ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

Medicinal product no longer authorised

1. NAME OF THE MEDICINAL PRODUCT

Airexar Spiromax 50 micrograms/500 micrograms inhalation powder

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each metered dose contains 50 micrograms of salmeterol (as salmeterol xinafoate) and 500 micrograms of fluticasone propionate.

Each delivered dose (the dose from the mouthpiece) contains 45 micrograms of salmeterol (as salmeterol xinafoate) and 465 micrograms of fluticasone propionate.

Excipient(s) with known effect:
Each dose contains approximately 10 milligrams of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation powder.

White powder.

White inhaler with a semi-transparent yellow mouthpiece cover.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Airexar Spiromax is indicated for use in adults aged 18 years and older only.

Asthma
Airexar Spiromax is indicated for the regular treatment of patients with severe asthma where use of a combination product (inhaled corticosteroid and long-acting β_2 agonist) is appropriate:

- patients not adequately controlled on a lower strength corticosteroid combination product

or

- patients already controlled on a high dose inhaled corticosteroid and long-acting β_2 agonist.

Chronic Obstructive Pulmonary Disease (COPD)
Airexar Spiromax is indicated for the symptomatic treatment of patients with COPD, with a FEV_1 <60% predicted normal (pre-bronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy.

4.2 Posology and method of administration

Airexar Spiromax is indicated in adults 18 years of age and older only.
Airexar Spiromax is not indicated for use in children, 12 years of age and younger or adolescents, 13 to 17 years of age.

Medicinal product no longer authorised

Posology

Route of administration: Inhalation use

Patients should be made aware that Airexar Spiromax must be used daily for optimum benefit, even when asymptomatic.

Patients should be regularly reassessed by a doctor, so that the strength of the salmeterol/fluticasone propionate inhaler they are receiving remains optimal and is only changed on medical advice. **The dose should be titrated to the lowest dose at which effective control of symptoms is maintained.** Airexar Spiromax is not available on the market at strengths lower than 50/500 microgram. When it is appropriate to titrate down to a lower strength not available for Airexar Spiromax, a change to an alternative fixed-dose combination of salmeterol and fluticasone propionate containing a lower dose of the inhaled corticosteroid is required.

Patients should be given a strength of salmeterol/fluticasone propionate inhaler containing the appropriate fluticasone propionate dosage for the severity of their disease. Airexar Spiromax is only appropriate for use in the treatment of patients with severe asthma. If an individual patient should require dosages outside the recommended regimen, appropriate doses of β_2 agonist and/or corticosteroid should be prescribed

Recommended doses:

Asthma
Adults aged 18 years and older.

One inhalation of 50 micrograms salmeterol and 500 micrograms fluticasone propionate twice daily.

Once control of asthma is attained treatment should be reviewed and consideration given as to whether patients should be stepped down to an alternative fixed-dose combination of salmeterol and fluticasone propionate containing a lower dose of the inhaled corticosteroid and then ultimately to an inhaled corticosteroid alone. Regular review of patients as treatment is stepped down is important.

A clear benefit has not been shown as compared with inhaled fluticasone propionate alone used as initial maintenance therapy when one or two of the criteria of severity are missing. In general inhaled corticosteroids remain the first line treatment for most patients.

Airexar Spiromax is for the treatment of patients with severe asthma only. It should not be used for the treatment of patients with mild or moderate asthma or for the initiation of treatment for patients with severe asthma unless the requirement for such a high dose of the corticosteroid together with a long-acting β_2 agonist has been established previously.

Airexar Spiromax is not intended as the treatment of asthma when a fixed-dose combination of salmeterol and fluticasone propionate is required for the first time. Patients should commence treatment with a fixed-dose combination containing a lower dose of the corticosteroid component and will then be titrated up in respect of the corticosteroid dose until control of asthma is achieved. Once control of asthma is achieved patients should be reviewed regularly and the dose of inhaled corticosteroid titrated downwards as appropriate to maintain disease control.

It is recommended to establish the appropriate dosage of inhaled corticosteroid before any fixed-dose combination can be used in patients with severe asthma.

Medicinal product no longer authorised

Paediatric population
Airexar Spiromax is not recommended for use in either children aged 12 years of age and younger or in adolescents aged 13 to 17 years. The safety and efficacy of Airexar Spiromax in children and adolescents aged less than 18 years of age has not been established.
No data are available.

COPD
One inhalation of 50 micrograms salmeterol and 500 micrograms fluticasone propionate twice daily.

Special patient groups
There is no need to adjust the dose in elderly patients or in those with renal impairment.

There are no data available on the use of Airexar Spiromax in patients with hepatic impairment.

Method of administration/Instructions for use

The Spiromax device 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. Patients with severe asthma and COPD were shown to be able to generate sufficient inspiratory flow rate when they breathed in forcefully through the Spiromax device to enable the delivery of the required therapeutic dose to the lungs (see also section 5.1 – last five paragraphs)

Required training
Airexar 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. All patients should be provided with training by the prescribing Health Care Professional on how to use Airexar Spiromax. This is to ensure that they understand how to use the inhaler correctly, and so that they understand the need to breathe in forcefully when inhaling to obtain the required dose. It is important to inhale forcefully to ensure optimal dosing.

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

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

Breathe: Breathe out gently (as far as is comfortable). Do not breathe through your inhaler. 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 device from the 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.

Patients should not block the air vents at any time, or breathe out through the Spiromax device when they are preparing the "Breathe" step. Patients are not required to shake the inhaler prior to use.

Patients should also be advised to rinse their mouth with water and spit the water out, and/or brush their teeth after inhaling (see section 4.4)

Patients may notice a taste when using Airexar Spiromax due to the lactose excipient.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Medicinal product no longer authorised

4.4 Special warnings and precautions for use

Asthma
Airexar Spiromax is for use in patients with severe asthma only. It should not be used to treat acute asthma symptoms for which a fast- and short-acting bronchodilator is required. Patients should be advised to have their inhaler to be used for relief in an acute asthma attack available at all times.

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

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

Increased requirements for use of reliever medication (short-acting bronchodilators), or decreased response to reliever medication indicate deterioration of asthma control and patients should be reviewed by a physician.

Sudden and progressive deterioration in control of asthma is potentially life-threatening and the patient should undergo urgent medical assessment. Consideration should be given to increasing corticosteroid therapy.

Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of the inhaled corticosteroid and therefore a change to an alternative fixed-dose combination of salmeterol and fluticasone propionate containing a lower dose of the inhaled corticosteroid is required. Regular review of patients as treatment is stepped down is important. The lowest dose of inhaled corticosteroid should be used.

COPD
For patients with COPD experiencing exacerbations, treatment with systemic corticosteroids is typically indicated, therefore patients should be instructed to seek medical attention if symptoms deteriorate with Airexar Spiromax.

Cessation of therapy
Treatment with Airexar Spiromax should not be stopped abruptly in patients with asthma due to risk of exacerbation. Therapy should be down-titrated under physician supervision. For patients with COPD cessation of therapy may also be associated with symptomatic decompensation and should be supervised by a physician.

Caution with special diseases
Airexar Spiromax should be administered with caution in patients with active or quiescent pulmonary tuberculosis and fungal, viral or other infections of the airway. Appropriate treatment should be promptly instituted, if indicated.

Rarely, Airexar Spiromax may cause cardiac arrhythmias e.g. supraventricular tachycardia, extrasystoles and atrial fibrillation, and a mild transient reduction in serum potassium at high therapeutic doses. Airexar Spiromax should be used with caution in patients with severe cardiovascular disorders or heart rhythm abnormalities and in patients with diabetes mellitus, thyrotoxicosis, uncorrected hypokalaemia or patients predisposed to low levels of serum potassium.
There have been very rare reports of increases in blood glucose levels (see section 4.8) and this should be considered when prescribing to patients with a history of diabetes mellitus.

