ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

BiResp Spiromax 160 micrograms / 4.5 micrograms inhalation powder

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each delivered dose (the dose that leaves the mouthpiece) 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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Asthma

BiResp Spiromax is indicated in adults and adolescents (12 years and older) for 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

BiResp Spiromax is indicated in adults, aged 18 years and older, for the symptomatic treatment of patients with COPD with forced expiratory volume in 1 second (FEV_1) < 70% predicted normal (post bronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators.

4.2 Posology and method of administration

Posology

Asthma

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

BiResp Spiromax is not an appropriate treatment for the adult or adolescent patient with only mild asthma.

The dosage of BiResp 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 adrenoceptor 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 BiResp Spiromax. Patients should be reassessed regularly by their prescriber/health care provider so that the dose of BiResp 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 BiResp 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.

For BiResp Spiromax there are two treatment approaches:

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

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

BiResp 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.

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

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

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

BiResp Spiromax maintenance and reliever therapy

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

For patients taking BiResp Spiromax as reliever, preventative use of BiResp Spiromax for allergen- or exercise-induced bronchoconstriction should be discussed between physician and patient; the recommended

use should take into consideration the frequency of need. In case of frequent need of bronchodilation without corresponding need for an increased dose of inhaled corticosteroids, an alternative reliever should be used.

BiResp 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 BiResp Spiromax as-needed inhalations.

Recommended doses:

Adults and adolescents (12 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 BiResp Spiromax in paediatric patients below 12 years of age have not been established. No data are available.

This medicinal product is not recommended for use in children under the age of 12 years.

Method of administration

For inhalation use only.

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).

BiResp 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 BiResp Spiromax follows three 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 BiResp 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

Dosing advice

Patients should be reassessed regularly by their prescriber/healthcare provider so that the dose of BiResp 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 BiResp Spiromax. When it is appropriate to titrate down to a lower strength than is available for BiResp 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 be advised to have their rescue inhaler available at all times, either BiResp Spiromax (for asthma patients using BiResp Spiromax as maintenance and reliever therapy) or a separate rapid-acting bronchodilator (for asthma patients using BiResp Spiromax as maintenance therapy only).

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

Patients should be reminded to take their BiResp Spiromax maintenance dose as prescribed, even when asymptomatic. The prophylactic use of BiResp Spiromax, e.g. before exercise, has not been studied. The reliever inhalations of BiResp Spiromax should be taken in response to symptoms but are not intended for regular prophylactic use, e.g. before exercise. In case of frequent need of bronchodilation without corresponding need for an increased dose of inhaled corticosteroids, an alternative reliever should be used.

Deterioration of disease

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

If patients find the treatment ineffective, or exceed the highest recommended dose of BiResp 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 not be initiated on BiResp Spiromax during an exacerbation, or if they have significantly worsening or acutely deteriorating asthma.

Systemic effects

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur with inhalation treatment than with oral corticosteroids.

Possible systemic effects include Cushing´s syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children) (see section 4.8).

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

Effects on bone density

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

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

Adrenal function

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

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.

Paradoxical bronchospasm

Paradoxical bronchospasm may occur, with an immediate increase in wheezing and shortness of breath, after dosing. If the patient experiences paradoxical bronchospasm BiResp 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).

Transfer from oral therapy

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.

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 (see section 4.2).

Paediatric population

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be re-evaluated with the aim of reducing the dose of inhaled corticosteroid 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.

COPD population

There are no clinical study data on BiResp 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).

Pneumonia
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 adrenoceptor agonists

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

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

Particular caution is recommended in unstable asthma with variable use of rescue bronchodilators, in acute severe asthma as the associated risk may be augmented by hypoxia and in other conditions when the likelihood for hypokalaemia is increased. It is recommended that serum potassium levels are monitored during these circumstances.

