

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DuoResp Spiromax 160 micrograms / 4.5 micrograms inhalation powder

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

DuoResp Spiromax is indicated in adults 18 years of age and older only.

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.

COPD

Symptomatic treatment of patients with COPD with forced expiratory volume in 1 second (FEV₁) < 70% predicted normal and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators.

4.2 Posology and method of administration

DuoResp Spiromax is indicated in adults 18 years of age and older only.

DuoResp Spiromax is not indicated for use in children, 12 years of age and younger or adolescents, 13 to 17 years of age.

Posology

Asthma

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

DuoResp Spiromax is not an appropriate treatment for the adult patient with only mild asthma who is not adequately controlled with an inhaled corticosteroid and “as needed” inhaled short-acting β_2 adrenoreceptor agonists.

The dosage 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 medicinal 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 adrenoreceptor agonists and/or corticosteroids by individual inhalers should be prescribed.

Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of DuoResp Spiromax. Patients should be reassessed regularly by their prescriber/health care 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.

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. When long-term control of symptoms is maintained with the lowest recommended dose, 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 dose regimen with a lower strength product, titration to a lower effective dose could include once daily dosing when, in the opinion of the prescriber, a long-acting bronchodilator is required to maintain control rather than treatment with an inhaled corticosteroid alone.

For DuoResp Spiromax there are two treatment approaches:

DuoResp Spiromax maintenance therapy: DuoResp Spiromax is taken as regular maintenance treatment with a separate rapid-acting bronchodilator reliever inhaler.

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

DuoResp Spiromax maintenance therapy

Patients should be advised to have their separate rapid-acting bronchodilator reliever inhaler 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.

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

DuoResp Spiromax maintenance and reliever therapy

Patients take a daily maintenance dose of DuoResp Spiromax and in addition take DuoResp Spiromax as needed in response to symptoms. Patients should be advised to always have DuoResp Spiromax available for rescue use.

DuoResp Spiromax maintenance and reliever therapy should especially be considered for patients with:

- inadequate asthma control and in frequent need of a reliever inhaler.
- asthma exacerbations in the past requiring medical intervention.

Close monitoring for dose-related adverse reactions is needed in patients who frequently take high numbers of DuoResp Spiromax as-needed inhalations.

Recommended doses:

Adults (18 years and older): The recommended maintenance dose is 2 inhalations per day, given either as one inhalation in the morning and evening or as 2 inhalations in either the morning or evening. For some patients a maintenance dose of 2 inhalations twice daily may be appropriate. Patients should take 1 additional inhalation as needed in response to symptoms. 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 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.

COPD

Recommended doses:

Adults (18 years and older): 2 inhalations twice daily

Special populations:

Elderly patients (≥ 65 years old)

There are no special dosing requirements for elderly patients.

Patients with renal or hepatic impairment

There are no data available for use of a fixed-dose combination of budesonide and formoterol fumarate dihydrate 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.

Paediatric population

The safety and efficacy of DuoResp Spiromax in children, 12 years and younger and adolescents, 13 to 17 years of age has not yet been established. No data are available.

This medicinal product is not recommended for use in children and adolescents under the age of 18 years.

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 $FEV_1 > 50\%$ predicted normal and with a post-bronchodilator $FEV_1 < 70\%$ 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).

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 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.

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.

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.

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.

Pneumonia in patients with COPD

An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, has been observed in patients with COPD receiving inhaled corticosteroids. There is some evidence of an increased risk of pneumonia with increasing steroid dose but this has not been demonstrated conclusively across all studies.

There is no conclusive clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products.

Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations.

Risk factors for pneumonia in patients with COPD include current smoking, older age, low body mass index (BMI) and severe COPD.

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 adrenoreceptor agonists. Concomitant treatment of β_2 adrenoreceptor 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 adrenoreceptor agonist.

Treatment with β_2 adrenoreceptor 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.

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 10% and 6%, respectively, compared with 4% and 3% in the placebo group ($p < 0.001$ and $p < 0.01$, respectively).

DuoResp Spiromax is not indicated in children and adolescents under the age of 18 years (see section 4.2).

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 ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1,000$, $< 1/100$), rare ($\geq 1/10,000$, $< 1/1,000$), 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	Aggression, 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. Healthcare professionals are asked to report any suspected adverse reactions via [the national reporting system listed in Appendix V](#).

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

Pharmacotherapeutic group: Drugs for obstructive airway diseases, adrenergics and other drugs for obstructive airway diseases.

ATC code: R03AK07

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

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.

Two 12-week paediatric studies have been performed in which 265 children aged 6-11 years were treated with a maintenance dose of budesonide/formoterol (2 inhalations of 80 micrograms /4.5 micrograms/inhalation twice daily), and a short acting β_2 adrenoceptor agonist as needed. In both studies, lung function was improved and the treatment was well tolerated compared to the corresponding dose of budesonide alone.

Budesonide/formoterol maintenance and reliever therapy

A total of 12076 asthma patients were included in 5 double-blind clinical studies (4447 were randomised 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) (see table below). 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.

Overview of severe exacerbations in clinical studies

Study No. Duration	Treatment groups	N	Severe exacerbations ^a	
			Events	Events/ patient-year
Study 735 6 months	Budesonide/Formoterol Furmarate Dihydrate 160/4.5 µg bd + as needed	1103	125	0.23^b
	Budesonide/Formoterol Furmarate Dihydrate 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
Study 734 12 months	Budesonide/Formoterol Furmarate Dihydrate 160/4.5 µg bd + as needed	1107	194	0.19^b
	Budesonide/Formoterol Furmarate Dihydrate 160/4.5 µg bd + formoterol 4.5 µg as needed	1137	296	0.29
	Budesonide/Formoterol Furmarate Dihydrate 160/4.5 µg bd + terbutaline 0.4 mg as needed	1138	377	0.37

^a Hospitalisation/emergency room treatment or treatment with oral steroids

^b Reduction in exacerbation rate is statistically significant (P value <0.01) for both comparisons

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.

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 severe COPD was evaluated. Median FEV₁ 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 FEV₁, budesonide/formoterol was not superior to treatment with formoterol alone.

