1 NAME OF THE MEDICINAL PRODUCT

DuoResp® Spiromax® Dry powder for inhalation 160 mcg/4.5 mcg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each delivered dose (the dose that leaves the mouthpiece of the Spiromax) contains 160 micrograms of budesonide and 4.5 micrograms of formoterol fumarate dihydrate.

This is equivalent to a metered dose of 200 micrograms budesonide and 6 micrograms of formoterol fumarate dihydrate.

Excipient(s) with known effect:

Each dose contains approximately 5 milligrams of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Inhalation powder.
White powder.
White inhaler with a semi-transparent wine red mouthpiece cover.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Asthma
DuoResp Spiromax is indicated in the treatment of asthma to achieve overall asthma control, including the prevention and relief of symptoms as well as the reduction of the risk of exacerbations.

DuoResp Spiromax is indicated for treatment of asthma, where the use of inhaled corticosteroids is appropriate.

Chronic Obstructive Pulmonary Disease (COPD)
Symptomatic treatment of patients with COPD with FEV1 <70% predicted normal (post-bronchodilator) and a history of repeated exacerbations, despite regular long-acting bronchodilator therapy (see section Special warnings and precautions for use).

4.2 Posology and method of administration

The dosage of DUORESP SPIROMAX should be individualised according to disease severity.

Asthma
DuoResp Siromax can be used according to different treatment approaches:
A. DuoResp anti-inflammatory reliever therapy.
B. DuoResp anti-inflammatory reliever plus maintenance therapy.

As an alternative, DuoResp can be used in a fixed dose therapy:
C. DuoResp maintenance therapy.

DuoResp anti-inflammatory reliever therapy (patients with mild disease):
DuoResp is taken as needed for the relief of asthma symptoms when they occur, and to prevent allergen- or exercise- induced bronchoconstriction (or to prevent symptoms in those circumstances recognised by the patient to precipitate an asthma attack). The formoterol component in DuoResp Spiromax provides fast onset of effect (within 1-3 minutes) with long-acting (at least 12 hours after a single dose) bronchodilation in reversible airways obstruction. Patients should be advised to always have DuoResp available for relief of symptoms.

Clinical studies have demonstrated that DuoResp anti-inflammatory reliever therapy provides significant reductions in severe exacerbations and was statistically superior on daily asthma symptom control compared to a short-acting β_2 agonist therapy alone (see section Pharmacodynamic properties). Asthma symptom control was inferior for DuoResp as needed compared to a maintenance dose of corticosteroid given with as needed short-acting β_2 agonist.

Recommended doses:
Physicians should discuss allergen exposure and exercise patterns with the patients and take these into consideration when recommending the dose frequency.

Adults and adolescents (12 years and older): Patients should take 1 inhalation as needed in response to symptoms and for the prevention of allergen- or exercise-induced bronchoconstriction to control asthma. If symptoms persist after a few minutes, an additional inhalation should be taken. Not more than 6 inhalations should be taken on any single occasion.

A total daily dose of more than 8 inhalations is normally not needed, however a total daily dose of up to 12 inhalations can be used temporarily. Patients using more than 8 inhalations daily should be reassessed for alternative explanations of persisting symptoms.

Children under 12 years: Efficacy and safety of DuoResp anti-inflammatory reliever therapy in children under 12 years have not been studied.

DuoResp anti-inflammatory reliever plus maintenance therapy:
When maintenance treatment with a combination of inhaled corticosteroid and long-acting β_2 agonist is required, DuoResp is taken as anti-inflammatory reliever therapy and in addition, patients take a daily maintenance dose of DuoResp. The as needed inhalations provide both rapid relief of symptoms and improved overall asthma control. Patients should be advised to have DuoResp available for relief of symptoms at all times. A separate inhaler for relief of symptoms is not necessary.

Clinical studies have demonstrated that DuoResp anti-inflammatory reliever plus maintenance therapy provides clinically meaningful reductions in severe exacerbations while maintaining symptom control, compared to DuoResp maintenance therapy with a separate short-acting bronchodilator (see section Pharmacodynamic properties).

Recommended doses:
Physicians should discuss allergen exposure and exercise patterns with the patients and take these into consideration when recommending the dose frequency.