Excipients

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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

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

4.8 Undesirable effects

Summary of the safety profile

Since BiResp Spiromax contains both budesonide and formoterol, the same pattern of adverse reactions as reported for these substances may occur. No increased incidence of adverse reactions has been seen following concurrent administration of the two compounds. The most common adverse reactions are pharmacologically predictable adverse reactions of β_2 adrenoceptor agonist therapy, such as tremor and palpitations. These tend to be mild and usually disappear within a few days of treatment. In a 3-year clinical trial with budesonide in COPD, skin bruises and pneumonia occurred at a frequency of 10% and 6%, respectively, compared with 4% and 3% in the placebo group ($p<0.001$ and $p<0.01$, respectively).

Tabulated list of adverse reactions

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

System Organ Class	Frequency	Adverse reaction

Infections and infestations	Common	Candida infections in the oropharynx, pneumonia (in COPD patients)
Immune system disorders	Rare	Immediate and delayed hypersensitivity reactions, e.g. exanthema, urticaria, pruritus, dermatitis, angioedema and anaphylactic reaction
Endocrine disorders	Very rare	Cushing´s syndrome, adrenal suppression, growth retardation, decrease in bone mineral density
Metabolism and nutrition disorders	Rare	Hypokalaemia
	Very rare	Hyperglycaemia
Psychiatric disorders	Uncommon	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, Dysphonia including 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. If oropharyngeal thrush occurs, patients should also rinse their mouth with water after the as-needed inhalations.

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. BiResp 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 BiResp 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

BiResp 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.

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-dependent, with an onset of effect within 1-3 minutes. The duration of effect is at least 12 hours after a single dose.

Clinical efficacy and safety

Asthma

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.

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 Fumarate Dihydrate 160/4.5 µg bd + as needed**	**1103**	**125**	**0.23**[b]
	Budesonide/Formoterol Fumarate 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 Fumarate Dihydrate 160/4.5 µg bd + as needed**	**1107**	**194**	**0.19**[b]
	Budesonide/Formoterol Fumarate Dihydrate 160/4.5 µg bd + formoterol 4.5 µg as needed	1137	296	0.29
	Budesonide/Formoterol Fumarate 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

Comparable efficacy and safety in adolescents and adults was demonstrated in 6 double-blind studies, comprising the 5 studies mentioned above and an additional study using a higher maintenance dose of

160/4.5 micrograms, two inhalations twice daily. These assessments were based on a total of 14385 asthma patients of whom 1847 were adolescents. The number of adolescent patients taking more than 8 inhalations on at least one day as part of budesonide/formoterol maintenance and reliever therapy was limited and such use was infrequent.

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

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 FEV_1 at inclusion in the trials was 36% of predicted normal. The mean number of exacerbations per year (as defined above) was significantly reduced with budesonide/formoterol as compared with treatment with formoterol alone or placebo (mean rate 1.4 compared with 1.8-1.9 in the placebo/formoterol group). The mean number of days on oral corticosteroids/patient during the 12 months was slightly reduced in the budesonide/formoterol group (7-8 days/patient/year compared with 11-12 and 9-12 days in the placebo and formoterol groups, respectively). For changes in lung-function parameters, such as FEV_1, budesonide/formoterol was not superior to treatment with formoterol alone.

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

Elimination

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

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

Pharmacokinetic/pharmacodynamic relationship(s)

The pharmacokinetics of budesonide or formoterol in children and patients with renal failure are unknown. The exposure of budesonide and formoterol may be increased in patients with liver disease.

BiResp Spiromax pharmacokinetic profile

In pharmacokinetic studies with and without a charcoal blockage, BiResp 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 (which contains milk proteins).

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

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/921/001
EU/1/14/921/002
EU/1/14/921/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28th April 2014
Date of latest renewal: 8th April 2019

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

BiResp Spiromax 320 micrograms/9 micrograms inhalation powder

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each delivered dose (the dose that leaves the mouthpiece) 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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Asthma
BiResp Spiromax is indicated in adults and adolescents (12 years and older) for 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

BiResp Spiromax is indicated in adults, aged 18 years and older, for the symptomatic treatment of patients with COPD with forced expiratory volume in 1 second (FEV_1) < 70% predicted normal (post bronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators.