Peak Inspiratory Flow Rate through the Spiromax Device

A randomised, open-label placebo study was performed in children and adolescents with asthma (aged 6-17 years), adults with asthma (aged 18-45 years), adults with chronic obstructive pulmonary disease (COPD – aged >50 years) and healthy volunteers (aged 18-45 years) to evaluate the peak inspiratory flow rate (PIFR) and other related inhalation parameters following inhalation from a Spiromax device (containing placebo) compared with inhalation from an already marketed multi-dose dry powder inhaler device (containing placebo). The impact of enhanced training in dry powder inhaler inhalation technique on inhalation speed and volume was also assessed in these subject groups. The data from the study indicated that regardless of age and underlying disease severity, children, adolescents and adults with asthma as well as patients with COPD were able to achieve inspiratory flow rates through the Spiromax device that were similar to those generated through the marketed multi-dose dry powder inhaler device. The mean PIFR achieved by patients with asthma or COPD was over 60L/min, a flow rate at which both devices studied are known to deliver comparable amounts of drug to the lungs. Very few patients had PIFRs below 40L/min; when PIFRs were less than 40L/min there appeared to be no clustering by age or disease severity.

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.

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

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 deformedylated 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.

DuoResp Spiromax pharmacokinetic profile

In pharmacokinetic studies with and without a charcoal blockage, DuoResp Spiromax was evaluated by comparing it with an alternative authorised fixed-dose combination inhaled product containing the same active substances, budesonide and formoterol and has been shown to be equivalent in both systemic exposure (safety) and pulmonary deposition (efficacy).

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.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

After opening the foil wrap: 6 months.

6.4 Special precautions for storage

Do not store above 25°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. MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Swensweg 5, 2031GA Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/920/001
EU/1/14/920/002
EU/1/14/920/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28th April 2014
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.com>

1. NAME OF THE MEDICINAL PRODUCT

DuoResp Spiromax 320 micrograms/9 micrograms inhalation powder

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

DuoResp Spiromax is indicated in adults 18 years of age and older only.

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.

COPD

Symptomatic treatment of patients with COPD with forced expiratory volume in 1 second (FEV₁) < 70% predicted normal and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators.

4.2 Posology and method of administration

DuoResp Spiromax is indicated in adults 18 years of age and older only.

DuoResp Spiromax is not indicated for use in children, 12 years of age and younger or adolescents, 13 to 17 years of age.

Posology

Asthma

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

DuoResp Spiromax is not an appropriate treatment for the adult patient with only mild asthma who is not adequately controlled with an inhaled corticosteroid and “as needed” inhaled short-acting β_2 adrenoreceptor agonists.

The dosage 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 medicinal 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 adrenoreceptor agonists and/or corticosteroids by individual inhalers should be prescribed.

Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of DuoResp Spiromax. Patients should be reassessed regularly by their prescriber/health care 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.

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. When long-term control of symptoms is maintained with the lowest recommended dose, 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 dose regimen with a lower strength product, titration to a lower effective dose could include once daily dosing when, in the opinion of the prescriber, a long-acting bronchodilator is required to maintain control rather than treatment with an inhaled corticosteroid alone.

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

Recommended doses:

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

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

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 (18 years and older):

1 inhalation twice daily

Special populations:

Elderly patients (≥ 65 years old)

There are no special dosing requirements for elderly patients.

Patients with renal or hepatic impairment

There are no data available for use of a fixed-dose combination of budesonide and formoterol fumarate dihydrate 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.

Paediatric population

The safety and efficacy of DuoResp Spiromax in children, 12 years and younger and adolescents, 13 to 17 years of age has not yet been established. No data are available.

This medicinal product is not recommended for use in children and adolescents under the age of 18 years.

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).

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 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.

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.

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.

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.

Pneumonia in patients with COPD

An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, has been observed in patients with COPD receiving inhaled corticosteroids. There is some evidence of an increased risk of pneumonia with increasing steroid dose but this has not been demonstrated conclusively across all studies.

There is no conclusive clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products.

Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations.

Risk factors for pneumonia in patients with COPD include current smoking, older age, low body mass index (BMI) and severe COPD.

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 adrenoreceptor agonists. Concomitant treatment of β_2 adrenoreceptor 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 adrenoreceptor agonist.

Treatment with β_2 adrenoreceptor 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.¹

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 10% and 6%, respectively, compared with 4% and 3% in the placebo group ($p < 0.001$ and $p < 0.01$, respectively).

DuoResp Spiromax is not indicated in children and adolescents under the age of 18 years (see section 4.2).

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 ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1,000$, $< 1/100$), rare ($\geq 1/10,000$, $< 1/1,000$), 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	Aggression, 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. Healthcare professionals are asked to report any suspected adverse reactions via [the national reporting system listed in Appendix V](#).

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

Pharmacotherapeutic group: Drugs for obstructive airway diseases, adrenergics and other drugs for obstructive airway diseases.

ATC code: R03AK07

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.

Two 12-week paediatric studies have been performed in which 265 children aged 6-11 years were treated with a maintenance dose of budesonide/formoterol (2 inhalations of 80 micrograms/4.5 micrograms/inhalation twice daily), and a short acting β_2 adrenoceptor agonist as needed. In both studies, lung function was improved and the treatment was well tolerated compared to the corresponding dose of budesonide alone.

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 severe COPD was evaluated.

Median FEV₁ 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 FEV₁, budesonide/formoterol was not superior to treatment with formoterol alone.

Peak Inspiratory Flow Rate through the Spiromax Device

A randomised, open-label placebo study was performed in children and adolescents with asthma (aged 6-17 years), adults with asthma (aged 18-45 years), adults with chronic obstructive pulmonary disease (COPD – aged >50 years) and healthy volunteers (aged 18-45 years) to evaluate the peak inspiratory flow rate (PIFR) and other related inhalation parameters following inhalation from a Spiromax device (containing placebo) compared with inhalation from an already marketed multi-dose dry powder inhaler device (containing placebo). The impact of enhanced training in dry powder inhaler inhalation technique on inhalation speed and volume was also assessed in these subject groups. The data from the study indicated that regardless of age and underlying disease severity, children, adolescents and adults with asthma as well as patients with COPD were able to achieve inspiratory flow rates through the Spiromax device that were similar to those generated through the marketed multi-dose dry powder inhaler device. The mean PIFR achieved by patients with asthma or COPD was over 60L/min, a flow rate at which both devices studied are known to deliver comparable amounts of drug to the lungs. Very few patients had PIFRs below 40L/min; when PIFRs were less than 40L/min there appeared to be no clustering by age or disease severity.