Adults and adolescents (12 years and older): Patients should take 1 inhalation as needed in response to symptoms and for the prevention of allergen- or exercise-induced bronchoconstriction to control asthma. If symptoms persist after a few minutes, an additional inhalation should be taken. Not more than 6 inhalations should be taken on any single occasion. Patients also take the recommended maintenance dose, which is 2 inhalations per day, given either as one inhalation in the morning and evening or as 2 inhalations in either the morning or the evening. For some patients, a maintenance dose of 2 inhalations twice daily may be appropriate.

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

Children under 12 years: DuoResp anti-inflammatory reliever plus maintenance therapy is not recommended for children under 12 years.

DuoResp maintenance therapy (fixed dose):
When maintenance treatment with a combination of inhaled corticosteroid and long-acting β_2 agonist is required, DuoResp is taken as a fixed daily dose treatment, with a separate short-acting bronchodilator for relief of symptoms. Patients should be advised to have their separate short-acting bronchodilator available for relief of symptoms 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. During worsening of asthma, the dose may temporarily be increased to a maximum of 4 inhalations twice daily.

COPD
Adults: 2 inhalations twice daily.

General information
If patients take DuoResp as a maintenance therapy, they should be instructed to take the maintenance dose of DuoResp Spiromax even when asymptomatic for optimal benefit.

Special patient groups: There is no need to adjust the dose in elderly patients. There are no data available for use of DuoResp Spiromax 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.

Method of administration
Inhalation use.

Spiromax is a breath actuated, inspiratory flow-driven inhaler, which means that the active substances are delivered into the airways when the patient inhales through the mouthpiece.

DuoResp Spiromax should be used correctly in order to achieve effective treatment. As such, the patients should be advised to read the patient information leaflet carefully and follow the instructions for use as detailed in the leaflet.

The use of DuoResp Spiromax follows three simple steps: open, breathe and close which are outlined below.

Open: Hold the Spiromax with the mouthpiece cover at the bottom and open the mouthpiece cover by folding it down until it is fully opened when one click is heard.

Breathe: Place the mouthpiece between the teeth with the lips closed around the mouthpiece, do not bite the mouthpiece of the inhaler. Breathe in forcefully and deeply through the mouthpiece. Remove the Spiromax from mouth and hold the breath for 10 seconds or as long as comfortable for the patients.

Close: Breathe out gently and close the mouthpiece cover.

It is also important to advise patients not to shake the inhaler before use and not to breathe out through the Spiromax and not to block the air vents when they are preparing the "Breathe" step.

Patients should also be advised to rinse their mouth with water after inhaling (see section 4.4)

The patient may notice a taste when using DuoResp Spiromax due to the lactose excipient.

4.3 Contraindications

Hypersensitivity to the active substances or the excipient listed in section 6.1.

4.4 Special warnings and precautions for use

General
It is recommended that the maintenance dose is tapered when the treatment is discontinued and the dosing should not be stopped abruptly. Complete withdrawal of inhaled corticosteroids should not be considered unless it is temporarily required to confirm the diagnosis of asthma.

If patients find the treatment ineffective, or exceed the highest recommended dose of DuoResp Spiromax, medical attention must be sought (see section 4.2). Sudden and progressive deterioration in control of asthma or COPD is potentially life-threatening 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. For treatment of severe exacerbations, a combination product of inhaled corticosteroid and long-acting β_2 agonist alone is not sufficient.

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

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

Asthma symptoms
Patients should be reassessed regularly by their prescriber/healthcare provider so that the dose of DuoResp Spiromax remains optimal. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of DuoResp Spiromax. When it is appropriate to titrate down to a lower strength than is available for DuoResp Spiromax, a change to an alternative fixed-dose combination of budesonide and formoterol fumarate containing a lower dose of the inhaled corticosteroid is required.

Regular review of patients as treatment is stepped down is important.

Patients should not be initiated on DuoResp Spiromax during an exacerbation, or if they have significantly worsening or acutely deteriorating asthma.

Serious asthma-related adverse reactions and exacerbations may occur during treatment with DuoResp Spiromax. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation with DuoResp Spiromax.

There are no clinical study data on DuoResp Spiromax available in COPD patients with a pre-bronchodilator FEV_1 >50% predicted normal and with a post-bronchodilator FEV1 <70% predicted normal (see section 5.1).

