1 NAME OF THE MEDICINAL PRODUCT

DuoResp® Spiromax® Dry powder for inhalation 320 mcg/9 mcg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each delivered dose (the dose that leaves the mouthpiece of the Spiromax) contains 320 micrograms of budesonide and 9 micrograms of formoterol fumarate dihydrate.

This is equivalent to a metered dose of 400 micrograms budesonide and 12 micrograms of formoterol fumarate dihydrate.

Excipient(s) with known effect:

Each dose contains approximately 10 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 regular treatment of asthma, where use of a combination (inhaled corticosteroid and long-acting β_2 adrenoceptor agonist) is appropriate:

- in patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short-acting β_2 adrenoceptor agonists.

or

- in patients already adequately controlled on both inhaled corticosteroids and long-acting β_2 adrenoceptor agonists.

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

Posology

Asthma

DuoResp Spiromax is not intended for the initial management of asthma.

The dosage of the components of DuoResp Spiromax 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 an individual patient should require a combination of doses other than those available in the combination inhaler, appropriate doses of β_2-agonists and/or corticosteroids by individual inhalers should be prescribed.

Recommended doses:

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

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

Patients should be regularly reassessed by their prescriber/healthcare provider, so that the dosage of DuoResp Spiromax remains optimal. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. When control of symptoms is maintained with the lowest recommended dosage, then the next step could include a test of inhaled corticosteroid alone.

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

DuoResp Spiromax 320 micrograms/9 micrograms should be used as maintenance therapy only. A lower strength of DuoResp Spiromax is available for the maintenance and reliever therapy regimen.

COPD

Recommended doses:

Adults: 1 inhalation twice daily

General information

Special patient groups: There are no special dosing requirements for 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.

Moderate and severe asthmatic patients were shown to be able to generate sufficient inspiratory flow rate for Spiromax to deliver the therapeutic dose (see section 5.1).

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 dose is tapered when the treatment is discontinued and should not be stopped abruptly.

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.

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 FEV1 >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 bronchospasm 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 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.

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 as 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-adrenoceptor 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).

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.

Paediatric population

Interaction studies have only been performed in adults.

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 1.0% 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 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

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 β_2 adrenoceptor 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. The inclusion criteria for both studies was pre-bronchodilator FEV1 <50% predicted normal. Median post-bronchodilator FEV1 at inclusion in the trials was 42% 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 FEV1, 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. In children 6-16 years of age the lung deposition falls in the same range as in adults for the same given dose. The resulting plasma concentrations were not determined (see paediatric population sub-heading in section 4.2).

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 children and patients with renal failure are 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 60 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

Norton (Waterford) Limited T/A
Teva Pharmaceuticals Ireland
Unit 27/35, IDA Industrial Park,
Cork Road, Waterford, Ireland.

8 DATE OF REVISION OF THE TEXT

09-2020

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