SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

FOXAIR 25/50 INHALER

FOXAIR 25/125 INHALER

FOXAIR 25/250 INHALER

Metered-dose inhaler

COMPOSITION:

Each single actuation of FOXAIR provides:

Salmeterol xinafoate equivalent to 25 μg of salmeterol and 50, 125 or 250 μg of fluticasone propionate.

Excipient: Hydrofluoralkane 134a propellant (HFA 134a).

PHARMACOLOGICAL CLASSIFICATION:

A 21.5.4 Corticosteroids - Other combinations

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

FOXAIR contains salmeterol and fluticasone propionate which have differing modes of action.

Salmeterol is a selective beta$_2$-adrenoceptor agonist. Salmeterol has been shown to produce long-lasting bronchodilatation of at least 12 hours in subjects with reversible airways obstruction. *In vitro* tests have shown salmeterol to be a potent and long-lasting

inhibitor of the release, from human lung, of mast cell derived mediators, such as histamine, leukotrienes and prostaglandin D_2. In man salmeterol inhibits the early and late phase response to inhaled allergen and after single dosing attenuates bronchial hyperresponsiveness.

Fluticasone propionate *in vitro* has a potent glucocorticoid anti-inflammatory action.

Pharmacokinetic properties:

Following oral administration 87-100 % of the dose is excreted in the faeces, up to 75 % as parent compound depending on the dose. There is a non-active major metabolite.

Following intravenous administration there is rapid plasma clearance suggestive of extensive hepatic extraction. The plasma elimination half-life is approximately 3 hours.

The volume of distribution is approximately 250 litres.

INDICATIONS:

FOXAIR INHALER is indicated in the regular prophylactic treatment of atopic asthma in children and adults, who have been stabilised on identical dosages of the components of FOXAIR given concurrently.

CONTRA-INDICATIONS:

FOXAIR INHALER is contra-indicated in patients with a history of hypersensitivity to any of the ingredients.

WARNINGS AND SPECIAL PRECAUTIONS:

FOXAIR is not for relief of acute symptoms for which a fast and short-acting bronchodilator is required. Patients should be advised to have their relief medication available at all times.

Increasing use of short-acting inhaled beta$_2$-agonists to control symptoms indicates deterioration of asthma control. Under these conditions, the patient should be reassessed.

Sudden and progressive deterioration in asthma control is potentially life-threatening and may have several causes.

Patients on corticosteroid therapy may have adrenocortical suppression.

Treatment with FOXAIR should not be stopped abruptly as adrenal insufficiency may be precipitated in this way.

Special care is necessary in patients with active or quiescent pulmonary tuberculosis.

FOXAIR should be administered with caution in patients with thyrotoxicosis.

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 adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. It is important, therefore, that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control is maintained.

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroid is regularly monitored.

Systemic corticosteroid effects may occur in patients on fluticasone treatment. Patients transferred from other inhaled steroids or oral steroids remain at risk of impaired adrenal reserve for a considerable time after transferring to inhaled fluticasone propionate.

Patients in a medical or surgical emergency, who require high doses of inhaled steroids and/or intermittent treatment with oral steroids, are at risk of impaired adrenal reserve.

The extent of the adrenal impairment may require specialist advice before elective procedures. The possibility of residual impaired adrenal response should always be borne

in mind in emergency and elective situations likely to produce stress and appropriate corticosteroid treatment must be considered.

In children taking recommended doses of inhaled fluticasone propionate adrenal function and adrenal reserve usually remain within the normal range. However, the possible effects of previous or intermittent treatment with oral steroids should not be discounted.

Patients with severe asthma may require high dose inhaled (see DOSAGE AND DIRECTIONS FOR USE) or oral corticosteroid therapy.

Sudden worsening of symptoms may require increased corticosteroid dosage which should be administered under urgent medical supervision.

Patients weaned off oral steroids whose adrenocortical function is still impaired should carry a steroid warning card indicating that they may need supplementary systemic steroid during periods of stress, e.g. worsening asthma attacks, chest infections, major intercurrent illness, surgery, trauma, etc.

In rare cases inhaled therapy may unmask underlying eosinophilic conditions (e.g. Churg Strauss syndrome). These cases have usually been associated with reduction or withdrawal of oral corticosteroid therapy. A direct causal relationship has not been established.

Lack of response or severe exacerbations of asthma should be treated by increasing the dose of inhaled fluticasone propionate or by giving a systemic steroid and/or an antibiotic if there is an infection.

Paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. This should be treated immediately with a fast-acting inhaled bronchodilator. FOXAIR should be discontinued immediately, the patient assessed, and if necessary alternative therapy instituted.

Effects on ability to drive and use machines:

FOXAIR is unlikely to produce an effect.

INTERACTIONS:

Due to the very low plasma concentrations achieved after inhaled dosing clinically significant drug interactions are unlikely. Care should be taken when co-administering known strong CYP3A4 inhibitors (e.g. ketoconazole, ritonavir) as there is potential for increased systemic exposure to fluticasone propionate.

Both non-selective and selective beta-blockers should be avoided in patients with reversible obstructive airways disease, unless there are compelling reasons for their use.

PREGNANCY AND LACTATION:

Safety in pregnancy and lactation has not been established.

Fluticasone propionate:

Safety during pregnancy and lactation has not been established.

Corticosteroids have been shown to be teratogenic in animals. As these agents are absorbed when inhaled, teratogenicity following inhalation cannot be excluded.

Salmeterol:

Safety in pregnancy has not been established. There is no experience of the use of salmeterol in breastfeeding mothers.

DOSAGE AND DIRECTIONS FOR USE:

FOXAIR INHALER is for oral inhalation use only.