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.

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

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 deformedylated 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.

DuoResp Spiromax pharmacokinetic profile

In pharmacokinetic studies with and without a charcoal blockage, DuoResp Spiromax was evaluated by comparing it with an alternative authorised fixed-dose combination inhaled product containing the same active substances, budesonide and formoterol and has been shown to be equivalent in both systemic exposure (safety) and pulmonary deposition (efficacy).

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.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

After opening the foil wrap: 6 months.

6.4 Special precautions for storage

Do not store above 25°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. MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.

Swensweg 5, 2031GA HaarlemThe Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/920/004

EU/1/14/920/005

EU/1/14/920/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28th April 2014

Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.com>

ANNEX II

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

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

Teva Pharmaceuticals Europe B.V.
Swensweg 5
NL-2031 GA Haarlem
The Netherlands

(For Poland only)
Teva Operations Poland Sp. z o.o.
Mogilska 80 Str. 31-546 Kraków
Poland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal products subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

DuoResp Spiromax 160 micrograms /4.5 micrograms inhalation powder

budesonide / formoterol fumarate dihydrate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Side panel: Each delivered dose contains 160 micrograms of budesonide and 4.5 micrograms of formoterol fumarate dihydrate.

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

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

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder

1 inhaler containing 120 doses.

2 inhalers each containing 120 doses.

3 inhalers each containing 120 doses.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Inhalation use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Front panel: Not for use in children and adolescents.

Side panel: For use in adults 18 years of age and older only.

Not for use in children or adolescents under 18 years of age.

8. EXPIRY DATE

EXP

Use the product within 6 months of removing from foil wrapping.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C. Keep the mouthpiece cover closed after the removal of foil wrap.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva Pharma B.V., Swensweg 5, 2031GA Haarlem, The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/920/001

EU/1/14/920/002

EU/1/14/920/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

DuoResp Spiromax 160 mcg/4.5 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>]

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:

SN:

NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS FOIL
--

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION
--

DuoResp Spiromax 160 micrograms / 4.5 micrograms inhalation powder

budesonide/ formoterol fumarate dihydrate

Inhalation use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT
--

Contains 1 inhaler.

6. OTHER

Keep the mouthpiece cover closed and use within 6 months of removing from foil wrapping.

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MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
INHALER

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

DuoResp Spiromax 160 mcg/4.5 mcg inhalation powder

budesonide/formoterol fumarate dihydrate

Inhalation use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

120 doses

6. OTHER

Start

Teva Pharma B.V.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

DuoResp Spiromax 320 micrograms/9 micrograms inhalation powder

budesonide/formoterol fumarate dihydrate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Side panel: Each delivered dose contains 320 micrograms of budesonide and 9 micrograms of formoterol fumarate dihydrate.

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

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

3. LIST OF EXCIPIENTS

Contains lactose. **See leaflet for further information**

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder

1 inhaler containing 60 doses.

2 inhalers each containing 60 doses.

3 inhalers each containing 60 doses.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Inhalation use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Front panel: Not for use in children and adolescents.

Side panel: For use in adults 18 years of age and older only.
Not for use in children or adolescents under 18 years of age.

8. EXPIRY DATE

EXP

Use the product within 6 months of removing from foil wrapping.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C. Keep the mouthpiece cover closed after the removal of foil wrap.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Teva Pharma B.V., Swensweg 5, 2031GA Haarlem, The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/920/004

EU/1/14/920/005

EU/1/14/920/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

DuoResp Spiromax 320 mcg/9 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>]

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:

SN:

NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS FOIL
--

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION
--

DuoResp Spiromax 320 micrograms/9 micrograms inhalation powder

budesonide/formoterol fumarate dihydrate

Inhalation use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT
--

Contains 1 inhaler.

6. OTHER

Keep the mouthpiece cover closed and use within 6 months of removing from foil wrapping.

Teva Pharma B.V.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS INHALER

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION
--

DuoResp Spiromax 320 mcg/9 mcg inhalation powder

budesonide/formoterol fumarate dihydrate

Inhalation use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT
--

60 doses

6. OTHER

Start

Teva Pharma B.V.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

DuoResp Spiromax 160 micrograms/4.5 micrograms, inhalation powder (budesonide/formoterol fumarate dihydrate)

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What DuoResp Spiromax is and what it is used for
2. What you need to know before you use DuoResp Spiromax
3. How to use DuoResp Spiromax
4. Possible side effects
5. How to store DuoResp Spiromax
6. Contents of the pack and other information

1. What DuoResp Spiromax is and what it is used for

DuoResp Spiromax contains two different active substances: budesonide and formoterol fumarate dihydrate.

- Budesonide belongs to a group of medicines called ‘corticosteroids’ also known as ‘steroids’. It works by reducing and preventing swelling and inflammation in your lungs and helps you to breathe more easily.
- Formoterol fumarate dihydrate belongs to a group of medicines called ‘long-acting β_2 adrenoceptor agonists’ or ‘bronchodilators’. It works by relaxing the muscles in your airways. This will help to open the airways and help you to breathe more easily.

DuoResp Spiromax is indicated for use in adults 18 years of age and older only.

DuoResp Spiromax is NOT indicated for use in children 12 years of age and younger or adolescents 13 to 17 years of age.

Your doctor has prescribed this medicine to treat asthma or chronic obstructive pulmonary disease (COPD).

Asthma

DuoResp Spiromax can be prescribed for asthma in two different ways.

a) You may be prescribed two asthma inhalers: DuoResp Spiromax together with a separate ‘reliever inhaler’ such as salbutamol.

- Use DuoResp Spiromax every day. This helps to prevent asthma symptoms such as breathlessness and wheezing from occurring.
- Use the ‘reliever inhaler’ when you get asthma symptoms, to make it easier to breathe again.

b) You may be prescribed DuoResp Spiromax as your only asthma inhaler.