Parodoxical bronchospasm
Paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid-acting bronchodilator and should be treated straightaway. Airexar Spiromax should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

Medicinal product no longer authorised

βeta 2 adrenoreceptor agonists
The pharmacological effects of β_2 agonist treatment, such as tremor, palpitations and headache, have been reported, but tend to be transient and reduce with regular therapy.

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 than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, 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 Paediatric population sub-heading below for information on the systemic effects of inhaled corticosteroids in children and adolescents). **It is important, therefore, that the patient is reviewed regularly and the dose of inhaled corticosteroid is reduced to the lowest dose at which effective control of asthma is maintained.**

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.

Adrenal function
Prolonged treatment of patients with high doses of inhaled corticosteroids may result in adrenal suppression and acute adrenal crisis. Very rare cases of adrenal suppression and acute adrenal crisis have also been described with doses of fluticasone propionate between 500 and less than 1000 micrograms. Situations, which could potentially trigger acute adrenal crisis include trauma, surgery, infection or any rapid reduction in dosage. Presenting symptoms are typically vague and may include anorexia, abdominal pain, weight loss, tiredness, headache, nausea, vomiting, hypotension, decreased level of consciousness, hypoglycaemia, and seizures. Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

The benefits of inhaled fluticasone propionate therapy should minimise the need for oral steroids, but patients transferring from oral steroids may remain at risk of impaired adrenal reserve for a considerable time. Therefore these patients should be treated with special care and adrenocortical function regularly monitored. Patients who have required high dose emergency corticosteroid therapy in the past may also be at risk. This possibility of residual impairment should always be borne in mind in emergency and elective situations likely to produce stress, and appropriate corticosteroid treatment must be considered. The extent of the adrenal impairment may require specialist advice before elective procedures.

Interactions with other medicinal products
Ritonavir can greatly increase the concentration of fluticasone propionate in plasma. Therefore, concomitant use should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects. There is also an increased risk of systemic undesirable effects when combining fluticasone propionate with other potent CYP3A inhibitors (see section 4.5).

Concomitant use of systemic ketoconazole significantly increases systemic exposure to salmeterol. This may lead to an increase in the incidence of systemic effects (e.g. prolongation in the QTc interval and palpitations). Concomitant treatment with ketoconazole or other potent CYP3A4 inhibitors should therefore be avoided unless the benefits outweigh the potentially increased risk of systemic undesirable effects of salmeterol treatment (see section 4.5).

Respiratory tract infections

Medicinal product no longer authorised

There was an increased reporting of lower respiratory tract infections (particularly pneumonia and bronchitis) in the TORCH study in patients with COPD receiving salmeterol/fluticasone propionate 50/500 micrograms twice daily compared with placebo as well as in studies SCO40043 and SCO100250 comparing a lower dose of salmeterol/fluticasone propionate 50/250 micrograms twice daily, (a dose not authorised for use in COPD) with salmeterol 50 micrograms twice daily only (see section 4.8 and section 5.1). A similar incidence of pneumonia in the salmeterol/fluticasone propionate group was seen across all studies. In TORCH, older patients, patients with a lower body mass index (<25 kg/m^2) and patients with very severe disease (FEV_1<30% predicted) were at greatest risk of developing pneumonia regardless of treatment.

Physicians should remain vigilant for the possible development of pneumonia and other lower respiratory tract infections in patients with COPD as the clinical features of such infections and exacerbation frequently overlap. If a patient with severe COPD has experienced pneumonia, treatment with Airexar Spiromax should be re-evaluated.

Pneumonia in patients with COPD

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

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

Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations. If a patient with severe COPD has experienced pneumonia, treatment with Airexar Spiromax should be re-evaluated.

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

Ethnic populations

Data from a large clinical trial (the Salmeterol Multi-Center Asthma Research Trial, SMART) suggested African-American patients were at increased risk of serious respiratory-related events or deaths when using salmeterol compared with placebo (see section 5.1). It is not known if this was due to pharmacogenetic or other factors. Patients of black African or Afro-Caribbean ancestry should therefore be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen whilst using Airexar Spiromax.

Paediatric Population

Airexar Spiromax is not indicated for use in children and adolescents under the age of 18 years (see Section 4.2). However, it should be noted that children and adolescents less than 16 years taking high doses of fluticasone propionate (typically ≥ 1000 micrograms/day) may be at particular risk. Systemic effects may occur, particularly at high doses prescribed for long periods. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, acute adrenal crisis and growth retardation in children and adolescents and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression. Consideration should be given to referring the child or adolescent to a paediatric respiratory specialist. It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. The dose of inhaled corticosteroid should always be reduced to the lowest dose at which effective control of asthma is maintained.

Oral infections

Due to the fluticasone propionate component, hoarseness and candidiasis (thrush) of the mouth and throat and, rarely of the oesophagus, can occur in some patients. Both hoarseness and the incidence of candidiasis of the mouth and throat may be relieved by rinsing the mouth with water and spitting the water out and/or

Medicinal product no longer authorised

brushing the teeth after using the product. Symptomatic candidiasis of the mouth and throat can be treated with topical anti-fungal therapy whilst still continuing with Airexar Spiromax.

Excipients
This medicinal product contains lactose. Patients with severe lactose intolerance should use this medicine with caution and those with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. The excipient lactose may contain small amounts of milk proteins which may cause allergic reactions in those with severe hypersensitivity or allergy to milk protein.

4.5 Interaction with other medicinal products and other forms of interaction

Beta adrenergic blockers may weaken or antagonise the effect of salmeterol. Both non-selective and selective β blockers should be avoided unless there are compelling reasons for their use. Potentially serious hypokalaemia may result from β_2 agonist therapy. Particular caution is advised in acute severe asthma as this effect may be potentiated by concomitant treatment with xanthine derivatives, steroids and diuretics.

Concomitant use of other β adrenergic-containing medicinal products can have a potentially additive effect.

Salmeterol
Potent CYP3A4 inhibitors
Co-administration of ketoconazole (400 mg orally once daily) and salmeterol (50 micrograms inhaled twice daily) in 15 healthy subjects for 7 days resulted in a significant increase in plasma salmeterol exposure (1.4-fold C_{max} and 15-fold AUC). This may lead to an increase in the incidence of other systemic effects of salmeterol treatment (e.g. prolongation of QTc interval and palpitations) compared with salmeterol or ketoconazole treatment alone (see section 4.4).

Clinically significant effects were not seen on blood pressure, heart rate, blood glucose and blood potassium levels. Co-administration with ketoconazole did not increase the elimination half-life of salmeterol or increase salmeterol accumulation with repeat dosing.

The concomitant administration of ketoconazole should be avoided, unless the benefits outweigh the potentially increased risk of systemic effects of salmeterol treatment. There is likely to be a similar risk of interaction with other potent CYP3A4 inhibitors (e.g. itraconazole, telithromycin, ritonavir).

Moderate CYP 3A4 inhibitors
Co-administration of erythromycin (500 mg orally three times a day) and salmeterol (50 micrograms inhaled twice daily) in 15 healthy subjects for 6 days resulted in a small but non-statistically significant increase in salmeterol exposure (1.4-fold C_{max} and 1.2-fold AUC). Co-administration with erythromycin was not associated with any serious adverse effects.

Fluticasone propionate
Under normal circumstances, low plasma concentrations of fluticasone propionate are achieved after inhaled dosing, due to extensive first pass metabolism and high systemic clearance mediated by cytochrome P450 3A4 in the gut and liver. Hence, clinically significant drug interactions mediated by fluticasone propionate are unlikely.