4.2 Posology and method of administration

Posology

Asthma

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

BiResp Spiromax is not an appropriate treatment for the adult or adolescent patient with only mild asthma.

The dosage of BiResp 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 adrenoceptor 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 BiResp Spiromax. Patients should be reassessed regularly by their prescriber/health care provider so that the dose of BiResp 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 BiResp 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.

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.

Adolescents (12 years and older): 1 inhalation twice daily.
Patients should be regularly reassessed by their prescriber/healthcare provider, so that the dosage of BiResp Spiromax remains optimal. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. When long-term control of symptoms is maintained with the lowest recommended dosage, then the next step could include a test of inhaled corticosteroid alone.

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

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

BiResp Spiromax 320 micrograms/9 micrograms should be used as maintenance therapy only. A lower strength of BiResp 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 BiResp Spiromax in paediatric patients below 12 years of age have not been established. No data are available.

This medicinal product is not recommended for use in children under the age of 12 years.

Method of administration

For inhalation use only.

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).

BiResp 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 BiResp Spiromax follows three 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 BiResp 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

Dosing advice

Patients should be reassessed regularly by their prescriber/healthcare provider so that the dose of BiResp 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 BiResp Spiromax. When it is appropriate to titrate down to a lower strength than is

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

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

Patients should be reminded to take their BiResp Spiromax maintenance dose as prescribed, even when asymptomatic. The prophylactic use of BiResp Spiromax, e.g. before exercise, has not been studied. The reliever inhalations of BiResp Spiromax should be taken in response to symptoms but are not intended for regular prophylactic use, e.g. before exercise. In case of frequent need of bronchodilation without corresponding need for an increased dose of inhaled corticosteroids, an alternative reliever should be used.

Deterioration of disease

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

If patients find the treatment ineffective, or exceed the highest recommended dose of BiResp 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 not be initiated on BiResp Spiromax during an exacerbation, or if they have significantly worsening or acutely deteriorating asthma.

Systemic effects

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur with inhalation treatment than with oral corticosteroids.

Possible systemic effects include Cushing´s syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children) (see section 4.8).

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

Effects on bone density

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

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

Adrenal function

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

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.

Paradoxical bronchospasm

Paradoxical bronchospasm may occur, with an immediate increase in wheezing and shortness of breath, after dosing. If the patient experiences paradoxical bronchospasm BiResp 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).

Transfer from oral therapy

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.

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 (see section 4.2).

Paediatric population

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be re-evaluated with the aim of reducing the dose of inhaled corticosteroid 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.

COPD population

There are no clinical study data on BiResp 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).

Pneumonia
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 adrenoceptor agonists

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

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

Particular caution is recommended in unstable asthma with variable use of rescue bronchodilators, in acute severe asthma as the associated risk may be augmented by hypoxia and in other conditions when the likelihood for hypokalaemia is increased. It is recommended that serum potassium levels are monitored during these circumstances.

Excipients

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

Potent inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, nefazodone and HIV protease inhibitors) are likely to markedly increase plasma levels of budesonide and concomitant use should be avoided. If this is not possible the time interval between administration of the inhibitor and budesonide should be as long as possible (see section 4.4).

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

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

Pharmacodynamic interactions

β adrenergic blockers can weaken or inhibit the effect of formoterol. A fixed-dose combination therapy of budesonide and formoterol fumarate dihydrate should therefore not be given together with β adrenergic blockers (including eye drops) unless there are compelling reasons.

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

In addition L-Dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards β_2 sympathomimetics.

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

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

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

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

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

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

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

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

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

During pregnancy, a fixed-dose combination therapy of budesonide and formoterol fumarate dihydrate should only be used when the benefits outweigh the potential risks. The lowest effective dose of budesonide needed to maintain adequate asthma control should be used.