- Use DuoResp Spiromax every day. This helps to prevent asthma symptoms such as breathlessness and wheezing from occurring.
- Use DuoResp Spiromax when you need to take extra inhalations or puffs to relieve asthma symptoms and to make it easier to breathe again. You do not need a separate ‘reliever inhaler’ for this.

Chronic obstructive pulmonary disease (COPD)

COPD is a long-term lung disease of the airways in the lungs, which is often caused by cigarette smoking. Symptoms include shortness of breath, cough, chest discomfort and coughing up mucus. DuoResp Spiromax can also be used to treat the symptoms of severe COPD in adults.

2. What you need to know before you use DuoResp Spiromax

Do not use DuoResp Spiromax if:

You are allergic to budesonide, formoterol fumarate dihydrate, or the other ingredient in this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking DuoResp Spiromax if

- you are diabetic.
- you have a lung infection.
- you have high blood pressure or you have ever had a heart problem (including an uneven heartbeat, a very fast pulse, narrowing of the arteries or heart failure).
- you have problems with your thyroid or adrenal glands.
- you have low levels of potassium in your blood.
- you have severe liver problems.

If you have been taking steroid tablets for your asthma or COPD, your doctor may reduce the number of tablets that you take, once you start to use DuoResp Spiromax. If you have been taking steroid tablets for a long time, your doctor may want you to have regular blood tests. When reducing steroid tablets, you may feel generally unwell even though your chest symptoms may be improving. You might experience symptoms such as a stuffy or runny nose, weakness or joint or muscle pain and rash (eczema). If any of these symptoms bother you, or if symptoms such as headache, tiredness, nausea (feeling sick) or vomiting (being sick) occur, please contact your doctor **immediately**. You may need to take other medicines if you develop allergic or arthritic symptoms. You should speak to your doctor if you are concerned as to whether you should continue to use DuoResp Spiromax.

Your doctor may consider adding steroid tablets to your usual treatment during periods of stress (for example, when you have a chest infection or before an operation).

Contact your doctor if you experience blurred vision or other visual disturbances.

Children and adolescents

This medicine should not be used in children or adolescents under the age of 18 years.

Other medicines and DuoResp Spiromax

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

In particular, tell your doctor or pharmacist if you are taking any of the following medicines:

- β blockers (such as atenolol or propranolol for high blood pressure or a heart condition), including eyedrops (such as timolol for glaucoma).
- Medicines for a fast or uneven heartbeat (such as quinidine).
- Medicines like digoxin, often used to treat heart failure.
- Diuretics, also known as 'water tablets' (such as furosemide). These are used to treat high blood pressure.
- Steroid medicines that you take by mouth (such as prednisolone).
- Xanthine medicines (such as theophylline or aminophylline). These are often used to treat asthma.
- Other bronchodilators (such as salbutamol).
- Tricyclic antidepressants (such as amitriptyline) and the antidepressant nefazodone.
- Phenothiazine medicines (such as chlorpromazine and prochlorperazine).

- Medicines called ‘HIV protease inhibitors’ (such as ritonavir) to treat HIV infection.
- Medicines to treat infections (such as ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin and telithromycin).
- Medicines for Parkinson’s disease (such as levodopa).
- Medicines for thyroid problems (such as levothyroxine).

Some medicines may increase the effects of DuoResp Spiromax and your doctor may wish to monitor you carefully if you are taking these medicines (including some medicines for HIV: ritonavir, cobicistat).

If any of the above applies to you, or if you are not sure, talk to your doctor, pharmacist or nurse before using DuoResp Spiromax.

Also tell your doctor, pharmacist or nurse if you are going to have a general anaesthetic for an operation or for dental work.

Pregnancy, breast-feeding and fertility

- If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor, pharmacist or nurse for advice before taking DuoResp Spiromax - do NOT use this medicine unless your doctor tells you to.
- If you get pregnant while using DuoResp Spiromax, do NOT stop using DuoResp Spiromax but talk to your doctor **immediately**.

Driving and using machines

DuoResp Spiromax is not likely to affect your ability to drive or to use tools or machines.

DuoResp Spiromax contains lactose

Lactose is a type of sugar found in milk. Lactose contains small amounts of milk protein which may cause allergic reactions. If you have been told by your doctor that you have an intolerance to some sugars, talk to your doctor before using this medicine.

3. How to use DuoResp Spiromax

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor, pharmacist or nurse if you are not sure.

- It is important to use DuoResp Spiromax every day, even if you have no asthma or COPD symptoms at the time.
- If you are using DuoResp Spiromax for asthma, your doctor will want to regularly check your symptoms.

Asthma

DuoResp Spiromax can be prescribed for asthma in two different ways. The amount of DuoResp Spiromax to use and when to use it depends on how it has been prescribed for you.

- If you have been prescribed DuoResp Spiromax and a separate reliever inhaler, read the section called **(A) Using DuoResp Spiromax and a separate ‘reliever inhaler’**.
- If you have been prescribed DuoResp Spiromax as your only inhaler, read the section called **(B) Using DuoResp Spiromax as your only asthma inhaler**.

(A) Using DuoResp Spiromax and a separate ‘reliever inhaler’

Use your DuoResp Spiromax every day. This helps to prevent asthma symptoms from occurring.

Recommended dose:

Adults (18 years and older)

1 or 2 inhalations (actuations), twice a day.

Your doctor may increase this to 4 inhalations, twice a day.

If your symptoms are well controlled, your doctor may ask you to take your medicine once a day.

Your doctor will help you to manage your asthma and will adjust the dose of this medicine to the lowest dose that controls your asthma. If your doctor feels that you need a lower dose than is available from your DuoResp Spiromax, your doctor may prescribe an alternative inhaler containing the same active substances as your DuoResp Spiromax but with a lower dose of the corticosteroid. However, do not adjust the number of inhalations your doctor has prescribed without talking to your doctor first.

Use your separate ‘reliever inhaler’ to treat asthma symptoms when they happen.

Always keep your ‘reliever inhaler’ with you and use it to relieve sudden attacks of breathlessness and wheezing. Do not use DuoResp Spiromax to treat these asthma symptoms.

(B) Using DuoResp Spiromax as your only asthma inhaler

Only use DuoResp Spiromax in this way if your doctor has told you to.

Use your DuoResp Spiromax every day. This helps to prevent asthma symptoms from occurring.