In an interaction study in healthy subjects with intranasal fluticasone propionate, ritonavir (a highly potent cytochrome P450 3A4 inhibitor) 100 mg twice daily increased the fluticasone propionate plasma concentrations several hundred fold, resulting in markedly reduced serum cortisol concentrations. Information about this interaction is lacking for inhaled fluticasone propionate, but a marked increase in fluticasone propionate plasma levels is expected. Cases of Cushing's syndrome and adrenal suppression have been reported. The combination should be avoided unless the benefit outweighs the increased risk of systemic glucocorticoid undesirable effects.

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In a small study in healthy volunteers, the slightly less potent CYP3A inhibitor ketoconazole increased the exposure of fluticasone propionate after a single inhalation by 150%. This resulted in a greater reduction of plasma cortisol as compared with fluticasone propionate alone. Co-treatment with other potent CYP3A inhibitors, such as itraconazole, and moderate CYP3A inhibitors, such as erythromycin, is also expected to increase the systemic fluticasone propionate exposure and the risk of systemic undesirable effects. Caution is recommended and long-term treatment with such drugs should if possible be avoided.

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 effects.

4.6 Fertility, pregnancy and lactation

Pregnancy
A moderate amount of data on pregnant women (between 300 to 1000 pregnancy outcomes) indicates no malformative or feto/neonatal toxicity of salmeterol and fluticasone propionate. Animal studies have shown reproductive toxicity after administration of β_2 adrenoreceptor agonists and glucocorticosteroids (see section 5.3).

Administration of Airexar Spiromax to pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus.

The lowest effective dose of fluticasone propionate needed to maintain adequate asthma control should be used in the treatment of pregnant women.

Breastfeeding
It is unknown whether salmeterol and fluticasone propionate /metabolites are excreted in human milk.

Studies have shown that salmeterol and fluticasone propionate and their metabolites, are excreted into the milk of lactating rats.

A risk to breastfed newborns/infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue Airexar Spiromax therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility
There are no data in humans. However, animal studies showed no effects of salmeterol or fluticasone propionate on fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of safety profile

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As Airexar Spiromax contains salmeterol and fluticasone propionate, the type and severity of adverse reactions associated with each of the active substance may be expected. There is no incidence of additional adverse events following concurrent administration of the two active substances.

Adverse reactions which have been associated with salmeterol/fluticasone propionate are given below, listed by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000) and not known (frequency cannot be estimated from the available data). Frequencies were derived from clinical trial data. The incidence in placebo was not taken into account.

System Organ Class	Adverse reaction	Frequency
Infections and infestations	Candidiasis of the mouth and throat	Common
	Pneumonia (in COPD patients)	Common[1,3,5]
	Bronchitis	Common[1,3]
	Oesophageal candidiasis	Rare
Immune system disorders	Hypersensitivity reactions with the following manifestations:	
	Cutaneous hypersensitivity reactions	Uncommon
	Angioedema (mainly facial and oropharyngeal oedema)	Rare
	Respiratory symptoms (dyspnoea)	Uncommon
	Respiratory symptoms (bronchospasm)	Rare
	Anaphylactic reactions including anaphylactic shock	Rare
Endocrine disorders	Cushing's syndrome, Cushingoid features, Adrenal suppression, Growth retardation in children and adolescents, Decreased bone mineral density	Rare[4]
Metabolism and nutrition disorders	Hypokalaemia	Common[3]
	Hyperglycaemia	Uncommon[4]
Psychiatric disorders	Anxiety	Uncommon
	Sleep disorders	Uncommon
	Behavioural changes, including psychomotor hyperactivity and irritability (predominantly in children)	Rare
	Depression, aggression (predominantly in children)	Not known
Nervous system disorders	Headache	Very Common[1]
	Tremor	Uncommon
Eye disorders	Cataract	Uncommon

Medicinal product no longer authorised

System Organ Class	Adverse reaction	Frequency
	Glaucoma	Rare[4]
	Vision, blurred (see also section 4.4)	Not Known
Cardiac disorders	Palpitations	Uncommon
	Tachycardia	Uncommon
	Cardiac arrhythmias (including supraventricular tachycardia and extrasystoles).	Rare
	Atrial fibrillation	Uncommon
	Angina pectoris	Uncommon
Respiratory, thoracic and mediastinal disorders	Nasopharyngitis	Very Common[2,3]
	Throat irritation	Common
	Hoarseness/dysphonia	Common
	Sinusitis	Common[1,3]
	Paradoxical bronchospasm	Rare[4]
Skin and subcutaneous tissue disorders	Contusions	Common[1,3]
Musculoskeletal and connective tissue disorders	Muscle cramps	Common
	Traumatic fractures	Common[1,3]
	Arthralgia	Common
	Myalgia	Common

1. Reported commonly in placebo
2. Reported very commonly in placebo
3. Reported over 3 years in a COPD study
4. See section 4.4
5. See section 5.1.

Description of selected adverse reactions

The pharmacological effects of β_2 agonist treatment, such as tremor, palpitations and headache, have been reported, but tend to be transient and reduce with regular therapy.

Paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid-acting bronchodilator and should be treated straightaway. Airexar Spiromax should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

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Due to the fluticasone propionate component, hoarseness and candidiasis (thrush) of the mouth and throat and, rarely, of the oesophagus, can occur in some patients. Both hoarseness and incidence of mouth and throat candidiasis may be relieved by rinsing the mouth with water and spitting the water out and/or brushing the teeth after using the product. Symptomatic mouth and throat candidiasis can be treated with topical anti-fungal therapy whilst still continuing with Airexar Spiromax.

Paediatric population
Airexar Spiromax is not indicated for use in children and adolescents under the age of 18 years (see Section 4.2). Possible systemic effects in these age groups include Cushing's syndrome, Cushingoid features, adrenal suppression and growth retardation in children and adolescents (see section 4.4). Children may also experience anxiety, sleep disorders and behavioural changes, including hyperactivity and irritability.

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

There are no data available from clinical trials on overdose with Airexar Spiromax, however data on overdose with both active substances are given below:

Salmeterol
The signs and symptoms of salmeterol overdose are dizziness, increases in systolic blood pressure, tremor, headache and tachycardia. If Airexar Spiromax therapy has to be withdrawn due to overdose of the β agonist component of the medicinal product, provision of appropriate replacement steroid therapy should be considered. Additionally, hypokalaemia can occur and therefore serum potassium levels should be monitored. Potassium replacement should be considered.

Fluticasone propionate
Acute: Acute inhalation of fluticasone propionate doses in excess of those recommended may lead to temporary suppression of adrenal function. This does not need emergency action as adrenal function is recovered in a few days, as verified by plasma cortisol measurements.

Chronic overdose: Adrenal reserve should be monitored and treatment with a systemic corticosteroid may be necessary. When stabilised, treatment should be continued with an inhaled corticosteroid at the recommended dose. See section 4.4: “Adrenal function”.

In cases of both acute and chronic fluticasone propionate overdose Airexar Spiromax therapy should be continued at a suitable dose for symptom control.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airway diseases, adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics, ATC code: R03AK06

Mechanism of action and pharmacodynamic effects
Airexar Spiromax contains salmeterol and fluticasone propionate, which have differing modes of action. The respective mechanisms of action of both active substances are discussed below.

Salmeterol:

Medicinal product no longer authorised

Salmeterol is a selective long-acting (12 hour) β_2 adrenoceptor agonist with a long side chain which binds to the exo-site of the receptor.
Salmeterol produces a longer duration of bronchodilation, lasting for at least 12 hours, than recommended doses of conventional short-acting β_2 agonists.