Paradoxical bronchospasm may occur, with an immediate increase in wheezing and shortness of breath, after dosing. If the patient experiences paradoxical bronchopasm DuoResp Spiromax 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
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) (see section 4.8).

Visual disturbance
Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Paediatric population
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. 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 paediatric 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.

Effects on bone density
Potential effects on bone density should be considered, particularly in patients on high doses for prolonged periods that have co-existing risk factors for osteoporosis.

Long-term studies with inhaled budesonide in children at mean daily doses of 400 micrograms (metered dose) or in adults at daily doses of 800 micrograms (metered dose) have not shown any significant effects on bone mineral density. No information regarding the effect of a budesonide/formoterol fumarate dihydrate fixed-dose combination at higher doses is available.

Adrenal function
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 a budesonide/formoterol fumarate fixed-dose combination therapy.

The benefits of inhaled budesonide therapy would normally minimise 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 hypothalamic pituitary adrenocortical (HPA) axis function should be monitored regularly.

High dose corticosteroids
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 hypoglycaemia.

Treatment with supplementary systematic steroids or inhaled budesonide should not be stopped abruptly.

Transfer from oral therapy
During transfer from oral therapy to a budesonide/formoterol fumarate fixed-dose combination therapy, 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.

Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

Oral infections
To minimise the risk of oropharyngeal candida infection, the patient should be instructed to rinse their mouth out with water after inhaling the dose. If oropharyngeal thrush occurs, patients should also rinse their mouth with water after the as-needed inhalations.

COPD population
There are no clinical study data on Budesonide/Formoterol available in COPD patients with a pre-bronchodilator FEV1 >50% predicted normal and with a post-bronchodilator FEV1 <70% predicted normal (see section Pharmacodynamic properties).

Clinical studies and meta-analyses indicate that treatment of COPD with inhaled corticosteroids may lead to an increased risk of pneumonia. However, the absolute risk for budesonide is small. A meta-analysis of 11 COPD double blind trials including 10,570 patients did not demonstrate a statistically significant increased risk of pneumonia in patients treated with budesonide (with or without formoterol) compared to non-budesonide containing treatments (placebo or formoterol). The incidence rate of pneumonia reported as a serious adverse event was 1.9% per year on budesonide containing treatments and 1.5% per year on non-budesonide containing treatments. The pooled hazard ratio comparing all budesonide-containing versus non-budesonide containing treatments was 1.15 (95% CI: 0.83, 1.57). The pooled hazard ratio comparing budesonide/formoterol versus formoterol or placebo was 1.00 (95% CI: 0.69, 1.44). A causal relationship with budesonide-containing products has not been established.

Interaction with other medicinal products
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 medicinal products should be as long as possible. In patients using potent CYP3A4 inhibitors, a budesonide/formoterol fumarate fixed-dose combination is not recommended.

Caution with special diseases
A fixed-dose combination of budesonide and formoterol fumarate dihydrate should be administered with caution in patients with thyrotoxicosis, phaeochromocytoma, diabetes mellitus, untreated hypokalaemia, hypertrophic obstructive cardiomyopathy, idiopathic subvalvular aortic stenosis, severe hypertension, aneurysm or other severe cardiovascular disorders, such as ischaemic 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, and dose of inhaled corticosteroids should be re-evaluated in patients with active or quiescent pulmonary tuberculosis, fungal and viral infections in the airways.

Additional blood glucose controls should be considered in diabetic patients.

β_2 adrenoreceptor agonists
Potentially serious hypokalaemia may result from high doses of β_2 adrenoceptor agonists. Concomitant treatment of β_2 adrenoceptor agonists with medicinal products which can induce hypokalaemia or potentiate a hypokalaemic effect, e.g. xanthine-derivatives, steroids and diuretics, may add to a possible hypokalaemic effect of the β_2 adrenoceptor agonist.

Treatment with β_2 adrenoceptor agonists may result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies.

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 hypokalaemia is increased. It is recommended that serum potassium levels are monitored during these circumstances.

Excipients
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. The excipient lactose contains small amounts of milk proteins which may cause allergic reactions.