Recommended dose

Adults (18 years and older)

1 inhalation in the morning **and** 1 inhalation in the evening

or

2 inhalations in the morning

or

2 inhalations in the evening.

Your doctor may increase this to 2 inhalations twice a day.

Also use DuoResp Spiromax as a ‘reliever inhaler’ to treat asthma symptoms when they occur.

- If you get asthma symptoms such as sudden attacks of breathlessness and wheezing, take 1 inhalation and wait a few minutes.
- If you do not feel better, take another inhalation.
- Do NOT take more than 6 inhalations at a single time.

Always keep your DuoResp Spiromax with you and use it to relieve sudden attacks of breathlessness and wheezing.

A total daily dose of more than 8 inhalations is not normally needed. However, your doctor may allow you to take up to 12 inhalations a day for a limited period.

If you regularly need to use 8 or more inhalations a day, make an appointment to see your doctor. They may need to change your treatment.

Do NOT use more than 12 inhalations in total in 24 hours.

If you are doing exercise and you get asthma symptoms, use DuoResp Spiromax as described here. However, do not use DuoResp Spiromax just before exercise to stop asthma symptoms from happening.

Chronic Obstructive Pulmonary Disease (COPD)

Recommended dose:

Adults (18 years and older):

2 inhalations twice a day.

Your doctor may also prescribe another bronchodilator medicine, for example an anticholinergic (such as tiotropium or ipratropium bromide) for your COPD disease.

Preparing your new DuoResp Spiromax

Before using your DuoResp Spiromax **for the first time**, you need to prepare it for use as follows:

- Open the foil pouch by tearing at the notch at the top of the foil pouch and take out the inhaler
- Check the dose indicator to see that there are 120 inhalations in the inhaler.
- Write the date you opened the foil pouch on the label of the inhaler.
- Do not shake your inhaler before use.

How to take an inhalation

Every time you need to take an inhalation, follow the instructions below.

1. **Hold your inhaler** with the semi-transparent wine red mouthpiece cover at the bottom.



2. Open the mouthpiece cover by folding it down until one loud click is heard. Your medicine is actively metered. Your inhaler is now ready for use.



3. Breathe out gently (as far as is comfortable). Do not breathe out through your inhaler.
4. Place the mouthpiece between your teeth. Do not bite the mouthpiece. Close your lips around the mouthpiece. Take care not to block the air vents.

Breathe in through your mouth as deeply and as hard as you can.



5. Remove your inhaler from your mouth. You may notice a taste when you take your inhalation.
6. Hold your breath for 10 seconds or as long as you comfortably can.
7. **Then breathe out gently** (do not breathe out through the inhaler). **Close the mouthpiece cover.**



If you are to take a second inhalation, repeat steps 1 to 7.

Rinse your mouth with water after every dose, and spit it out.

Do not try to take your inhaler apart, remove or twist the mouthpiece cover, it is fixed to your inhaler and must not be taken off. Do not use your Spiromax if it has been damaged or if the mouthpiece has come apart from your Spiromax. Do not open and close the mouthpiece cover unless you are about to use your inhaler.

Cleaning your Spiromax

Keep your Spiromax dry and clean.

If necessary you may wipe the mouthpiece of your Spiromax after use with a dry cloth or tissue.

When to start using a new Spiromax

- The dose indicator tells you how many doses (inhalations) are left in your inhaler, starting with 120 inhalations when it is full.



- The dose indicator, on the rear of the device, shows the number of inhalations remaining in even numbers only.
- For inhalations remaining from 20 downwards to '8', '6', '4', '2' the numbers are displayed in red on a white background. When the numbers become red in the window, you should consult your doctor and obtain a new inhaler.

Note:

- The mouthpiece will still 'click' even when your Spiromax is empty. If you open and close the mouthpiece without taking an inhalation the dose indicator will still register it as a count. This dose will be securely held inside the inhaler for when the next inhalation is due. It is impossible to accidentally take extra medicine or a double dose in one inhalation.
Keep the mouthpiece closed all the time unless you are about to use your inhaler.

Important information about your asthma or COPD symptoms

If you feel you are getting breathless or wheezy while using DuoResp Spiromax, you should continue to use DuoResp Spiromax but go to see your doctor as soon as possible, as you may need additional treatment.

Contact your doctor **immediately** if:

- Your breathing is getting worse or you often wake up at night with breathlessness and wheezing.
- Your chest starts to feel tight in the morning or your chest tightness lasts longer than usual.

These signs could mean that your asthma or COPD is not being properly controlled and you may need different or additional treatment **immediately**.

Once your asthma is well controlled your doctor may consider it appropriate to gradually reduce the dose of DuoResp Spiromax.

If you use more DuoResp Spiromax than you should

It is important that you take your dose as advised by your doctor. You should not exceed your prescribed dose without seeking medical advice.

If you use more DuoResp Spiromax than you should, contact your doctor, pharmacist or nurse for advice. The most common symptoms that may occur after if you use more DuoResp Spiromax than you should are trembling, headache or a rapid heartbeat.

If you forget to use DuoResp Spiromax

If you forget to take a dose, take it as soon as you remember. However do **not** take a double dose to make up for a forgotten dose. If it is nearly time for your next dose just take your next dose at the usual time.

If you become wheezy or breathless, or develop any other symptoms of an asthma attack, **use your 'reliever inhaler'**, then seek medical advice.

If you stop using DuoResp Spiromax

Do not stop using your inhaler without telling your doctor first.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If any of the following happen to you, stop using DuoResp Spiromax and talk to your doctor immediately:

Rare side effects: may affect up to 1 in 1,000 people

- Swelling of your face, particularly around your mouth (tongue and/or throat and/or difficulty to swallow) or hives together with difficulties to breathe (angioedema) and/or sudden feeling of faintness. This may mean that you are having an allergic reaction, which may also include rash and itching.
- Bronchospasm (tightening of the muscles in the airways which causes wheezing and shortness of breath). If the wheezing comes on suddenly after using this medicine stop using it and talk to your doctor **immediately**.

Very rare side effects: may affect up to 1 in 10,000 people

- Sudden acute wheezing and/or shortness of breath immediately after using your inhaler (also referred to as 'paradoxical bronchospasm'). If either of these symptoms occur, **stop using DuoResp Spiromax straightaway** and use your 'reliever inhaler'. Contact your doctor **immediately** as you may need to have your treatment changed.