Fluticasone propionate:
Fluticasone propionate given by inhalation at recommended doses has a glucocorticoid anti-inflammatory action within the lungs, resulting in reduced symptoms and exacerbations of asthma, with less adverse effects than when corticosteroids are administered systemically.

Clinical efficacy and safety

The studies described below (GOAL, TORCH and SMART) were carried out with this same fixed-dose combination, salmeterol xinafoate and fluticasone propionate, but studied a previously authorised product; the studies described were not carried out with Airexar Spiromax.

Salmeterol/Fluticasone propionate - Asthma clinical trials
A twelve month study (Gaining Optimal Asthma ControL, GOAL), in 3416 adult and adolescent patients with persistent asthma, compared the safety and efficacy of salmeterol/fluticasone propionate versus inhaled corticosteroid (fluticasone propionate) alone to determine whether the goals of asthma management were achievable. Treatment was stepped up every 12 weeks until ***total control* was achieved or the highest dose of study drug was reached. GOAL showed more patients treated with salmeterol/fluticasone propionate achieved asthma control than patients treated with inhaled corticosteroid (ICS) alone and this control was attained at a lower corticosteroid dose.

**Well controlled* asthma was achieved more rapidly with salmeterol/fluticasone propionate than with ICS alone. The time on treatment for 50% of subjects to achieve a first individual *well controlled* week was 16 days for salmeterol/fluticasone propionate compared with 37 days for the ICS group. In the subset of steroid naive asthmatics the time to an individual *well controlled* week was 16 days in the salmeterol/fluticasone propionate treatment compared with 23 days following treatment with ICS.

The overall study results showed:

Percentage of Patients Attaining *Well Controlled (WC) and **Totally Controlled (TC) Asthma over 12 months				
Pre-Study Treatment	**Salmeterol/FP**		**FP**	
	WC	**TC**	**WC**	**TC**
No ICS (SABA alone)	78%	50%	70%	40%
Low dose ICS (≤500 micrograms BDP or equivalent/day)	75%	44%	60%	28%
Medium dose ICS (>500 to 1000 micrograms BDP or equivalent/day)	62%	29%	47%	16%
Pooled results across the 3 treatment levels	71%	41%	59%	28%

*Well controlled asthma - less than or equal to 2 days with symptom score greater than 1 (symptom score 1 defined as 'symptoms for one short period during the day'), SABA use on less than or equal to 2 days and less than or equal to 4 occasions/week, greater than or equal to 80% predicted morning peak expiratory flow, no night-time awakenings, no exacerbations and no side effects enforcing a change in therapy
**Total control of asthma - no symptoms, no SABA use, greater than or equal to 80% predicted morning peak expiratory flow, no night-time awakenings, no exacerbations and no side effects enforcing a change in therapy

The results of this study suggest that salmeterol/fluticasone propionate 50/100 micrograms twice daily may be considered as initial maintenance therapy in patients with moderate persistent asthma for whom rapid control of asthma is deemed essential (see section 4.2).

Medicinal product no longer authorised

A double blind, randomised, parallel group study in 318 patients with persistent asthma aged ≥18 years evaluated the safety and tolerability of administering two inhalations twice daily (double dose) of salmeterol/fluticasone propionate for two weeks. The study showed that doubling the inhalations of each strength of salmeterol/fluticasone propionate for up to 14 days resulted in a small increase in β agonist-related adverse events (tremor - 1 patient [1%] vs 0, palpitations - 6 [3%] vs 1 [<1%], muscle cramps –6 [3%] vs 1 [<1%]) and a similar incidence of inhaled corticosteroid related adverse events (e.g. oral candidiasis - 6 [6%] vs 16 [8%], hoarseness - 2 [2%] vs 4 [2%]) compared with one inhalation twice daily. The small increase in β agonist-related adverse events should be taken into account if doubling the dose of salmeterol/fluticasone propionate is considered by the physician in adult patients requiring additional short-term (up to 14 days) inhaled corticosteroid therapy.

Salmeterol/fluticasone propionate COPD - clinical trials
TORCH was a 3-year study to assess the effect of treatment with salmeterol/fluticasone propionate inhalation powder 50/500 micrograms twice daily, salmeterol inhalation powder 50 micrograms twice daily, fluticasone propionate (FP) inhalation powder 500 micrograms twice daily or placebo on all-cause mortality in patients with COPD. COPD patients with a baseline (pre-bronchodilator) FEV_1 <60% of predicted normal were randomised to double-blind medication. During the study, patients were permitted usual COPD therapy with the exception of other inhaled corticosteroids, long-acting bronchodilators and long-term systemic corticosteroids. Survival status at 3 years was determined for all patients regardless of withdrawal from study medication. The primary endpoint was reduction in all-cause mortality at 3 years for salmeterol/fluticasone propionate vs placebo.

	Placebo N = 1524	**Salmeterol 50 N = 1521**	**FP 500 N = 1534**	**Salmeterol/fluticasone propionate 50/500 N = 1533**
All cause mortality at 3 years				
Number of deaths (%)	231 (15.2%)	205 (13.5%)	246 (16.0%)	193 (12.6%)
Hazard Ratio vs Placebo (CIs) p value	N/A	0.879 (0.73, 1.06) 0.180	1.060 (0.89, 1.27) 0.525	0.825 (0.68, 1.00) 0.052[1]
Hazard Ratio fluticasone propionate/salmeterol 500/50 vs components (CIs) p value	N/A	0.932 (0.77, 1.13) 0.481	0.774 (0.64, 0.93) 0.007	N/A

1. Non-significant p value after adjustment for 2 interim analyses on the primary efficacy comparison from a log-rank analysis stratified by smoking status

There was a trend towards improved survival in subjects treated with salmeterol/fluticasone propionate compared with placebo over 3 years however this did not achieve the statistical significance level p≤0.05.

The percentage of patients who died within 3 years due to COPD-related causes was 6.0% for placebo, 6.1% for salmeterol, 6.9% for FP and 4.7% for salmeterol/fluticasone propionate.

The mean number of moderate to severe exacerbations per year was significantly reduced with salmeterol/fluticasone propionate (FP) as compared with treatment with salmeterol, FP and placebo (mean rate in the salmeterol/fluticasone propionate group 0.85 compared with 0.97 in the salmeterol group, 0.93 in the FP group and 1.13 in the placebo). This translates to a reduction in the rate of moderate to severe exacerbations of 25% (95% CI: 19% to 31%; p<0.001) compared with placebo, 12% compared with salmeterol (95% CI: 5% to 19%, p=0.002) and 9% compared with FP (95% CI: 1% to 16%, p=0.024). Salmeterol and FP significantly reduced exacerbation rates compared with placebo by 15% (95% CI: 7% to 22%; p<0.001) and 18% (95% CI: 11% to 24%; p<0.001) respectively.

Medicinal product no longer authorised

Health Related Quality of Life, as measured by the St George's Respiratory Questionnaire (SGRQ) was improved by all active treatments in comparison with placebo. The average improvement over three years for salmeterol/fluticasone propionate compared with placebo was -3.1 units (95% CI: -4.1 to -2.1; p<0.001) and when compared with salmeterol was -2.2 units (p<0.001) and when compared with FP was -1.2 units (p=0.017). A 4-unit decrease is considered clinically relevant.