Breast-feeding

Budesonide is excreted in breast milk. However, at therapeutic doses no effects on the suckling child are anticipated. It is not known whether formoterol passes into human breast milk. In rats, small amounts of formoterol have been detected in maternal milk. Administration of a fixed-dose combination therapy of budesonide and formoterol fumarate dihydrate to women who are breast-feeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

Since BiResp Spiromax contains both budesonide and formoterol, the same pattern of adverse reactions as reported for these substances may occur. No increased incidence of adverse reactions has been seen

following concurrent administration of the two compounds. The most common adverse reactions are pharmacologically predictable adverse reactions of β_2 adrenoceptor agonist therapy, such as tremor and palpitations. These tend to be mild and usually disappear within a few days of treatment. In a 3-year clinical trial with budesonide in COPD, skin bruises and pneumonia occurred at a frequency of 10% and 6%, respectively, compared with 4% and 3% in the placebo group ($p<0.001$ and $p<0.01$, respectively).

Tabulated list of adverse reactions

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

System Organ Class	**Frequency**	**Adverse reaction**
Infections and infestations	Common	Candida infections in the oropharynx, pneumonia (in COPD patients)
Immune system disorders	Rare	Immediate and delayed hypersensitivity reactions, e.g. exanthema, urticaria, pruritus, dermatitis, angioedema and anaphylactic reaction
Endocrine disorders	Very rare	Cushing´s syndrome, adrenal suppression, growth retardation, decrease in bone mineral density
Metabolism and nutrition disorders	Rare	Hypokalaemia
	Very rare	Hyperglycaemia
Psychiatric disorders	Uncommon	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, Dysphonia including 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. If

oropharyngeal thrush occurs, patients should also rinse their mouth with water after the as-needed inhalations.

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. BiResp 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 BiResp 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

BiResp Spiromax contains formoterol and budesonide, which have different modes of action and show additive effects in terms of reduction of asthma exacerbations.

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-dependent, with an onset of effect within 1-3 minutes. The duration of effect is at least 12 hours after a single dose.

Clinical efficacy and safety

Asthma

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.

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 FEV_1 at inclusion in the trials was 36% of predicted normal. The mean number of exacerbations per year (as defined above) was significantly reduced with budesonide/formoterol as compared with treatment with formoterol alone or placebo (mean rate 1.4 compared with 1.8-1.9 in the placebo/formoterol group). The mean number of days on oral corticosteroids/patient during the 12 months was slightly reduced in the budesonide/formoterol group (7-8 days/patient/year compared with 11-12 and 9-12 days in the placebo and formoterol groups, respectively). For changes in lung-function parameters, such as FEV_1, budesonide/formoterol was not superior to treatment with formoterol alone.

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

Elimination

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

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

Pharmacokinetic/pharmacodynamic relationship(s)

The pharmacokinetics of budesonide or formoterol in children and patients with renal failure are unknown. The exposure of budesonide and formoterol may be increased in patients with liver disease.

BiResp Spiromax pharmacokinetic profile

In pharmacokinetic studies with and without a charcoal blockage, BiResp 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 (which contains milk proteins).

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

Any unused medicinal product or waste material should be disposed of in accordance with local requirements..

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/921/004
EU/1/14/921/005
EU/1/14/921/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28th April 2014
Date of latest renewal: 8th April 2019

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

Name and address of the 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

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 (PSURs)**

The requirements for submission of PSURs 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 marketing authorisation holder (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

BiResp 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

Read the package leaflet before use.
Inhalation 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 under 12 years of age.

Side panel: For use in adults and adolescents 12 years of age and older only.
Not for use in children under 12 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/1/14/921/001
EU/1/14/921/002
EU/1/14/921/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

BiResp 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

BiResp 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.

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

BiResp 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

BiResp 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

Read the package leaflet before use.
Inhalation 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 under 12 years of age.

Side panel: For use in adults and adolescents 12 years of age and older only.
Not for use in children under 12 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/1/14/921/004
EU/1/14/921/005
EU/1/14/921/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

BiResp 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

BiResp 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

BiResp 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

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

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

BiResp 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.