Other possible side effects:

Common: may affect up to 1 in 10 people

- Palpitations (awareness of your heart beating), trembling or shaking. If these effects occur, they are usually mild and usually disappear as you continue to use DuoResp Spiromax.
- Thrush (a fungal infection) in the mouth. This is less likely to occur if you rinse your mouth out with water after using your medicine.
- Mild sore throat, coughing and a hoarse voice.
- Headache.
- Pneumonia (infection to the lung) in COPD patients.

Tell your doctor if you have any of the following while taking DuoResp Spiromax they could be symptoms of a lung infection:

- Fever or chills
- Increased mucus production, change in mucus colour
- Increased cough or increased breathing difficulties

Uncommon: may affect up to 1 in 100 people

- Feeling restless, nervous, agitated, anxious or angry.
- Disturbed sleep.
- Feeling dizzy.
- Nausea (feeling sick).
- Fast heartbeat.
- Bruising of the skin.
- Muscle cramps
- Blurred vision.

Rare:

- Low levels of potassium in your blood.
- Uneven heartbeat.

Very rare:

- Depression.
- Changes in behaviour, especially in children.
- Chest pain or tightness in the chest (angina pectoris).
- Disturbance of the heart's electrical system (prolongation of the QTc-interval).
- An increase in the amount of sugar (glucose) in your blood.
- Taste changes, such as an unpleasant taste in the mouth.

- Changes in your blood pressure.

Inhaled corticosteroids can affect the normal production of steroid hormones in your body, particularly if you use high doses for a long time. The effects include:

- changes in bone mineral density (thinning of the bones)
- cataract (clouding of the lens in the eye)
- glaucoma (increased pressure in the eye)
- a slowing of the rate of growth of children and adolescents
- an effect on the adrenal gland (a small gland next to the kidney)

These effects happen very rarely and are much less likely to happen with inhaled corticosteroids than with corticosteroid tablets.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store DuoResp Spiromax

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton or on the label of your inhaler after EXP. The expiry date refers to the last day of that month.
- Do not store above 25 °C. **Keep the mouthpiece cover closed after removal of the foil wrapping.**
- **Use within 6 months of removing from the foil wrapping.** Use the label on the inhaler to write down the opening date of the foil pouch.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What DuoResp Spiromax contains

- The active substances are budesonide and formoterol fumarate dihydrate. Each delivered (inhaled) dose contains 160 micrograms of budesonide and 4.5 micrograms of formoterol fumarate dihydrate. This is equivalent to a metered dose of 200 micrograms of budesonide and 6 micrograms of formoterol fumarate dihydrate.
- The other ingredient is lactose monohydrate (see section 2 under ‘DuoResp Spiromax contains lactose’)

What DuoResp Spiromax looks like and contents of the pack

DuoResp Spiromax is an inhalation powder.

Each DuoResp Spiromax inhaler contains 120 inhalations and has a white body with a semi-transparent wine red mouthpiece cover.

Packs of 1, 2, and 3 inhalers. Not all pack sizes may be marketed in your country.

Marketing Authorisation Holder

Teva Pharma B.V.,
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Manufacturer

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Teva Pharmaceuticals Europe B.V., Swensweg 5, 2031 GA Haarlem, Netherlands

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in month YYYY.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: <http://www.ema.europa.eu>.

Package leaflet: Information for the patient

DuoResp Spiromax 320 micrograms/9 micrograms, inhalation powder (budesonide/formoterol fumarate dihydrate)

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What DuoResp Spiromax is and what it is used for
2. What you need to know before you use DuoResp Spiromax
3. How to use DuoResp Spiromax
4. Possible side effects
5. How to store DuoResp Spiromax
6. Contents of the pack and other information

1. What DuoResp Spiromax is and what it is used for

DuoResp Spiromax contains two different active substances: budesonide and formoterol fumarate dihydrate.

- Budesonide belongs to a group of medicines called ‘corticosteroids’ also known as ‘steroids’. It works by reducing and preventing swelling and inflammation in your lungs and helps you to breathe more easily.
- Formoterol fumarate dihydrate belongs to a group of medicines called ‘long-acting β_2 adrenoceptor agonists’ or ‘bronchodilators’. It works by relaxing the muscles in your airways. This will help to open the airways and help you to breathe more easily.

DuoResp Spiromax is indicated for use in adults 18 years of age and older only.

DuoResp Spiromax is NOT indicated for use in children, 12 years of age and younger or adolescents, 13 to 17 years of age.

Your doctor has prescribed this medicine to treat asthma or chronic obstructive pulmonary disease (COPD).

Asthma

When used for asthma, your doctor will prescribe DuoResp Spiromax together with a separate ‘reliever inhaler’ such as salbutamol.

- Use DuoResp Spiromax every day. This helps to prevent asthma symptoms such as breathlessness and wheezing from occurring.
- Use the ‘reliever inhaler’ when you get asthma symptoms, to make it easier to breathe again.

Do not use DuoResp Spiromax 320/9 micrograms as a ‘reliever inhaler’.

Chronic obstructive pulmonary disease (COPD)

COPD is a long-term lung disease of the airways in the lungs, which is often caused by cigarette smoking. Symptoms include shortness of breath, cough, chest discomfort and coughing up mucus. DuoResp Spiromax can also be used to treat the symptoms of severe COPD in adults.

2. What you need to know before you use DuoResp Spiromax

Do not use DuoResp Spiromax if:

You are allergic to budesonide, formoterol fumarate dihydrate, or the other ingredient in this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking DuoResp Spiromax if

- you are diabetic.
- you have a lung infection.
- you have high blood pressure or you have ever had a heart problem (including an uneven heartbeat, a very fast pulse, narrowing of the arteries or heart failure).
- you have problems with your thyroid or adrenal glands.
- you have low levels of potassium in your blood.
- you have severe liver problems.