The estimated 3-year probability of having pneumonia reported as an adverse event was 12.3% for placebo, 13.3% for salmeterol, 18.3% for FP and 19.6% for salmeterol/fluticasone propionate (hazard ratio for salmeterol/fluticasone propionate vs placebo: 1.64, 95% CI: 1.33 to 2.01, p<0.001). There was no increase in pneumonia related deaths; deaths while on treatment that were adjudicated as primarily due to pneumonia were 7 for placebo, 9 for salmeterol, 13 for FP and 8 for salmeterol/fluticasone propionate. There was no significant difference in probability of bone fracture (5.1% placebo, 5.1% salmeterol, 5.4% FP and 6.3% salmeterol/fluticasone propionate; hazard ratio for salmeterol/fluticasone propionate vs placebo: 1.22, 95% CI: 0.87 to 1.72, p=0.248.

Placebo-controlled clinical trials, over 6 and 12 months, have shown that regular use of salmeterol/fluticasone propionate 50/500 micrograms improves lung function and reduces breathlessness and the use of relief medication.

Studies SCO40043 and SCO100250 were randomised, double-blind, parallel-group, replicate studies comparing the effect of salmeterol/fluticasone propionate 50/250 micrograms twice daily (a dose not licensed for COPD treatment in the European Union) with salmeterol 50 micrograms twice daily, on the annual rate of moderate/severe exacerbations in subjects with COPD with FEV_1 less than 50% predicted and a history of exacerbations. Moderate/ severe exacerbations were defined as worsening symptoms that required treatment with oral corticosteroids and/or antibiotics or in-patient hospitalisation.

The trials had a 4 week run-in period during which all subjects received open-label salmeterol/FP 50/250 to standardize COPD pharmacotherapy and stabilise disease prior to randomisation to blinded study medication for 52 weeks. Subjects were randomised 1:1 to salmeterol/FP 50/250 (total ITT n=776) or salmeterol (total ITT n=778). Prior to run-in, subjects discontinued use of previous COPD medications except short-acting bronchodilators. The use of concurrent inhaled long-acting β_2 agonists and anticholinergic drugs, salbutamol/ipratropium bromide combination products, oral β_2 agonists and theophylline preparations were not allowed during the treatment period. Oral corticosteroids and antibiotics were allowed for the acute treatment of COPD exacerbations with specific guidelines for use. Subjects used salbutamol on an as-needed basis throughout the studies.

The results of both studies showed that treatment with salmeterol/fluticasone propionate 50/250 resulted in a significantly lower annual rate of moderate/severe COPD exacerbations compared with salmeterol (SCO40043: 1.06 and 1.53 per subject per year, respectively, rate ratio of 0.70, 95% CI: 0.58 to 0.83, p<0.001; SCO100250: 1.10 and 1.59 per subject per year, respectively, rate ratio of 0.70, 95% CI: 0.58 to 0.83, p<0.001). Findings for the secondary efficacy measures (time to first moderate/severe exacerbation, the annual rate of exacerbations requiring oral corticosteroids, and pre-dose morning (AM) FEV_1) significantly favoured salmeterol/fluticasone propionate 50/250 micrograms twice daily over salmeterol. Adverse event profiles were similar with the exception of a higher incidence of pneumonias and known local side effects (candidiasis and dysphonia) in the salmeterol/fluticasone propionate 50/250 micrograms twice daily group compared with salmeterol. Pneumonia-related events were reported for 55 (7%) subjects in the salmeterol/fluticasone propionate 50/250 micrograms twice daily group and 25 (3%) in the salmeterol group. The increased incidence of reported pneumonia with salmeterol/fluticasone propionate 50/250 micrograms twice daily appears to be of similar magnitude to the incidence reported following treatment with salmeterol/fluticasone propionate 50/500 micrograms twice daily in TORCH.

The Salmeterol Multi-center Asthma Research Trial (SMART)

SMART was a multi-centre, randomised, double blind, placebo-controlled, parallel group 28-week study in the US which randomised 13,176 patients to salmeterol (50 micrograms twice daily) and 13,179 patients to placebo in addition to the patients' usual asthma therapy. Patients were enrolled if ≥12 years of age, with

Medicinal product no longer authorised

asthma and if currently using asthma medication (but not a LABA). Baseline ICS use at study entry was recorded, but not required in the study. The primary endpoint in SMART was the combined number of respiratory-related deaths and respiratory-related life-threatening experiences.

Key findings from SMART: primary endpoint

Patient group	Number of primary endpoint events /number of patients		Relative Risk (95% confidence intervals)
	salmeterol	placebo	
All patients	50/13,176	36/13,179	1.40 (0.91, 2.14)
Patients using inhaled steroids	23/6,127	19/6,138	1.21 (0.66, 2.23)
Patients not using inhaled steroids	27/7,049	17/7,041	1.60 (0.87, 2.93)
African-American patients	**20/2,366**	**5/2,319**	**4.10 (1.54, 10.90)**

(Risk in bold is statistically significant at the 95% level.)

Key findings from SMART by inhaled steroid use at baseline: secondary endpoints

	Number of secondary endpoint events/number of patients		Relative Risk (95% confidence intervals)
	salmeterol	placebo	
Respiratory -related death			
Patients using inhaled steroids	10/6127	5/6138	2.01 (0.69, 5.86)
Patients not using inhaled steroids	14/7049	6/7041	2.28 (0.88, 5.94)
Combined asthma-related death or life-threatening experience			
Patients using inhaled steroids	16/6127	13/6138	1.24 (0.60, 2.58)
Patients not using inhaled steroids	**21/7049**	**9/7041**	**2.39 (1.10, 5.22)**
Asthma-related death			
Patients using inhaled steroids	4/6127	3/6138	1.35 (0.30, 6.04)
Patients not using inhaled steroids	9/7049	0/7041	*

(*=could not be calculated because of no events in placebo group. Risk in bold figures is statistically significant at the 95% level. The secondary endpoints in the table above reached statistical significance in the whole population.) The secondary endpoints of combined all cause death or life-threatening experience, all cause death, or all cause hospitalisation did not reach statistical significance in the whole population.

Peak Inspiratory Flow Rate through the Spiromax Device

A randomised, open-label cross-over study was performed in children and adolescents with asthma (aged 4-17 years), adults with asthma (aged 18-45 years), adults with chronic obstructive pulmonary disease (COPD) (aged older than 55 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 optimal training (i.e. breathing in forcefully upon inhalation) in dry powder inhaler inhalation technique on inhalation speed and volume was assessed in these subject groups, together with assessment of potential differences in inhalation outputs according to the devices used.

The data from the study indicated that regardless of age and underlying disease severity, children, adolescents and adults with asthma as well as patients with COPD were able to achieve inspiratory flow rates through the Spiromax device that were similar to those generated through the marketed multi-dose dry powder inhaler device. The mean PIFR achieved by patients with asthma or COPD with optimal training (i.e.

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forceful inhalation) was over 60 L/min, a flow rate at which both devices studied are known to deliver comparable amounts of drug to the lungs.

All subjects with asthma or COPD achieved PIFR values greater than 60L/min after optimal training. It is important to inhale forcefully to ensure optimal dosing.

A flow rate of greater than 60L/min is required for optimal delivery of drugs to the lungs through the multi-dose dry powder Spiromax inhaler.

In order to ensure that patients achieve the PIFR needed to deliver the required dose, the patient is required to be trained on the use of the Spiromax device including instruction on the need to inhale forcefully (see Section 4.2).

Paediatric population

Airexar Spiromax is not recommended for use in children and adolescents aged less than 18 years. The safety and efficacy of Airexar Spiromax in this young population have not been established. The data presented below refer to a lower dose of the fixed-dose combination containing these two actives, a dose and strength which is not available for Airexar Spiromax. The studies described were carried out with a previously authorised product available in three different strengths; the studies were not carried out with Airexar Spiromax.