4.5 Interaction 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 (see section 4.4). In patients using potent CYP3A4 inhibitors, a fixed-dose combination of budesonide and formoterol fumarate dihydrate 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 3 mg) on average six-fold. When ketoconazole was administered 12 hours after budesonide the concentration was on average increased only three-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 increases in plasma levels (on average four fold) may occur if itraconazole, 200 mg once daily, is administered concomitantly with inhaled budesonide (single dose of 1000 micrograms).

Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects.

Pharmacodynamic interactions
β adrenergic blockers can weaken or inhibit the effect of formoterol. A fixed-dose combination therapy of budesonide and formoterol fumarate dihydrate should therefore not be given together with β 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 β_2 sympathomimetics.

Concomitant treatment with monoamine oxidase inhibitors including medicinal products with similar properties such as furazolidone and procarbazine may precipitate hypertensive reactions.

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

Concomitant use of other β adrenergic medicinal products and anticholinergic medicinal products can have a potentially additive bronchodilating effect.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy
For a fixed-dose combination therapy of budesonide and formoterol fumarate dihydrate or the concomitant treatment with formoterol and budesonide, no clinical data on exposed pregnancies are available. Data from an embryo-fetal development study in the rat, showed no evidence of any additional effect from the combination.

There are no adequate data from use of formoterol in pregnant women. In animal studies formoterol has caused adverse reactions in reproduction studies 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 behaviour at exposures below the teratogenic dose range.

During pregnancy, a fixed-dose combination therapy of budesonide and formoterol fumarate dihydrate 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.

Breast-feeding
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 a fixed-dose combination therapy of budesonide and formoterol fumarate dihydrate to women who are breast-feeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

Fertility
There is no data available on the potential effect of budesonide on fertility. Animal reproduction studies with formoterol have shown a somewhat reduced fertility in male rats at high systemic exposure (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of safety profile
Since DuoResp Spiromax contains both budesonide and formoterol, the same pattern of adverse reactions 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 adverse reactions are pharmacologically predictable adverse reactions of β_2 adrenoceptor agonist therapy, such as tremor and palpitations. These tend to be mild and usually disappear within a few days of treatment. In a 3-year clinical trial with budesonide in COPD, skin bruises and pneumonia occurred at a frequency of 10% and 6%, respectively, compared with 4% and 3% in the placebo group ($p<0.001$ and $p<0.01$, respectively).

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

System Organ Class	Frequency	Adverse reaction
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, adrenal suppression, growth retardation, decrease in bone mineral density
Metabolism and nutrition disorders	Rare	Hypokalaemia
	Very rare	Hyperglycaemia
Psychiatric disorders	Uncommon	Agitation, psychomotor hyperactivity, anxiety, sleep disorders
	Very rare	Depression, behavioural changes (predominantly in children)
Nervous system disorders	Common	Headache, tremor
	Uncommon	Dizziness
	Very rare	Taste disturbances
Eye disorders	Very rare	Cataract and glaucoma
	Uncommon	Vision, blurred (see also section 4.4)
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
	Very rare	Paradoxical bronchospasm
Gastrointestinal disorders	Uncommon	Nausea
Skin and subcutaneous tissue disorders	Uncommon	Bruises
Musculoskeletal and connective tissue disorders	Uncommon	Muscle cramps

Description of selected adverse reactions
Candida infection in the oropharynx is due to active substance deposition. Advising the patient to rinse the mouth out with water after each dose will minimise the risk. Oropharyngeal Candida infection usually responds to topical anti-fungal treatment without the need to discontinue the inhaled corticosteroid.

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. DuoResp Spiromax should be discontinued immediately, the patient should be assessed and an alternative therapy is instituted if necessary (see section 4.4).

Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing´s syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. 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 β_2 adrenoceptor agonists may result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 Overdose

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

Acute overdose 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 DuoResp Spiromax therapy has to be withdrawn due to overdose of the formoterol component of the medicinal product, provision of appropriate inhaled corticosteroid therapy must be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action and pharmacodynamic effects
DuoResp Spiromax 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 either as maintenance and reliever therapy, or as maintenance treatment of asthma. The mechanisms of action of the two substances respectively are discussed below.