BiResp Spiromax is indicated for use in adults and adolescents 12 years of age and older only.

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

Asthma
BiResp Spiromax can be prescribed for asthma in two different ways.

a) You may be prescribed two asthma inhalers: BiResp Spiromax together with a separate 'reliever inhaler' such as salbutamol.
- Use BiResp 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 BiResp Spiromax as your only asthma inhaler.
- Use BiResp Spiromax every day. This helps to prevent asthma symptoms such as breathlessness and wheezing from occurring.
- Use BiResp Spiromax when you need to take extra inhalations or puffs for relief of asthma symptoms, to make it easier to breathe again and if agreed with the doctor also to prevent asthma symptoms from happening (for example, when exercising or on exposure to allergens). They do not need a separate 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. BiResp Spiromax can also be used to treat the symptoms of severe COPD in adults only.

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

Do not use BiResp 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 BiResp 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.
- you regularly drink alcohol

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 BiResp 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 BiResp Spiromax.

Your doctor may consider adding steroid tablets to your usual treatment if you have an illness such as a chest infection or before an operation.

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

Children
Do not give this medicine to children under the age of 12 years.

Other medicines and BiResp Spiromax
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

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).
- Oxytocin which is given to pregnant women to induce labour.
- Medicines for a fast or uneven heartbeat (such as quinidine, disopyramide, procainamide and terfenadine).
- 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 tablets 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.

- Antidepressant medicines such as monoamine oxidase inhibitors and those with similar properties (such as the antibiotic furazolidone and the chemotherapy medicine procarbazine).
- Antipsychotic 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 BiResp 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 BiResp Spiromax.

Also tell your doctor, pharmacist or nurse if you are going to have a general anaesthetic for an operation or for dental work to help lower any risk of interaction with the anesthetic you receive.

Pregnancy and breast-feeding
- 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 BiResp Spiromax do NOT use this medicine unless your doctor tells you to.
- If you get pregnant while using BiResp Spiromax, do NOT stop using BiResp Spiromax but talk to your doctor **immediately.**

Driving and using machines
BiResp Spiromax is not likely to affect your ability to drive or to use tools or machines.

BiResp Spiromax contains lactose
Lactose is a type of sugar found in milk. 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 BiResp 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 BiResp Spiromax every day, even if you have no asthma or COPD symptoms at the time.
- If you are using BiResp Spiromax for asthma, your doctor will want to regularly check your symptoms.

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

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

(A) Using BiResp Spiromax and a separate 'reliever inhaler'
Use your BiResp 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, taken in the morning and in the evening.
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.

Adolescents (12 years and older)
1 or 2 inhalations twice daily.

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 BiResp Spiromax, your doctor may prescribe an alternative inhaler containing the same active substances as your BiResp Spiromax but with a lower dose of the corticosteroid. If your symptoms are well controlled, your doctor may ask you to take your medicine once a day. 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 BiResp Spiromax to treat these asthma symptoms.

(B) Using BiResp Spiromax as your only asthma inhaler

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

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

Recommended dose
Adults and adolescents (12 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 BiResp Spiromax as a 'reliever inhaler' to treat asthma symptoms when they happen and to prevent asthma symptoms from happening (for example, when exercising or on exposure to allergens).
- If you get asthma symptoms, 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 BiResp 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 BiResp Spiromax as described here. However, do not use BiResp Spiromax just before exercise to stop asthma symptoms from happening.

It is important that you discuss with your doctor the use of BiResp Spiromax to prevent asthma symptoms from happening; how often you exercise or how often you are exposed to allergens could impact the treatment that is prescribed to you.

Chronic Obstructive Pulmonary Disease (COPD)

Recommended dose:
Adults (18 years and older) only:
2 inhalations twice a day, taken in the morning and in the evening

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 BiResp Spiromax

Before using your new BiResp 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.