In a study in 158 children aged 6 to 16 years with symptomatic asthma, the combination of salmeterol/ fluticasone propionate/ is as efficacious as doubling the dose of fluticasone propionate in respect of symptom control and lung function. This study was not designed to investigate the effect on exacerbations.

In a 12-week trial of children aged 4 to 11 years [n=257] treated with either salmeterol/fluticasone propionate 50/100 or salmeterol 50 micrograms + fluticasone propionate 100 micrograms both twice daily, both treatment arms experienced a 14% increase in peak expiratory flow rate as well as improvements in symptom score and *rescue* salbutamol use. There were no differences between the two treatment arms. There were no differences in safety parameters between the two treatment arms.

In a 12-week trial of children 4 to 11 years of age [n=203] randomized in a parallel-group study with persistent asthma and who were symptomatic on inhaled corticosteroid, safety was the primary objective. Children received either salmeterol/fluticasone propionate (50/100 micrograms) or fluticasone propionate (100 micrograms) alone twice daily. Two children on salmeterol/fluticasone propionate/ and 5 children on fluticasone propionate withdrew because of worsening asthma. After 12 weeks no children in either treatment arm had abnormally low 24-hour urinary cortisol excretion. There were no other differences in safety profile between the treatment arms.

5.2 Pharmacokinetic properties

For pharmacokinetic purposes each component can be considered separately.

Salmeterol

Salmeterol acts locally in the lung therefore plasma levels are not an indication of therapeutic effects. In addition there are only limited data available on the pharmacokinetics of salmeterol because of the technical difficulty of assaying the drug in plasma due to the low plasma concentrations at therapeutic doses (approximately 200 picogram/mL or less) achieved after inhaled dosing.

Fluticasone propionate

The absolute bioavailability of a single dose of inhaled fluticasone propionate in healthy subjects varies between approximately 5 to 11% of the nominal dose depending on the inhalation device used. In patients with asthma or COPD a lesser degree of systemic exposure to inhaled fluticasone propionate has been observed.

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Absorption
Systemic absorption occurs mainly through the lungs and is initially rapid then prolonged. The remainder of the inhaled dose of fluticasone propionate may be swallowed but contributes minimally to systemic exposure due to the low aqueous solubility and presystemic metabolism, resulting in oral availability of less than 1%. There is a linear increase in systemic exposure with increasing inhaled dose.

Distribution
The disposition of fluticasone propionate is characterised by high plasma clearance (1150 mL/min), a large volume of distribution at steady-state (approximately 300 L) and a terminal half-life of approximately 8 hours. Plasma protein binding is 91%.

Biotransformation
Fluticasone propionate is cleared very rapidly from the systemic circulation. The main pathway is metabolism to an inactive carboxylic acid metabolite, by the cytochrome P450 enzyme CYP3A4. Other unidentified metabolites are also found in the faeces.

Elimination
The renal clearance of fluticasone propionate is negligible. Less than 5% of the dose is excreted in urine, mainly as metabolites. The main part of the dose is excreted in faeces as metabolites and unchanged drug.

Paediatric population

Airexar Spiromax is not recommended for use in children and adolescents aged less than 18 years. The safety and efficacy of Airexar Spiromax in this young population have not been established. The data presented below refer to a lower dose of the fixed-dose combination containing these two actives, a dose and strength which is not available for Airexar Spiromax.

In a population pharmacokinetic analysis from 9 controlled clinical trials of 350 patients with asthma aged 4 to 77 years (174 patients 4 to 11 years of age) higher fluticasone propionate systemic exposure following treatment with salmeterol/fluticasone propionate inhalation powder 50/100 compared with fluticasone propionate inhalation powder 100 was seen.

5.3 Preclinical safety data

The only safety concerns for human use derived from animal studies of salmeterol and fluticasone propionate given separately were effects associated with exaggerated pharmacological actions.

In animal reproduction studies, glucocorticosteroids have been shown to induce malformations (cleft palate, skeletal malformations). However, these animal experimental results do not seem to be relevant for man given recommended doses. Animal studies with salmeterol have shown embryofetal toxicity only at high exposure levels. Following co-administration, increased incidences of transposed umbilical artery and incomplete ossification of occipital bone were found in rats at doses associated with known glucocorticoid-induced abnormalities.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate.

6.2 Incompatibilities

Not applicable.

Medicinal product no longer authorised

6.3 Shelf life

2years.
After opening the foil wrap: 3 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 yellow 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 or 3 inhalers.

Not all pack-sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1123/001
EU/1/16/1123/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18th August 2016

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.eu

Medicinal product no longer authorised

Medicinal product no longer authorised

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. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

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
The Netherlands

Teva Operations Poland Sp. z.o.o.
ul. Mogilska 80
31-546 Kraków
Poland

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

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

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

Medicinal product no longer authorised

- 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.

Medicinal product no longer authorised

ANNEX III

LABELLING AND PACKAGE LEAFLET

Medicinal product no longer authorised

A. LABELLING

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Airexar Spiromax 50 micrograms/500 micrograms inhalation powder
salmeterol/fluticasone propionate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each metered dose contains 50 micrograms of salmeterol (as salmeterol xinafoate) and 500 micrograms of fluticasone propionate.

Each delivered dose (the dose from the mouthpiece) contains 45 micrograms of salmeterol (as salmeterol xinafoate) and 465 micrograms of fluticasone propionate.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder
1 inhaler containing 60 doses.
3 inhalers each containing 60 doses.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet carefully 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

Use as directed by your doctor.

Front panel: Not for use in children and adolescents.

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

Medicinal product no longer authorised

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

8. EXPIRY DATE

EXP
Use within 3 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 B.V., Swensweg 5, 2031 GA Haarlem, Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1123/001
EU/1/16/1123/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Airexar Spiromax 50 mcg/500 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

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

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

Medicinal product no longer authorised

PC:
SN:
NN:

Medicinal product no longer authorised

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

FOIL

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

Airexar Spiromax 50 micrograms/500 micrograms inhalation powder

salmeterol /fluticasone propionate

Inhalation use

2. METHOD OF ADMINISTRATION

Read the package leaflet

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 3 months of removing from foil wrapping.

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MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

INHALER

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

Airexar Spiromax 50 micrograms/500 micrograms
Inhalation powder

salmeterol/fluticasone propionate

Inhalation use

2. METHOD OF ADMINISTRATION

Read the package leaflet carefully before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

60 doses

6. OTHER

Adults only.

Contains lactose.

Start:

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B. PACKAGE LEAFLET

Medicinal product no longer authorised

Package leaflet: Information for the patient

Airexar Spiromax 50 micrograms/500 micrograms inhalation powder
salmeterol/fluticasone propionate

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 Airexar Spiromax is and what it is used for

Airexar Spiromax contains two medicines, salmeterol and fluticasone propionate:

- Salmeterol is a long-acting bronchodilator. Bronchodilators help the airways in the lungs to stay open. This makes it easier for air to get in and out. The effects last for at least 12 hours.
- Fluticasone propionate is a corticosteroid which reduces swelling and irritation in the lungs.

Your doctor has prescribed this medicine for the treatment of either
- Severe asthma, to help prevent attacks of breathlessness and wheeziness,

or
- Chronic obstructive pulmonary disease (COPD), to reduce the number of flare ups of symptoms.

You must use Airexar Spiromax every day as directed by your doctor. This will make sure that it works properly in controlling your asthma or COPD.

Airexar Spiromax helps to stop breathlessness and wheeziness coming on. However, Airexar Spiromax should not be used to relieve an attack of breathlessness or wheezing. If this happens you need to use a fast-acting 'reliever' ('rescue') inhaler, such as salbutamol. You should always have your fast-acting 'rescue' inhaler with you.

