainamide, phenothiazines, antihistamines (terfenadine) and tricyclic antidepressants can prolong the QTc-interval and increase the risk of ventricular arrhythmias.

In addition, L-dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards beta$_2$-sympathomimetics.

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

Additive effects may occur when used with other beta-adrenergic drugs.

Hypokalemia may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides.

Hypokalemia may result from beta$_2$-agonist therapy and may be potentiated by concomitant treatment with xanthine derivatives, corticosteroids and diuretics (see section 4.4).

Budesonide and formoterol have not been observed to interact with any other drugs used in the treatment of asthma.

Additional information on special populations
Pediatric population
Interaction studies have only been conducted in adults.

4.6 Fertility, pregnancy and lactation

General recommendation
Pregnancy category is C

Women of child-bearing potential/Contraception
Due to the general risk of inadequate asthma control in asthmatic patients, including women with childbearing potential and pregnant women with asthma, it is extremely important that these patients, including asthmatic women of childbearing potential, receive an ideal antiasthmatic therapy.

- Treatment with the budesonide/formoterol fumarate dihydrate combination poses no additional significant clinical risk to the pregnant woman or her fetus and therefore no active contraception is required.
- The budesonide/formoterol fumarate dihydrate combination has no effect on the contraceptive methods known as of today.

Pregnancy
There are no adequate data from the use of budesonide/formoterol in pregnant women.

Studies on animals have shown that reproductive toxicity exists (see section 5.3). The potential risk for humans is unknown.

During pregnancy, ROLASTYM should only be used when the benefits outweigh the potential risks. The lowest effective dose of budesonide needed to maintain adequate asthma control should be used.

For ROLASTYM or the concomitant treatment with formoterol and budesonide, no clinical data on exposed pregnancies are available. Data from an embryo-fetal development study in rats showed no evidence of any additional effect from the combination.

There are no adequate data from use of formoterol in pregnant women. In animal reproduction studies, formoterol has caused adverse effects at very high systemic exposure levels (see section 5.3).

Data on approximately 2000 exposed pregnancies indicate no increased teratogenic risk associated with the use of inhaled budesonide. In animal studies, glucocorticosteroids have been shown to induce malformations (see section 5.3). This is not likely to be relevant for humans given recommended doses.

Animal studies have also identified an involvement of excess prenatal glucocorticoids in increased risks for intrauterine growth retardation, adult cardiovascular disease and permanent changes in glucocorticoid receptor density, neurotransmitter turnover and behavior at exposures below the teratogenic dose range.

Breastfeeding
Budesonide is excreted in breast milk. However, at therapeutic doses no effects on the suckling child are anticipated. It is not known whether formoterol passes into human breast milk. In rats, small amounts of formoterol have been detected in maternal milk. Administration of ROLASTYM to women who are breastfeeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

4.7. Effects on ability to drive and use machines

ROLASTYM has no or negligible influence on the ability to drive and use machines.

4.8. Undesirable effects

Since ROLASTYM contains both budesonide and formoterol, the same pattern of undesirable effects as reported for these substances may occur. No increased incidence of adverse reactions has been seen following concurrent administration of the two compounds. The most common drug related adverse reactions are pharmacologically predictable side-effects of beta$_2$-agonist therapy, such as tremor and palpitations. These tend to be mild and usually disappear within a few days of treatment.

Adverse reactions, which have been associated with budesonide or formoterol, are given below, listed by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100), rare (≥1/10 000 to <1/1000) and very rare (<1/10 000) and not known (cannot be estimated from the available data).