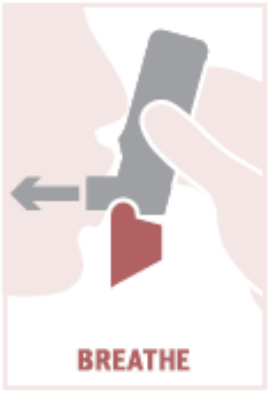
1. **Hold your inhaler** with the semi-transparent wine red mouthpiece cover at the bottom.

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 and ending with 0 (zero) inhalations when it is empty.

- The dose indicator, on the rear of the device, shows the number of inhalations remaining as even numbers. The spaces between the even numbers represent the odd number of remaining inhalations..
- 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 BiResp Spiromax, you should continue to use BiResp 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 BiResp Spiromax.

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

If you forget to use BiResp 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 BiResp 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 BiResp 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** (see below).

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

- Sudden, unexpected and 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 BiResp Spiromax straightaway** and use your 'reliever inhaler' if you have one. 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 BiResp 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 BiResp 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 which does not cause symptoms (prolongation of the QTc-interval)
- An increase in the amount of sugar (glucose) in your blood, when you have a blood test
- 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). Symptoms of adrenal gland suppression could be tiredness, weakness, stomach problems including nausea, vomiting, pain and diarrhoea, darkening of the skin and weight loss.

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 BiResp 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 ^{o}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 date you open 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 BiResp 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, which contains milk proteins (see section 2 under 'BiResp Spiromax contains lactose').

What BiResp Spiromax looks like and contents of the pack

BiResp Spiromax is an inhalation powder.
Each BiResp 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.,
Swensweg 5, 2031GA Haarlem, The Netherlands.

Manufacturer

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

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

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

België/Belgique/Belgien
Teva Pharma Belgium N.V./S.A./AG
Tel/Tél: +32 3 820 73 73

Luxembourg/Luxemburg
Teva Pharma Belgium N.V./S.A./AG
Belgique/Belgien
Tel/Tél: +32 3 820 73 73

България
Тева Фарма ЕАДТел: +359 2 489 95 85

Magyarország
Teva Gyógyszergyár Zrt.
Tel.: +36 1 288 64 00

Česká republika
Teva Pharmaceuticals CR, s.r.o.
Tel: +420 251 007 111

Malta
Teva Pharmaceuticals Ireland
L-Irlanda
Tel: +44 207 540 7117

Danmark
Teva Denmark A/S
Tlf: +45 44 98 55 11

Nederland
Teva Nederland B.V.
Tel: +31 800 0228 400

Deutschland
Teva GmbH
Tel: +49 731 402 08

Norge
Teva Norway AS
Tlf: +47 6677 55 90

Eesti
UAB Teva Baltics Eesti filiaal
Tel: +372 661 0801

Österreich
ratiopharm Arzneimittel Vertriebs-GmbH
Tel: +43 1 97007 0

Ελλάδα
Teva Ελλάς Α.Ε.
Τηλ: +30 210 880 5000

Polska
Teva Pharmaceuticals Polska Sp. z o.o.
Tel.: +48 22 345 93 00

España
Laboratorios BIAL, S.A.
Tel.: +34 915624196

Portugal
Teva Pharma - Produtos Farmacêuticos, Lda.
Tel: +351 21 476 75 50

France

România

Teva Santé
Tél: +33 1 55 91 7800

Ireland
Teva Pharmaceuticals Ireland
Tel: +44 207 540 7117

Ísland
Alvogen ehf.
Sími: + 354 522 2900

Italia
Teva Italia S.r.l.
Tel: +39 028 917 981

Κύπρος
Specifar A.B.E.E.
Ελλάδα
Τηλ: +30 211 880 5000

Latvija
UAB Teva Baltics filiāle Latvijā
Tel: +371 67 323 666

Lietuva
UAB Teva Baltics
Tel: +370 5 266 02 03

Teva Pharmaceuticals S.R.L
Tel: +4021 230 6524

Slovenija
Pliva Ljubljana d.o.o.
Tel: +386 1 58 90 390

Slovenská republika
Teva Pharmaceuticals Slovakia s.r.o.
Tel: +421 2 5726 7911

Suomi/Finland
Teva Finland Oy
Puh/Tel: +358 20 180 5900

Sverige
Teva Sweden AB
Tel: +46 42 12 11 00

United Kingdom (Northern Ireland)
Teva Pharmaceuticals Ireland
Ireland
Tel: +44 207 540 7117