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

Formoterol
Formoterol is a selective β_2 adrenoceptor 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-dependant, 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 as an anti-inflammatory reliever: anti- inflammatory reliever therapy (therapy A) and anti-inflammatory reliever plus maintenance therapy (therapy B) in asthma (see section Posology and method of administration)
Overall, 20140 asthma patients were included in 7 double-blind clinical studies, of which 7831 were randomised to a therapy which included Budesonide/Formoterol as an anti- inflammatory reliever, both with a maintenance (therapy B) and without a maintenance dosing (therapy A).

A total of 8064 asthma patients with mild asthma were included in 2 double-blind efficacy and safety studies (SYGMA 1 and SYGMA 2 studies), of which 3384 patients were randomised to Budesonide/Formoterol anti-inflammatory reliever therapy (therapy A) for 12 months. Patients were required to be uncontrolled on only short-acting inhaled bronchodilator as needed or controlled on a low dose of inhaled corticosteroids or LTRA (leukotriene receptor antagonist) plus short-acting inhaled bronchodilator as needed.

In the SYGMA 2 study, Budesonide/Formoterol 160/4.5 micrograms used as needed in response to symptoms (anti-inflammatory reliever therapy – therapy A) was comparable to a maintenance dose of budesonide (1 inhalation of 200 micrograms/inhalation twice daily) given with as-needed short-acting β_2 agonist in terms of the rate of severe exacerbations (Table 2). Protection against severe exacerbation was achieved with a 75% reduction in median inhaled steroid load and without requiring adherence to maintenance inhaled corticosteroids treatment. The SYGMA 1 study showed that Budesonide/Formoterol anti-inflammatory reliever therapy provided statistically significant and clinically meaningful reduction in the rate of annual severe exacerbation by 64% compared with as-needed use of a short-acting β_2 agonist (Table 2). Reduction in the annual rate of moderate to severe exacerbations was consistent (60%) with that observed for severe exacerbations ([RR] 0.40, 95% CI 0.32 to 0.49, p-value <0.001).

In the SYGMA 1 study, as-needed use of Budesonide/Formoterol 160/4.5 micrograms provided superior daily asthma symptom control compared to as-needed short-acting β_2 agonist (OR 1.14, 95% CI 1.00 to 1.30, p-value 0.046), showing a mean percentage of weeks with well-controlled asthma of 34.4% and 31.1%, respectively. Asthma symptom control was inferior for Budesonide/Formoterol as needed compared to a maintenance dose of budesonide (1 inhalation of 200 micrograms/inhalation twice daily) given with as- needed short-acting β_2 agonist (OR 0.64, 2-sided 95% CI 0.57 to 0.73, lower limit of the CI ≥ 0.8 for non-inferiority), showing a mean percentage of well-controlled asthma weeks of 34.4% and 44.4%, respectively. Improvements in asthma control (as defined by ACQ5) in patients using Budesonide/Formoterol anti-inflammatory reliever therapy were superior to improvements in patients using a short-acting β_2 agonist as needed (-0.15, 95% CI -0.20 to -0.11, p-value <0.001). Improvements in asthma control were lower for Budesonide/Formoterol as needed compared to a maintenance dose of budesonide (1 inhalation of 200 micrograms/inhalation twice daily) given with a short-acting β_2 agonist to be used as needed (SYGMA 1: 0.15, 95% CI 0.10 to 0.20; SYGMA 2: 0.11, 95% CI 0.07 to 0.15, both p-value <0.001). For both comparisons, mean differences in treatments' effect upon ACQ5 are not clinically meaningful (as assessed by a difference of greater than or equal to 0.5). These results were observed in a clinical study setting with considerably higher adherence to budesonide maintenance dosing than expected in real life.

In the SYGMA studies, increases in lung function compared to baseline (mean pre- bronchodilator FEV1) were statistically significantly larger for patients on Budesonide/Formoterol anti-inflammatory reliever therapy compared to patients on as-needed short-acting β_2 agonist treatment. Statistically significantly smaller increases were observed for Budesonide/Formoterol as needed compared to a maintenance dose of budesonide (1 inhalation of 200 micrograms/inhalation twice daily) given with a short-acting β_2 agonist to be used as needed. For both comparisons, mean differences in treatments' effect were small (approximately 30 to 55 mL, equating to approximately 2% of the baseline mean).