Infections and infestations	Common	Candida infections in the oropharynx Pneumonia (in COPD patients)
Immune system disorders	Rare	Immediate and delayed hypersensitivity reactions, e.g. exanthema, urticaria, pruritus, dermatitis, angioedema and anaphylactic reaction
Endocrine disorders	Very rare	Cushing's syndrome, signs or symptoms of systemic corticosteroid effects e.g. adrenal suppression, growth retardation, decrease in bone mineral density
Metabolism and nutrition disorders	Rare	Hypokalemia
	Very rare	Hyperglycemia
Psychiatric disorders	Uncommon	Agitation, psychomotor hyperactivity, anxiety, sleep disorders
	Very rare	Depression, behavioral changes (predominantly in children)
Nervous system disorders	Common	Headache, tremor
	Uncommon	Dizziness
	Very rare	Taste disturbances
Eye disorders	Very rare	Cataract and glaucoma
Cardiac disorders	Common	Palpitations
	Uncommon	Tachycardia
	Rare	Cardiac arrhythmias, e.g. atrial fibrillation, supraventricular tachycardia, extrasystoles
	Very rare	Angina pectoris, prolongation of QTc-interval

Vascular disorders	Very rare	Variations in blood pressure
Respiratory, thoracic and mediastinal disorders	Common	Mild irritation in the throat, coughing, hoarseness
	Rare	Bronchospasm
Gastrointestinal disorders	Uncommon	Nausea
Skin and subcutaneous tissue disorders	Uncommon	Bruises
Musculoskeletal and connective tissue disorders	Uncommon	Muscle cramps

Candida infection in the oropharynx is due to drug deposition. Advising the patient to rinse the mouth out with water after each dose will minimize the risk. Oropharyngeal Candida infection usually responds to topical anti-fungal treatment without the need to discontinue the inhaled corticosteroid. If thrush occurs in the oropharynx, patients should also rinse their mouth with water after as-needed inhalation.

As with other inhalation therapy, paradoxical bronchospasm may occur very rarely, affecting less than 1 in 10,000 people, with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid-acting inhaled bronchodilator and should be treated straightaway. ROLASTYM should be discontinued immediately, the patient should be assessed and an alternative therapy instituted if necessary (see section 4.4).

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 Cushing's syndrome, Cushingoid features, adrenal insufficiency, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. Increased susceptibility to infections and impairment of the ability to adapt to stress may also occur. Effects are probably dependent on dose, exposure time, concomitant and previous steroid exposure and individual sensitivity.

Treatment with beta$_2$-agonists may result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies.

Pediatric population
It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids be regularly monitored (see section 4.4).

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

An overdose of formoterol would likely lead to effects that are typical for β_2-agonists: tremor, headache, palpitations. Symptoms reported from isolated cases are tachycardia, hyperglycemia, hypokalemia, prolonged QTc-interval, arrhythmia, nausea and vomiting. Supportive and symptomatic treatment may be indicated. A dose of 90 mcg of formoterol administered during three hours in patients with acute bronchial obstruction raised no safety concerns.

Acute overdosage with budesonide, even in excessive doses, is not expected to be a clinical problem. When used chronically in excessive doses, systemic glucocorticosteroid effects, such as hypercorticism and adrenal suppression, may appear.

If ROLASTYM therapy has to be withdrawn due to overdose of the formoterol component of the drug, provision of appropriate inhaled corticosteroid therapy must be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Adrenergics and other drugs used in obstructive airway diseases
ATC code: R03AK07

Mechanisms of action and pharmacodynamic effects
ROLASTYM contains formoterol and budesonide, which have different modes of action and show additive effects in terms of reduction of asthma exacerbations. The specific properties of budesonide and formoterol allow the combination to be used both as maintenance and reliever therapy, or as maintenance treatment of asthma.

Budesonide
Budesonide is a glucocorticosteroid which when inhaled has a dose-dependent antiinflammatory action in the airways, resulting in reduced symptoms and fewer asthma exacerbations. Inhaled budesonide has less severe adverse effects than systemic corticosteroids. The exact mechanism responsible for the anti-inflammatory effect of glucocorticosteroids is unknown.

Formoterol
Formoterol is a selective beta$_2$-adrenergic agonist that when inhaled results in rapid and long-acting relaxation of bronchial smooth muscle in patients with reversible airways obstruction. The bronchodilating effect is dose dependent, with an onset of effect within 1-3 minutes. The duration of effect is at least 12 hours after a single dose.