Hrvatska
Pliva Hrvatska d.o.o.
Tel: + 385 1 37 20 000

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

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

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

BiResp 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.

BiResp Spiromax is indicated for use in adults and adolescents 12 years of age and older only.

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

Asthma
When used for asthma, your doctor will prescribe BiResp Spiromax together with a separate 'reliever inhaler' such as salbutamol.

- Use BiResp 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 BiResp 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. BiResp Spiromax can also be used to treat the symptoms of severe COPD in adults only.

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

Do not use BiResp 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 BiResp 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.
- you regularly drink alcohol.

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 BiResp 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 BiResp Spiromax.

Your doctor may consider adding steroid tablets to your usual treatment if you have an illness such as a chest infection or before an operation.

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

Children
Do not give this medicine to children under the age of 12 years.

Other medicines and BiResp Spiromax
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

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).
- Oxytocin which is given to pregnant women to induce labour.
- Medicines for a fast or uneven heartbeat (such as quinidine, disopyramide, procainamide and terfenadine).
- 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 tablets 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.
- Antidepressant medicines such as monoamine oxidase inhibitors and those with similar properties (such as the antibiotic furazolidone and the chemotherapy medicine procarbazine).
- Antipsychotic 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 BiResp 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 BiResp Spiromax.

Also tell your doctor, pharmacist or nurse if you are going to have a general anaesthetic for an operation or for dental work to help lower any risk of interaction with the anesthetic you receive.

Pregnancy and breast-feeding
- 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 BiResp Spiromax - do NOT use this medicine unless your doctor tells you to.
- If you get pregnant while using BiResp Spiromax, do NOT stop using BiResp Spiromax but talk to your doctor **immediately.**

Driving and using machines
BiResp Spiromax is not likely to affect your ability to drive or to use tools or machines.

BiResp Spiromax contains lactose
Lactose is a type of sugar found in milk. 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 BiResp 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 BiResp Spiromax every day, even if you have no asthma or COPD symptoms at the time.
- If you are using BiResp Spiromax for asthma, your doctor will want to regularly check your symptoms.

Asthma

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

Recommended dose:

Adults (18 years and older)
1 inhalation (actuation), twice a day, taken in the morning and in the evening.
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.

Adolescents (12 years and older)
1 inhalation twice daily.

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 BiResp Spiromax, your doctor may prescribe an alternative inhaler containing the same active substances as your BiResp Spiromax but with a lower dose of the corticosteroid. If your symptoms are well controlled, your doctor may ask you to take your medicine once a day. 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 BiResp Spiromax to treat these asthma symptoms. It is important that you discuss with your doctor the use of BiResp Spiromax to prevent asthma symptoms from happening; how often you exercise or how often you are exposed to allergens could impact the treatment that is prescribed to you.

Chronic Obstructive Pulmonary Disease (COPD)

Recommended dose:

Adults (18 years and older) only:
- 1 inhalation twice a day, taken in the morning and in the evening.

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 BiResp Spiromax
Before using your new BiResp 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.

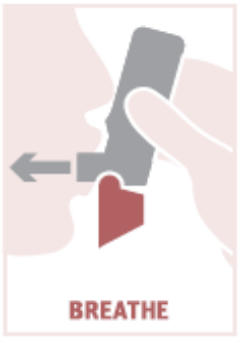
How to take an inhalation
Every time you need to take an inhalation, follow the instructions below.

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 and ending with 0 (zero) inhalations when it is empty.