Airexar Spiromax should only be used to treat severe asthma in adults aged 18 years and older and adults with COPD.

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

Do not use Airexar Spiromax:
- if you are allergic (hypersensitive) to salmeterol, fluticasone propionate or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Medicinal product no longer authorised

Talk to your doctor, pharmacist or nurse before using Airexar Spiromax if you have:
- Heart disease, including an irregular or fast heart beat
- Overactive thyroid gland
- High blood pressure
- Diabetes mellitus (Airexar Spiromax may increase your blood sugar)
- Low potassium in your blood
- Tuberculosis (TB) now or have had in the past, or have other lung infections

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

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

Other medicines and Airexar Spiromax
Tell your doctor or pharmacist if you are taking or, have recently taken or might use any other medicines. This includes other medicines for asthma or any medicines obtained without a prescription. Airexar Spiromax may not be suitable to be taken with some other medicines.

Tell your doctor if you are taking the following medicines, before starting to use Airexar Spiromax:
- Beta blockers (such as atenolol, propranolol and sotalol). Beta blockers are mostly used for high blood pressure or heart conditions such as angina.
- Medicines to treat infections (such as ritonavir, ketoconazole, itraconazole and erythromycin). Some of these medicines may increase the amount of salmeterol or fluticasone propionate in your body. This can increase your risk of side effects with Airexar Spiromax, including irregular heartbeats, or may make side effects worse.
- Corticosteroids (by mouth or by injection). Recent use of these medicines might increase the risk of Airexar Spiromax affecting your adrenal glands.
- Diuretics, also known as 'water tablets' used to treat high blood pressure.
- Other bronchodilators (such as salbutamol).
- Xanthine medicines such as aminophylline and theophylline. These are often used to treat asthma.

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

Pregnancy and breastfeeding
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

It is not known whether this medicine can pass into breast milk. If you are breastfeeding, check with your doctor or pharmacist for advice before taking this medicine.

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

Airexar Spiromax contains lactose
Lactose is a type of sugar found in milk. Lactose contains small amounts of milk protein which may cause allergic reactions. If you have been told by your doctor that you have an intolerance or allergy to lactose, other sugars, or milk, contact your doctor before taking this medicinal product.

3. How to use Airexar Spiromax

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

- Use your Airexar Spiromax every day until your doctor advises you to stop. Do not take more than the recommended dose. Check with your doctor or pharmacist if you are not sure.

Medicinal product no longer authorised

- Do not stop taking Airexar Spiromax or reduce the dose of Airexar Spiromax without talking to your doctor first.
- Airexar Spiromax should be inhaled through the mouth into the lungs.

The recommended dose is:

Severe asthma in adults 18 years of age and older

One inhalation twice a day

Chronic Obstructive Pulmonary Disease (COPD)

One inhalation twice a day

If you are using Airexar Spiromax for asthma, your doctor will want to check your symptoms regularly.

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 Airexar Spiromax, your doctor may prescribe an alternative inhaler containing the same active substances as your Airexar Spiromax but with a lower dose of the corticosteroid. However, do not change the number of inhalations your doctor has prescribed without talking to your doctor first.

If your asthma or breathing gets worse tell your doctor straight away. If you feel more wheezy, your chest feels tight more often or you need to use more of your fast-acting 'reliever' medicine, your chest condition may be getting worse and you could become seriously ill. You should continue to take Airexar Spiromax but do not increase the number of puffs you take. See your doctor at once as you may need additional treatment.

Instructions for use

Training
Your doctor, nurse or pharmacist should provide you with training on how to use your inhaler, including how to take a dose effectively. This training is important to ensure you receive the dose you require. If you have not received this training please ask your doctor, nurse or pharmacist to show you how to use your inhaler properly before you use it for the first time.

Your doctor, nurse or pharmacist should also check how you use your Spiromax device from time to time to ensure that you are using the device properly and as prescribed. If you are not using Airexar Spiromax properly and/or you are not breathing in **forcefully** enough, this may mean that you are not getting enough of the medicine into your lungs. If you are not getting enough medicine into your lungs, it will not help your asthma or COPD as it should

Preparing your Airexar Spiromax

Before using your Airexar Spiromax **for the first time**, you need to prepare it for use as follows:
- 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 on the inhaler.
- You do not need to shake your inhaler before you use it.

How to take an inhalation

1. **Hold your inhaler** with the semi-transparent yellow mouthpiece cover at the bottom. You do not need to shake your inhaler.

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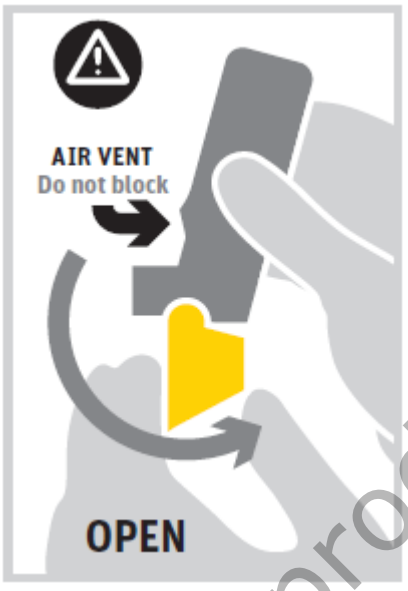
2. Open the mouthpiece cover by folding it down until you hear one loud click. Your inhaler is now ready for use.



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 forcefully as you can.
   Note that it is important that you breathe in **forcefully**.

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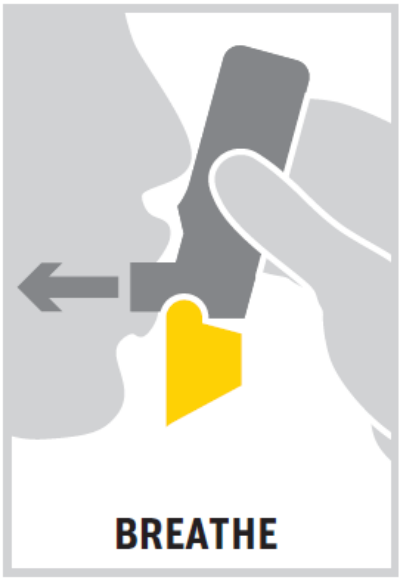

5. Hold your breath for 10 seconds or as long as you comfortably can.

6. Remove your inhaler from your mouth. You may notice a taste when you take your inhalation.

7. **Then breathe out gently** (do not breathe out through the inhaler). **Close the mouthpiece cover**.

Afterwards, rinse your mouth with water and spit it out and/or brush your teeth. This may help to stop you getting thrush in your mouth and/or becoming hoarse.

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

If you open and close the mouthpiece without taking an inhalation the dose will be securely held inside the inhaler ready for the next inhalation. It is impossible to accidentally take extra medicine or a double dose in one inhalation.

Keep the mouthpiece closed all the times unless you are about to use your inhaler.

Cleaning your Inhaler
Keep your inhaler dry and clean.
If necessary you may wipe the mouthpiece of your inhaler after use with a dry cloth or tissue.

When to start using a new Airexar Spiromax
- The dose indicator on the rear of the device tells you how many doses (inhalations) are left in your inhaler, starting with 60 inhalations when it is full.

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

Note:
- The mouthpiece will still ‘click’ even when your inhaler is empty. If you open and close the mouthpiece without taking an inhalation the dose indicator will still register it as a count.

If you use more Airexar Spiromax than you should
It is important to use the inhaler as instructed. If you accidentally take more doses than is recommended, talk to your doctor or pharmacist. You may notice your heart beating faster than usual and that you feel shaky. You may also have dizziness, a headache, muscle weakness and aching joints.