Clinical efficacy and safety

Asthma

Clinical efficacy for budesonide/formoterol maintenance therapy
Clinical studies in adults have shown that the addition of formoterol to budesonide improved asthma symptoms and lung function, and reduced exacerbations. In two 12- week studies the effect on lung function of budesonide/formoterol was equal to that of the free combination of budesonide and formoterol, and exceeded that of budesonide alone. All treatment arms used a short-acting beta$_2$-agonist as needed. There was no sign of attenuation of the anti-asthmatic effect over time.

In a 12-week pediatric study 85 children aged 6-11 years were treated with a maintenance dose of budesonide/formoterol (2 inhalations of 80/4.5 mcg/inhalation twice daily), and a short-acting beta2-agonist as needed. Lung function was improved and the treatment was well tolerated compared to the corresponding dose of budesonide.

Clinical efficacy for formoterol/budesonide maintenance and reliever therapy
A total of 12076 asthma patients were included in 5 double-blind efficacy and safety studies, of which 4447 were randomized to budesonide/formoterol maintenance and reliever therapy, for 6 or 12 months. Patients were required to be symptomatic despite use of inhaled glucocorticosteroids.

Budesonide/formoterol maintenance and reliever therapy provided statistically significant and clinically meaningful reductions in severe exacerbations for all comparisons in all 5 studies. This included a comparison with budesonide/formoterol at a higher maintenance dose with terbutaline as reliever (study 735) and budesonide/formoterol at the same maintenance dose with either formoterol or terbutaline as reliever (study 734) (Table 1). In study 735, lung function, symptom control and reliever use were similar in all treatment groups. In study 734, symptoms and reliever use were reduced and lung function improved, compared with both comparator treatments. In the 5 studies combined, patients receiving budesonide/formoterol maintenance and reliever therapy used, on average, no reliever inhalations on 57% of treatment days. There was no sign of development of tolerance over time.

Table 1 - Overview of severe exacerbations in clinical studies

Study No. Duration	Treatment groups	N	Severe exacerbations[a]	
			Events	Events/ patient-year
Study735 6 months	Budesonide/formoterol 160/4.5 mcg bd + as needed	1103	125	0.23[b]
	Budesonide/formoterol 320/9 mcg bd + terbutaline 0.4 mg as needed	1099	173	0.32
	Salmeterol/fluticasone 2 x 25/125 mcg bd + terbutaline 0.4 mg as needed	1119	208	0.38
Study734 12 months	Budesonide/formoterol160/4.5 mcg bd + as needed	1107	194	0.19[b]
	Budesonide/formoterol 160/4.5 mcg bd + formoterol 4.5 mcg as needed	1137	296	0.29
	Budesonide/formoterol 160/4.5 mcg bd + terbutaline 0.4 mg as needed	1138	337	0.37

[a] Hospitalization/emergency room treatment or treatment with oral steroids
[b] Reduction in exacerbation rate is statistically significant (P value <0.01) for both comparisons

Comparable efficacy and safety in adolescents and adults was demonstrated in 6 double-blind studies, comprising the 5 studies mentioned above and an additional study using a higher maintenance dose of 160/4.5 mcg, two inhalations twice daily. These assessments were based on a total of 14385 asthma patients, of whom 1847 were adolescents. The number of adolescent patients taking more than inhalations on at least one day as part of budesonide/formoterol maintenance and reliever therapy was limited, and such use was infrequent.

In 2 other studies with patients seeking medical attention due to acute asthma symptoms, budesonide/formoterol provided rapid and effective relief of bronchoconstriction similar to salbutamol and formoterol.