Patients should be made aware that FOXAIR INHALER must be used regularly for optimum benefit, even when asymptomatic.

Patients should be regularly reassessed by a doctor so that the dosage of FOXAIR 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.

FOXAIR INHALER is not for relief of acute symptoms for which a fast and short-acting bronchodilator is required. Patients should be advised to have their relief medication available at all times.

Increasing use of short-acting bronchodilators to relieve asthma symptoms indicates deterioration of asthma control.

Sudden and progressive deterioration in control of asthma is potentially life-threatening and the patient should be reviewed. Consideration should be given to increasing corticosteroid therapy. Also, where the current dosage of FOXAIR has failed to give adequate control of reversible obstructive airways disease, the patient should be reviewed. Consideration should be given to additional corticosteroid therapies, and to include administration of antibiotics if an infection is present.

Treatment with FOXAIR should not be stopped abruptly.

Recommended Doses:

Shake the inhaler well before use.

Adults and adolescents 12 years and older:

Two inhalations of FOXAIR 25/50 twice daily.

OR

Two inhalations of FOXAIR 25/125 twice daily.

OR

Two inhalations of FOXAIR 25/250 twice daily.

Special patient groups:

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

SIDE EFFECTS:

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 and < 1/10), uncommon (≥ 1/1 000 and < 1/100), rare (≥ 1/10 000 and < 1/1 000) and very rare (< 1/10 000) including isolated reports.

As FOXAIR contains salmeterol and fluticasone propionate, the type and severity of adverse reactions associated with each of the compounds may be expected.

Adverse events which have been associated with salmeterol or fluticasone propionate are given below.

Salmeterol:

Clinical trials data:

Immune system disorders:

Hypersensitivity reactions:

Uncommon: rash

Nervous system disorders:

Common: tremor, headache

Cardiac disorders:

Common: palpitations

Musculoskeletal and connective tissue disorders:

Common: muscle cramps.

Post-marketing data:

Immune system disorders: hypersensitivity reactions: oedema and angioedema

Metabolism and nutrition disorders: hypokalaemia

Cardiac disorders: cardiac arrythmias including atrial fibrillation, supraventricular tachycardia and extrasystoles

Respiratory, thoracic and mediastinal disorders: oropharyngeal irritation

Musculoskeletal and connective tissue disorders: arthralgia.

Fluticasone propionate:

Clinical trials data:

Infections and infestations:

Very common: candidiasis of mouth and throat

Candidiasis of the mouth and throat (thrush) may occur. Such patients may find it helpful to gargle with water after using FOXAIR. Symptomatic candidiasis can be treated with topical anti-fungal therapy whilst still continuing with FOXAIR INHALER

Immune system disorders:

Hypersensitivity reactions with the following manifestations have been reported:

Uncommon: cutaneous hypersensitivity reactions

Respiratory, thoracic and mediastinal disorders:

Common: hoarseness

Hoarseness may occur. Such patients may find it helpful to gargle with water after using the INHALER.

Post-marketing data:

Endocrine disorders: possible systemic effects include (see WARNINGS AND SPECIAL PRECAUTIONS) adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract, glaucoma

Immune system disorders: angioedema (mainly facial and oropharyngeal oedema), respiratory symptoms (dyspnoea and/or bronchospasm) and anaphylactic reactions

Respiratory, thoracic and mediastinal disorders: paradoxical bronchospasm.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

The symptoms and signs of salmeterol overdosage are tremor, headache and tachycardia. The preferred antidote for overdosage with salmeterol inhaler is a cardio-selective beta-blocking agent. Both non-selective and selective beta-blockers should be avoided in patients with reversible obstructive airways disease, unless there are compelling reasons for their use.

Acute - Inhalation of fluticasone propionate at dosages in excess of those recommended may lead to temporary suppression of adrenal function. This does not necessitate emergency action being taken. In these patients treatment with fluticasone propionate by inhalation should be continued at a dose sufficient to control asthma; adrenal function recovers in a few days and can be verified by measuring plasma cortisol.

Chronic - Use of inhaled fluticasone propionate at doses in excess of those recommended over prolonged periods may lead to some degree of adrenal suppression. Monitoring of adrenal reserve may be indicated. Treatment with inhaled fluticasone propionate should be continued at a dose sufficient to control asthma.

IDENTIFICATION:

Actuator and metal can with concave base fitted with a metering valve. The canister contains a white to off-white suspension.

PRESENTATION:

The suspension is contained in an aluminium alloy can sealed with a metering valve. The canisters are fitted into plastic actuators incorporating an atomising orifice and fitted with dustcaps. FOXAIR INHALER has been formulated in three strengths and one pack size, delivering 120 actuations per inhaler. FOXAIR INHALER is packed in a carton.

STORAGE INSTRUCTIONS:

Store below 30 ºC.

Protect from frost and direct sunlight.

Keep out of reach of children.

REGISTRATION NUMBER:

FOXAIR 25/50 INHALER – 42/21.5.4/0244

FOXAIR 25/125 INHALER – 42/21.5.4/0245

FOXAIR 25/250 INHALER – 42/21.5.4/0246

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE REGISTRATION CERTIFICATE:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

DATE OF PUBLICATION OF THE PACKAGE INSERT:

26 November 2010

HISTORY:

Compliant PI submitted to MCC 28 June 2010
PIL alignedwith MCC letter dated 25 August 2010
Registered 26 November 2010
Annotated 7 Dec 2010 – Applicant change to GSK

Amended: 10 Dec 2015 (Notification to bring in line with Reg 9 & !0). Implement 11 Dec 2015