If you have used too many doses of Airexar Spiromax for a long time, you should talk to your doctor or pharmacist for advice. This is because using too much Airexar Spiromax may reduce the amount of steroid hormones produced by your adrenal glands.

If you forget to use Airexar Spiromax
Do not take a double dose to make up for a forgotten dose. Just take your next dose at the usual time.

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If you stop using Airexar Spiromax
It is very important that you take your Airexar Spiromax every day as directed. **Keep taking it until your doctor tells you to stop. Do not stop or suddenly reduce your dose of Airexar Spiromax**. This could make your breathing worse.

In addition, if you suddenly stop taking Airexar Spiromax or reduce your dose of Airexar Spiromax this may (very rarely) cause you to have problems with your adrenal glands (adrenal insufficiency) which sometimes causes side effects.

These side effects may include any of the following:

- Stomach pain
- Tiredness and loss of appetite, feeling sick
- Sickness and diarrhoea
- Weight loss
- Headache or drowsiness
- Low levels of sugar in your blood
- Low blood pressure and seizures (fits)

When your body is under stress such as from fever, trauma (such as an accident or injury), infection, or surgery, adrenal insufficiency can get worse and you may have any of the side effects listed above.

If you get any side effects, talk to your doctor or pharmacist. To prevent these symptoms, your doctor may prescribe extra corticosteroids in tablet form (such as prednisolone).

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. To reduce the chance of side effects your doctor will prescribe the lowest dose of this combination of drugs to control your asthma or COPD.

Allergic reactions: you may notice your breathing suddenly gets worse immediately after using Airexar Spiromax. You may be very wheezy and cough or be short of breath. You may also notice itching, a rash (hives) and swelling (usually of the face, lips, tongue or throat), or you may suddenly feel that your heart is beating very fast or you feel faint and light headed (which may lead to collapse or loss of consciousness). **If you get any of these effects or if they happen suddenly after using Airexar Spiromax, stop using Airexar Spiromax and tell your doctor straight away**. Allergic reactions to Airexar Spiromax are uncommon (they may affect up to 1 in 100 people).

Other side effects are listed below:

Very common (may affect more than 1 in 10 people)
- Headache - this usually gets better as treatment continues.
- Increased number of colds have been reported in patients with chronic obstructive pulmonary disease (COPD).

Common (may affect up to 1 in 10 people)
- Thrush (sore, creamy-yellow, raised patches) in the mouth and throat. Also sore tongue and hoarse voice and throat irritation. Rinsing your mouth out with water and spitting it out immediately and/or brushing your teeth after taking each dose of your medicine may help. Your doctor may prescribe an anti-fungal medicine to treat the thrush.
- Aching, swollen joints and muscle pain.
- Muscle cramps.

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The following side effects have also been reported in patients with chronic obstructive pulmonary disease (COPD):

- Pneumonia and bronchitis (lung infection). Tell your doctor if you notice any of the following symptoms while taking Airexar Spiromax as they could be symptoms of a lung infection: fever or chills; increased mucus production, changes in mucus colour; increased cough or increased breathing difficulties.
- Bruising and fractures.
- Inflammation of sinuses (sinusitis, a feeling of tension or fullness in the nose, cheeks and behind the eyes, sometimes with a throbbing ache).
- A reduction in the amount of potassium in the blood (you may get an uneven heartbeat, muscle weakness, cramp).

Uncommon (may affect up to 1 in 100 people)

- Increases in the amount of sugar (glucose) in your blood (hyperglycaemia). If you have diabetes, more frequent blood sugar monitoring and possibly adjustment of your usual diabetic treatment may be required.
- Cataract (cloudy lens in the eye).
- Very fast heart beat (tachycardia).
- Feeling shaky (tremor) and fast or uneven heart beat (palpitations) - these are usually harmless and get less as treatment continues.
- Chest pain.
- Feeling worried (although this effect occurs mainly in children when prescribed this combination of drugs but in a lower strength).
- Disturbed sleep.
- Allergic skin rash.

Rare (may affect up to 1 in 1,000 people)

- **Breathing difficulties or wheezing that gets worse straight after taking Airexar Spiromax.** If this happens **stop using your Airexar Spiromax inhaler**. Use your fast acting 'reliever' inhaler to help your breathing and **tell your doctor straight away**.
- Airexar Spiromax may affect the normal production of steroid hormones in the body, particularly if you have taken high doses for long periods of time. The effects include:
  - Slowing of growth in children and adolescents
  - Thinning of the bones
  - Glaucoma
  - Weight gain
  - Rounded (moon shaped) face (Cushing's syndrome)

  Your doctor will check you regularly for any of these side effects and make sure you are taking the lowest dose of this combination of drugs to control your asthma.

- Behavioural changes, such as being unusually active and irritable (although these effects occur mainly in children when prescribed this combination of drugs but in a lower strength).
- Uneven or irregular heart beat or an extra heart beat (arrhythmias). Tell your doctor, but do not stop taking Airexar Spiromax unless the doctor tells you to stop.
- A fungal infection in the oesophagus (food canal), which might cause difficulties in swallowing.

Frequency not known, but may also occur:

- Depression or aggression (although these effects are more likely to occur in children when prescribed this combination of drugs but in a lower strength).
- Blurred vision

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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 Airexar 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 and 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 3 months of removing from the foil wrapping.** Use the label on the inhaler to write down the opening date of the foil pouch.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Airexar Spiromax contains
- The active substances are salmeterol and fluticasone propionate. Each metered dose contains 50 micrograms salmeterol (as salmeterol xinafoate) and 500 micrograms fluticasone propionate. Each delivered dose (the dose that leaves the mouthpiece) contains 45 micrograms of salmeterol (as salmeterol xinafoate) and 465 micrograms of fluticasone propionate.
- The other ingredient is lactose monohydrate (see section 2 under 'Airexar Spiromax contains lactose').

What Airexar Spiromax looks like and contents of the pack
Airexar Spiromax is an inhalation powder.
Each Airexar Spiromax inhaler contains 60 inhalations and has a white body with a semi-transparent yellow mouthpiece cover.

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

Marketing Authorisation Holder

Teva B.V.
Swensweg 5, 2031 GA Haarlem, 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 Poland only) Teva Operations Poland Sp. z o.o. Mogilska 80 Str. 31-546 Kraków, Poland

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

Lietuva
UAB "Sicor Biotech"
Tel: +370 5 266 02 03

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България
Тева Фармасютикълс България ЕООД
Тел: +359 2 489 95 82

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

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

Deutschland
Teva GmbH
Tel: +49 731 402 08

Eesti
Teva Eesti esindus UAB Sicor Biotech Eesti filiaal
Tel: +372 661 0801

Ελλάδα
Teva Ελλάς Α.Ε.
Τηλ: +30 210 72 79 099

España
Teva Pharma S.L.U.
Tél: +34 91 387 32 80

France
Teva Santé
Tél: +33 1 55 91 7800

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

Ireland
Teva Pharmaceuticals Ireland
Tel: +353 51 321 740

Ísland
Vistor
Simi: +354 535 7000

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

Κύπρος
Teva Ελλάς Α.Ε.
Ελλάδα

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

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

Malta
Teva Pharmaceuticals Ireland
L-Irlanda
Tel: +353 51 321 740

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

Norge
Teva Norway AS
Tlf: +47 6677 55 90

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

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

Portugal
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 FinlandPuh/Tel: +358 20 180 5900

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

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Τηλ: +30 210 72 79 099

Latvija
Sicor Biotech filiāle Latvijā
Tel: +371 67 323 666

United Kingdom
Teva UK Limited
Tel: +44 1977 628 500

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

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