- The dose indicator, on the rear of the device, shows the number of inhalations remaining as even numbers. The spaces between the even numbers represent the odd number of remaining inhalations.
- 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 BiResp Spiromax, you should continue to use BiResp 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 BiResp Spiromax.

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

If you forget to use BiResp 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 BiResp 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 BiResp 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** (see below)**.**

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

- Sudden, unexpected and 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 BiResp Spiromax straightaway** and use your 'reliever inhaler' if you have one. 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 BiResp 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 BiResp 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 which does not cause symptoms (prolongation of the QTc-interval)
- An increase in the amount of sugar (glucose) in your blood, when you have a blood test
- 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). Symptoms of adrenal gland suppression could be tiredness, weakness, stomach problems, including nausea, vomiting, pain and diarrhoea, darkening of the skin and weight loss.

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 BiResp 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 date you open 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 BiResp 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, which contains milk proteins (see section 2 under ‘BiResp Spiromax contains lactose’).

What BiResp Spiromax looks like and contents of the pack

BiResp Spiromax is an inhalation powder.
Each BiResp 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

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

Manufacturer

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

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

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

België/Belgique/Belgien
Teva Pharma Belgium N.V./S.A./AG
Tel/Tél: +32 3 820 73 73

Luxembourg/Luxemburg
Teva Pharma Belgium N.V./S.A./AG
Belgique/Belgien
Tel/Tél: +32 3 820 73 73

България
Тева Фарма ЕАД
Тел: +359 2 489 95 85

Magyarország
Teva Gyógyszergyár Zrt.
Tel.: +36 1 288 64 00

Česká republika
Teva Pharmaceuticals CR, s.r.o.
Tel: +420 251 007 111

Malta
Teva Pharmaceuticals Ireland
L-Irlanda
Tel: +44 207 540 7117

Danmark
Teva Denmark A/S
Tlf: +45 44 98 55 11

Nederland
Teva Nederland B.V.
Tel: +31 800 0228 400

Deutschland
Teva GmbH
Tel: +49 731 402 08

Norge
Teva Norway AS
Tlf: +47 6677 55 90

Eesti
UAB Teva Baltics Eesti filiaal
Tel: +372 661 0801

Österreich
ratiopharm Arzneimittel Vertriebs GmbH
Tel: +43 1 97007 0

Ελλάδα
Specifar A.B.E.E.
Τηλ: +30 211 880 5000

Polska
Teva Pharmaceuticals Polska Sp. z o.o.
Tel.: +48 22 345 93 00

España

Portugal

Laboratorios BIAL, S.A.
Tel.: +34 915624196

France
Teva Santé
Tél: +33 1 55 91 7800

Ireland
Teva Pharmaceuticals Ireland
Tel: +44 207 540 7117

Ísland
Alvogen ehf.
Sími: + 354 522 2900

Italia
Teva Italia S.r.l.
Tel: +39 028 917 981

Κύπρος
Specifar A.B.E.E.
Ελλάδα
Τηλ: +30 211 880 5000

Latvija
UAB Teva Baltics filiāle Latvijā
Tel: +371 67 323 666

Lietuva
UAB Teva Baltics
Tel: +370 5 266 02 03

Teva Pharma - Produtos Farmacêuticos, Lda
Tel: +351 21 476 75 50

România
Teva Pharmaceuticals S.R.L.
Tel: +4021 230 6524

Slovenija
Pliva Ljubljana d.o.o.
Tel: +386 1 58 90 390

Slovenská republika
Teva Pharmaceuticals Slovakia s.r.o.
Tel: +421 2 5726 7911

Suomi/Finland
Teva Finland Oy
Puh/Tel: +358 20 180 5900

Sverige
Teva Sweden AB
Tel: +46 42 12 11 00

United Kingdom (Northern Ireland)
Teva Pharmaceuticals Ireland
Ireland
Tel: +44 207 540 7117

Hrvatska
Pliva Hrvatska d.o.o.
Tel: + 385 1 37 20 000

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.