5.2 Pharmacokinetic properties

Absorption

Budesonide/formoterol combination and the corresponding mono products have been shown to be bioequivalent with regard to systemic exposure of budesonide and formoterol, respectively. In spite of this, a small increase in cortisol suppression was seen after administration of

budesonide/formoterol combination compared to the mono products. The difference is considered not to have an impact on clinical safety.
There was no evidence of pharmacokinetic interactions between budesonide and formoterol.

Pharmacokinetic parameters for the respective substances were comparable after the administration of budesonide and formoterol as mono products or as combination. For budesonide, AUC was slightly higher, rate of absorption more rapid and maximal plasma concentration higher after administration of the fixed combination. Peak plasma concentrations were similar when formoterol is used alone or in combination .Inhaled budesonide is rapidly absorbed and the maximum plasma concentration is reached within 30 minutes after inhalation. In studies, mean lung deposition of budesonide after inhalation ranged from 32% to 44% of the delivered dose. The systemic bioavailability is approximately 49% of the delivered dose.

Inhaled formoterol is rapidly absorbed and the maximum plasma concentration is reached within 10 minutes after inhalation. In studies the mean lung deposition of formoterol after inhalation ranged from 28% to 49% of the delivered dose. The systemic bioavailability is about 61% of the delivered dose.

Distribution
Plasma protein binding is approximately 50% for formoterol and 90% for budesonide. Volume of distribution is about 4 L/kg for formoterol and 3 L/kg for budesonide.

Biotransformation
Formoterol is inactivated via conjugation reactions (active O-demethylated and deformylated metabolites are formed, but they are seen mainly as inactivated conjugates).
Budesonide undergoes an extensive degree (approximately 90%) of biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6-β-hydroxy-budesonide and 16-α-hydroxy-prednisolone, is less than 1% of that of budesonide. There are no indications of any metabolic interactions or any displacement reactions between formoterol and budesonide.

Elimination
The major part of a dose of formoterol is transformed by liver metabolism followed by renal elimination. After inhalation, 8% to 13% of the delivered dose of formoterol is excreted unmetabolised in the urine. Formoterol has a high systemic clearance (approximately 1.4 L/min) and the terminal elimination half-life averages 17 hours.

Budesonide is eliminated via metabolism mainly catalyzed by the enzyme CYP3A4. The metabolites of budesonide are eliminated in urine as such or in conjugated form. Only negligible amounts of unchanged budesonide have been detected in the urine. Budesonide has a high systemic clearance (approximately 1.2 L/min) and the plasma elimination half-life after IV dosing averages 4 hours.

There is no information on the pharmacokinetics of budesonide and formoterol in children and patients with renal impairment.
The systemic availability of budesonide and formoterol may be increased in patients with hepatic impairment.

Linearity/Non-linearity
Systemic exposure for both budesonide and formoterol correlates in a linear fashion to administered

dose.

5.3 Preclinical safety data

The toxicity observed in animal studies with budesonide and formoterol, given in combination or separately, were effects associated with exaggerated pharmacological activity.

In animal reproduction studies, corticosteroids such as budesonide have been shown to induce malformations (cleft palate, skeletal malformations). However, these animal experimental results do not seem to be relevant in humans at the recommended doses. Animal reproduction studies with formoterol have shown a somewhat reduced fertility in male rats at high systemic exposure and implantation losses as well as decreased early postnatal survival and birth weight at considerably higher systemic exposures than those reached during clinical use. However, these animal experimental results do not seem to be relevant in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone (PVP) K 25
Polyethylene glycol (PEG) 1000
HFA 227 ea Pharma Grade

6.2 Incompatibilities

None.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at room temperature below 25°C. Protect from frost and direct sunlight.
Do not puncture the aerosol can and do not bring it close to fire.

6.5 Nature and contents of container

Aluminum tube with metering valve placed in plastic sprayer (actuator) with dust cap.

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 Küçükçekmese – ISTANBUL/TURKEY

8. MARKETING AUTHORIZATION NUMBER

2017/938

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization: 19.12.2017
Date of last renewal: -

10. DATE OF REVISION OF THE TEXT

18.11.2020