If you have been taking steroid tablets for your asthma or COPD, your doctor may reduce the number of tablets that you take, once you start to use DuoResp Spiromax. If you have been taking steroid tablets for a long time, your doctor may want you to have regular blood tests. When reducing steroid tablets, you may feel generally unwell even though your chest symptoms may be improving. You might experience symptoms such as a stuffy or runny nose, weakness or joint or muscle pain and rash (eczema). If any of these symptoms bother you, or if symptoms such as headache, tiredness, nausea (feeling sick) or vomiting (being sick) occur, please contact your doctor **immediately**. You may need to take other medicines if you develop allergic or arthritic symptoms. You should speak to your doctor if you are concerned as to whether you should continue to use DuoResp Spiromax.

Your doctor may consider adding steroid tablets to your usual treatment during periods of stress (for example, when you have a chest infection or before an operation).

Contact your doctor if you experience blurred vision or other visual disturbances.

Children and adolescents

This medicine should not be used in children or adolescents under the age of 18 years.

Other medicines and DuoResp Spiromax

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

In particular, tell your doctor or pharmacist if you are taking any of the following medicines:

- β blockers (such as atenolol or propranolol for high blood pressure or a heart condition), including eyedrops (such as timolol for glaucoma).
- Medicines for a fast or uneven heartbeat (such as quinidine).
- Medicines like digoxin, often used to treat heart failure.
- Diuretics, also known as 'water tablets' (such as furosemide). These are used to treat high blood pressure.
- Steroid medicines that you take by mouth (such as prednisolone).
- Xanthine medicines (such as theophylline or aminophylline). These are often used to treat asthma.
- Other bronchodilators (such as salbutamol).
- Tricyclic antidepressants (such as amitriptyline) and the antidepressant nefazodone.
- Phenothiazine medicines (such as chlorpromazine and prochlorperazine).
- Medicines called 'HIV protease inhibitors' (such as ritonavir) to treat HIV infection.
- Medicines to treat infections (such as ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin and telithromycin).
- Medicines for Parkinson's disease (such as levodopa).
- Medicines for thyroid problems (such as levothyroxine).

Some medicines may increase the effects of DuoResp Spiromax and your doctor may wish to monitor you carefully if you are taking these medicines (including some medicines for HIV: ritonavir, cobicistat).

If any of the above applies to you, or if you are not sure, talk to your doctor, pharmacist or nurse before using DuoResp Spiromax.

Also tell your doctor, pharmacist or nurse if you are going to have a general anaesthetic for an operation or for dental work.

Pregnancy, breast-feeding and fertility

- If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor, pharmacist or nurse for advice before taking DuoResp Spiromax - do NOT use this medicine unless your doctor tells you to.
- If you get pregnant while using DuoResp Spiromax, do NOT stop using DuoResp Spiromax but talk to your doctor **immediately**.

Driving and using machines

DuoResp Spiromax is not likely to affect your ability to drive or to use tools or machines.

DuoResp Spiromax contains lactose

Lactose is a type of sugar found in milk. Lactose contains small amounts of milk protein which may cause allergic reactions. If you have been told by your doctor that you have an intolerance to some sugars, talk to your doctor before using this medicine.

3. How to use DuoResp Spiromax

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor, pharmacist, or nurse if you are not sure.

- It is important to use DuoResp Spiromax every day, even if you have no asthma or COPD symptoms at the time.
- If you are using DuoResp Spiromax for asthma, your doctor will want to regularly check your symptoms.

Asthma

Use your DuoResp Spiromax every day. This helps to prevent asthma symptoms from occurring..

Recommended dose:

Adults (18 years and older)

1 inhalation (actuation), twice a day.

Your doctor may increase this to 2 inhalations, twice a day.

If your symptoms are well controlled, your doctor may ask you to take your medicine once a day.

Your doctor will help you to manage your asthma and will adjust the dose of this medicine to the lowest dose that controls your asthma. If your doctor feels that you need a lower dose than is available from your DuoResp Spiromax, your doctor may prescribe an alternative inhaler containing the same active substances as your DuoResp Spiromax but with a lower dose of the corticosteroid. However, do not adjust the number of inhalations your doctor has prescribed without talking to your doctor first.

Use your separate ‘reliever inhaler’ to treat asthma symptoms when they happen.

Always keep your ‘reliever inhaler’ with you and use it to relieve sudden attacks of breathlessness and wheezing. Do not use DuoResp Spiromax to treat these asthma symptoms.

Chronic Obstructive Pulmonary Disease (COPD)

Recommended dose:

Adults (18 years and older):

- 1 inhalation twice a day.

Your doctor may also prescribe another bronchodilator medicine for example an anticholinergic (such as tiotropium or ipratropium bromide) for your COPD disease.

Preparing your new DuoResp Spiromax

Before using your DuoResp Spiromax **for the first time**, you need to prepare it for use as follows:

- Open the foil pouch by tearing at the notch at the top of the foil pouch and take out the inhaler
- Check the dose indicator to see that there are 60 inhalations in the inhaler.
- Write the date you opened the foil pouch on the label of the inhaler.
- Do not shake your inhaler before use.

How to take an inhalation

Every time you need to take an inhalation, follow the instructions below.

1. **Hold your inhaler** with the semi-transparent wine red mouthpiece cover at the bottom.



2. Open the mouthpiece cover by folding it down until one loud click is heard. Your medicine is actively metered. Your inhaler is now ready for use.



3. Breathe out gently (as far as is comfortable). Do not breathe out through your inhaler.

4. Place the mouthpiece between your teeth. Do not bite the mouthpiece. Close your lips around the mouthpiece. Take care not to block the air vents.

Breathe in through your mouth as deeply and as hard as you can.



5. Remove your inhaler from your mouth. You may notice a taste when you take your inhalation
6. Hold your breath for 10 seconds or as long as you comfortably can..
7. **Then breathe out gently** (do not breathe out through the inhaler). **Close the mouthpiece cover.**



If you are to take a second inhalation, repeat steps 1 to 7.

Rinse your mouth with water after every dose and spit it out.

Do not try to take your inhaler apart, remove or twist the mouthpiece cover, it is fixed to your inhaler and must not be taken off. Do not use your Spiromax if it has been damaged or if the mouthpiece has come apart from your Spiromax. Do not open and close the mouthpiece cover unless you are about to use your inhaler.

Cleaning your Spiromax

Keep your Spiromax dry and clean.

If necessary you may wipe the mouthpiece of your Spiromax after use with a dry cloth or tissue.