Overall, the results of the SYGMA studies show that Budesonide/Formoterol anti-inflammatory reliever therapy is a more effective treatment than a short-acting β_2 agonist as needed in patients with mild asthma. In addition, these studies suggest that the as-needed use of Budesonide/Formoterol may be considered an alternative treatment option for patients with mild asthma who are eligible for inhaled corticosteroid treatment.

In a separate clinical programme, a total of 12076 asthma patients were included in 5 double-blind efficacy and safety studies (4447 were randomised to Budesonide/Formoterol anti- inflammatory reliever plus maintenance therapy – therapy B) for 6 or 12 months. Patients were required to be symptomatic despite use of inhaled glucocorticosteroids.

Budesonide/Formoterol anti-inflammatory reliever plus maintenance 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 2). 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 anti-inflammatory reliever plus maintenance therapy used, on average, no reliever inhalations on 57% of treatment days. There was no sign of development of tolerance over time.

Table 2 Overview of severe exacerbations in clinical studies

Study No. Duration	Treatment groups[a]	N	Severe exacerbations[b]	
			Events	Events/ patient-year[c]
SYGMA 1 (Therapy A[*]) >12 years	**Budesonide/Formoterol 160/4.5 µg as needed**	1277	77	0.07
	Terbutaline 0.4 mg as needed	1277	188	0.20[d]
	Budesonide 200 µg bd + terbutaline 0.4 mg as needed	1282	89	0.09[e]
SYGMA 2 (Therapy A[*]) >12 years	**Budesonide/Formoterol 160/4.5 µg as needed**	2084	217	0.11
	Budesonide 200 µg bd + terbutaline 0.4 mg as needed	2083	221	0.12[f]
6-month double-blind studies				
Study 735 (Therapy B[**]) 6 months	**Budesonide/Formoterol 160/4.5 µg bd + as needed**	**1103**	**125**	**0.23[***]**
	Budesonide/Formoterol 320/9 µg bd + terbutaline 0.4 mg as needed	1099	173	0.32
	Salmeterol/fluticasone 2 x 25/125 µg bd + terbutaline 0.4 mg as needed	1119	208	0.38
12-month double-blind studies				
Study 734 (Therapy B[**]) 12 months	**Budesonide/Formoterol 160/4.5 µg bd + as needed**	**1107**	**194**	**0.19[***]**
	Budesonide/Formoterol 160/4.5 µg bd + formoterol 4.5 µg as needed	1137	296	0.29
	Budesonide/Formoterol 160/4.5 µg bd + terbutaline 0.4 mg as needed	1138	377	0.37

[*] Budesonide/Formoterol anti-inflammatory reliever therapy.
[**] Budesonide/Formoterol anti-inflammatory reliever plus maintenance therapy.
[***] Reduction in exacerbation rate is statistically significant (p-value <0.01) (for both comparisons where applicable).
[a] All doses expressed as delivered dose. Budesonide 160 µg and 320 µg (delivered doses) correspond to Budesonide 200 µg and 400 µg (metered doses), respectively.
[b] Defined as hospitalisation/emergency room treatment or treatment with oral steroids due to asthma.
[c] Data normalised to 12 months for studies 735 and 734.
[d] Reduction in exacerbation rate is statistically significant (p-value <0.001) for the comparison of Budesonide/Formoterol as needed vs Terbutaline as needed.
[e] Reduction in exacerbation rate is not statistically significantly different (p-value 0.279) when comparing Budesonide/Formoterol as needed vs Budesonide 200 µg bd + terbutaline 0.4 mg as needed in SYGMA 1.
[f] Budesonide/Formoterol as needed was non-inferior to Budesonide 200 µg bd + terbutaline 0.4 mg as needed in reducing the severe exacerbation rate in SYGMA 2. The upper limit (1.16) of the 95% CI for the rate ratio (RR) was below the pre-specified non-inferiority limit (1.20).