When to start using a new Spiromax

- The dose indicator tells you how many doses (inhalations) are left in your inhaler, starting with 60 inhalations when it is full.



- The dose indicator, on the rear of the device, shows the number of inhalations remaining in even numbers only.
- For inhalations remaining from 20 downwards to ‘8’, ‘6’, ‘4’, ‘2’ the numbers are displayed in red on a white background. When the numbers become red in the window, you should consult your doctor and obtain a new inhaler.

Note:

- The mouthpiece will still ‘click’ even when your Spiromax is empty.
- If you open and close the mouthpiece without taking an inhalation, the dose indicator will still register it as a count. This dose will be securely held inside the inhaler for when the next inhalation is due. It is impossible to accidentally take extra medicine or a double dose in one inhalation.
- Keep the mouthpiece closed all the time unless you are about to use your inhaler.

Important information about your asthma or COPD symptoms

If you feel you are getting breathless or wheezy while using DuoResp Spiromax, you should continue to use DuoResp Spiromax but go to see your doctor as soon as possible, as you may need additional treatment.

Contact your doctor **immediately** if:

- Your breathing is getting worse or you often wake up at night with breathlessness and wheezing.
- Your chest starts to feel tight in the morning or your chest tightness lasts longer than usual.

These signs could mean that your asthma or COPD is not being properly controlled and you may need different or additional treatment **immediately**.

Once your asthma is well controlled your doctor may consider it appropriate to gradually reduce the dose of DuoResp Spiromax.

If you use more DuoResp Spiromax than you should

It is important that you take your dose as advised by your doctor. You should not exceed your prescribed dose without seeking medical advice.

If you use more DuoResp Spiromax than you should, contact your doctor, pharmacist or nurse for advice. The most common symptoms that may occur after if you use more DuoResp Spiromax than you should are trembling, headache or a rapid heartbeat.

If you forget to use DuoResp Spiromax

If you forget to take a dose, take it as soon as you remember. However, do **not** take a double dose to make up for a forgotten dose. If it is nearly time for your next dose just take your next dose at the usual time.

If you become wheezy or breathless, or develop any other symptoms of an asthma attack, **use your ‘reliever inhaler’**, then seek medical advice.

If you stop using DuoResp Spiromax

Do not stop using your inhaler without telling your doctor first.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If any of the following happen to you, stop using DuoResp Spiromax and talk to your doctor immediately:

Rare side effects: may affect up to 1 in 1,000 people

- Swelling of your face, particularly around your mouth (tongue and/or throat and/or difficulty to swallow) or hives together with difficulties to breathe (angioedema) and/or sudden feeling of faintness. This may mean that you are having an allergic reaction, which may also include rash and itching.
- Bronchospasm (tightening of the muscles in the airways which causes wheezing and shortness of breath). If the wheezing comes on suddenly after using this medicine stop using it and talk to your doctor **immediately**.

Very rare side effects: may affect up to 1 in 10,000 people

- Sudden acute wheezing and/or shortness of breath immediately after using your inhaler (also referred to as 'paradoxical bronchospasm'. If either of these symptoms occur, **stop using DuoResp Spiromax straightaway** and use your 'reliever inhaler' Contact your doctor **immediately** as you may need to have your treatment changed.

Other possible side effects:

Common: may affect up to 1 in 10 people

- Palpitations (awareness of your heart beating), trembling or shaking. If these effects occur, they are usually mild and usually disappear as you continue to use DuoResp Spiromax.
- Thrush (a fungal infection) in the mouth. This is less likely to occur if you rinse your mouth out with water after using your medicine.
- Mild sore throat, coughing and a hoarse voice.
- Headache.
- Pneumonia (infection to the lung) in COPD patients.

Tell your doctor if you have any of the following while taking DuoResp Spiromax they could be symptoms of a lung infection:

- Fever or chills
- Increased mucus production, change in mucus colour
- Increased cough or increased breathing difficulties

Uncommon: may affect up to 1 in 100 people

- Feeling restless, nervous, agitated, anxious or angry.
- Disturbed sleep.
- Feeling dizzy.
- Nausea (feeling sick).
- Fast heartbeat.
- Bruising of the skin.
- Muscle cramps
- Blurred vision.

Rare:

- Low levels of potassium in your blood.
- Uneven heartbeat.

Very rare:

- Depression.
- Changes in behaviour, especially in children.
- Chest pain or tightness in the chest (angina pectoris).
- Disturbance of the heart's electrical system (prolongation of the QTc-interval).
- An increase in the amount of sugar (glucose) in your blood.
- Taste changes, such as an unpleasant taste in the mouth.
- Changes in your blood pressure.

Inhaled corticosteroids can affect the normal production of steroid hormones in your body, particularly if you use high doses for a long time. The effects include:

- changes in bone mineral density (thinning of the bones)
- cataract (clouding of the lens in the eye)
- glaucoma (increased pressure in the eye)
- a slowing of the rate of growth of children and adolescents
- an effect on the adrenal gland (a small gland next to the kidney)

These effects happen very rarely and are much less likely to happen with inhaled corticosteroids than with corticosteroid tablets.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store DuoResp Spiromax

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton or on the label of your inhaler after EXP. The expiry date refers to the last day of that month.
- Do not store above 25°C. **Keep the mouthpiece cover closed after removal of the foil wrapping.**
- **Use within 6 months of removing from the foil wrapping.** Use the label on the inhaler to write down the opening date of the foil pouch.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information**What DuoResp Spiromax contains**

- The active substances are budesonide and formoterol fumarate dihydrate. Each delivered (inhaled) dose contains 320 micrograms of budesonide and 9 micrograms of formoterol fumarate dihydrate. This is equivalent to a metered dose of 400 micrograms of budesonide and 12 micrograms of formoterol fumarate dihydrate.
- The other ingredient is lactose monohydrate (see section 2 under 'DuoResp Spiromax contains lactose')

What DuoResp Spiromax looks like and contents of the pack

DuoResp Spiromax is an inhalation powder.

Each DuoResp Spiromax inhaler contains 60 inhalations and has a white body with a semi-transparent wine red mouthpiece cover.

Packs of 1, 2, and 3 inhalers. Not all pack sizes may be marketed in your country.

Marketing Authorisation Holder

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: <http://www.ema.europa.eu>.