Analysis of time to first severe exacerbation in the SYGMA 1 study showed that the likelihood of experiencing a severe exacerbation was statistically significantly higher for the as-needed use of a short-acting β_2 agonist compared to the as-needed use of Budesonide/Formoterol (Budesonide/Formoterol anti-inflammatory reliever therapy - therapy A) over the 1 year treatment period, with a risk reduction of 56% ([HR] 0.44, 95% CI: 0.33-0.58, p-value <0.001). There were no differences in the probability of experiencing a severe exacerbation between Budesonide/Formoterol anti-inflammatory reliever therapy (therapy A) and a therapy including a maintenance dose of budesonide (1 inhalation of 200 micrograms/inhalation twice daily) and a short-acting β_2 agonist used as needed.

In Study 735, Budesonide/Formoterol anti-inflammatory reliever plus maintenance therapy (therapy B) significantly prolonged the time to the first exacerbation compared to the other treatment groups. The rate of exacerbations was reduced by 28% compared to twice the maintenance dose of Budesonide/Formoterol with terbutaline as reliever. Lung function, symptom control, and reliever use were similar in all treatment groups.

In Study 734, Budesonide/Formoterol anti-inflammatory reliever plus maintenance therapy (therapy B) prolonged the time to the first exacerbation compared to Budesonide/Formoterol at the same maintenance dose with either formoterol or terbutaline as reliever. The rate of exacerbations was reduced by 33% and 48%, respectively. Symptoms and reliever use were reduced and lung function improved, compared with both comparator treatments.

In 2 separate 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.

Clinical Efficacy in asthma for Budesonide/Formoterol maintenance therapy (therapy C)
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 β_2-agonist as needed. There was no sign of attenuation of the anti-asthmatic effect over time.

In a 12-week paediatric study 85 children aged 6-11 years were treated with a maintenance dose of Budesonide/Formoterol (2 inhalations of 80/4.5 micrograms/inhalation twice daily), and a short-acting β_2-agonist as needed. Lung function was improved and the treatment was well tolerated compared to the corresponding dose of Budesonide Turbuhaler.

COPD
In two 12-month studies, the effect on lung function and the rate of exacerbation (defined as courses of oral steroids and/or course of antibiotics and/or hospitalisations) in patients with moderate to severe COPD was evaluated. Median FEV_1 at inclusion in the trials was 36% of predicted normal.

The mean number of exacerbations per year (as defined above) was significantly reduced with budesonide/formoterol as compared with treatment with formoterol alone or placebo (mean rate 1.4 compared with 1.8-1.9 in the placebo/formoterol group). The mean number of days on oral corticosteroids/patient during the 12 months was slightly reduced in the budesonide/formoterol group (7-8 days/patient/year compared with 11-12 and 9-12 days in the placebo and formoterol groups, respectively). For changes in lung-function parameters, such as FEV_1, budesonide/formoterol was not superior to treatment with formoterol alone.

5.2 Pharmacokinetic properties

Absorption
The fixed-dose combination of budesonide and formoterol, and the corresponding monoproducts 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 fixed-dose combination compared to the monoproducts. 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 monoproducts or as the fixed-dose combination. For budesonide, AUC was slightly higher, rate of absorption more rapid and maximal plasma concentration higher after administration of the fixed combination. For formoterol, maximal plasma concentration was similar after administration of the fixed 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 via the powder inhaler 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 via the powder inhaler ranged from 28% to 49% of the delivered dose. The systemic bioavailability is about 61% of the delivered dose.

Distribution and metabolism
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. 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-beta-hydroxy-budesonide and 16-alfa-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 catalysed 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 i.v. dosing averages 4 hours.

Pharmacokinetic/pharmacodynamic relationship(s)
The pharmacokinetics of budesonide or formoterol in patients with renal failure is unknown. The exposure of budesonide and formoterol may be increased in patients with liver disease.

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

Lactose monohydrate (which contains milk proteins).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please refer to expiry date on the outer carton.
After opening the foil wrap: 3 months.

6.4 Special precautions for storage

Do not store above 30 °C.
Keep the mouthpiece cover closed after removal of the foil wrap.

6.5 Nature and contents of container

The inhaler is white with a semi-transparent wine red mouthpiece cover.
The drug/mucosal contact parts of the inhaler are made of acrylonitrile butadiene styrene (ABS), polyethylene (PE), and polypropylene (PP). Each inhaler contains 120 doses and is foil-wrapped.

Pack sizes of 1, 2 or 3 inhalers.
Not all pack-sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MANUFACTURER

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