AUSTRALIAN PRODUCT INFORMATION - FOSTAIR 100/6 (BECLOMETASONE DIPROPIONATE AND FORMOTEROL (EFORMOTEROL) FUMARATE DIHYDRATE) PRESSURISED INHALATION SOLUTION

1. NAME OF THE MEDICINE

Beclometasone dipropionate and formoterol (eformoterol) fumarate dihydrate.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

FOSTAIR is a pressurised metered dose inhaler (pMDI). Each metered dose (ex-valve) contains: 100 micrograms of beclometasone dipropionate and 6 micrograms of formoterol fumarate dihydrate.

This is equivalent to a delivered dose (ex-actuator) of 84.6 micrograms of beclometasone dipropionate and 5.0 micrograms of formoterol fumarate dihydrate.

Excipient with known effect: ethanol absolute.

For the full list of excipients see section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

Pressurised inhalation solution.

Colourless to yellowish solution.
The inhalation solution is contained in a pressurised aluminium container sealed with a metering valve. The canister is inserted into a polypropylene plastic actuator which incorporates a mouthpiece and is fitted with a plastic protective cap. The actuator is light purplish-red with a dark purplish-red cap. The actuator has a dose counter.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Asthma
FOSTAIR is indicated in adults (18 years and older) in the regular treatment of asthma where use of a combination product (inhaled corticosteroid and long-acting $beta_2$-agonist) is appropriate:

- patients not adequately controlled with inhaled corticosteroids (ICS) and 'as needed' inhaled rapid-acting $beta_2$-agonist or
- patients already adequately controlled on both ICS and long-acting $beta_2$-agonists (LABA).

COPD
Symptomatic treatment of adults with severe COPD (FEV_1 < 50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators.

4.2 DOSE AND METHOD OF ADMINISTRATION

FOSTAIR is for inhalation use.

DOSAGE

ASTHMA

FOSTAIR is not intended for the initial management of asthma. The dosage of the components of FOSTAIR is individual and should be adjusted to the severity of the disease. This should be considered not only when treatment with combination products is initiated but also when the dose is adjusted. If an individual patient should require a combination of doses other than those available in the combination inhaler, appropriate doses of $beta_2$-agonists and/or corticosteroids by individual inhalers should be prescribed.

There are two treatment approaches:

A. Maintenance therapy: FOSTAIR is taken as regular maintenance treatment with a separate as needed rapid-acting bronchodilator.
B. Maintenance and reliever therapy: FOSTAIR is taken as regular maintenance treatment and as needed in response to asthma symptoms.

A. Maintenance therapy

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

Dose recommendations for adults 18 years and above:

One or two inhalations twice daily.
The maximum daily dose is 4 inhalations.

FOSTAIR can be taken as maintenance therapy either as 1 or 2 inhalations twice daily. The starting dose for maintenance therapy is 1 inhalation, twice daily for patients inadequately controlled with an ICS and SABA or adequately controlled with an ICS and LABA. If the patient's asthma is poorly controlled with 1 inhalation, twice daily of FOSTAIR; the total number of inhalations should be increased to 2 inhalations, twice daily of FOSTAIR.

B. Maintenance and reliever therapy

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

FOSTAIR maintenance and reliever therapy should especially be considered for patients with:
- not fully controlled asthma and in need of reliever medication;
- asthma exacerbations in the past requiring medical intervention

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

Dose recommendations for adults 18 years and above:

The recommended maintenance dose is 1 inhalation twice daily (one inhalation in the morning and one inhalation in the evening).

Patients should take 1 additional inhalation as needed in response to symptoms. If symptoms persist after a few minutes, an additional inhalation should be taken. Patients should not take more than 6 inhalations on any single occasion.

The maximum daily dose is 8 inhalations.

Patients who require 6 rescue inhalations per day for two consecutive days will be requested to contact their physician for asthma re-evaluation.

Patients should be regularly reassessed by a doctor, so that the dosage of FOSTAIR 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. When control of symptoms is maintained with the lowest recommended dosage, then the next step could include a test of inhaled corticosteroid alone.

Patients should be advised to take FOSTAIR every day even when asymptomatic.

COPD

Dose recommendations for adults 18 years and above:

Two inhalations twice daily.

Special patient groups:

There is no need to adjust the dose in elderly patients. There are no data available for use of FOSTAIR in patients with hepatic or renal impairment (see section 5.2 PHARMACOKINETIC PROPERTIES).

METHOD OF ADMINISTRATION

To ensure proper administration of the drug, the patient should be shown how to use the inhaler correctly by a physician or other health professional. Correct use of the pMDI is essential in order that treatment is successful. The patient should be advised to read the Patient Information Leaflet carefully and follow the instructions for use as given in the Leaflet.

FOSTAIR inhaler is provided with a counter on the back of the actuator, which shows how many doses are left. For the 120 doses presentation each time the patient presses the canister, a puff of medicine is

released, and the counter counts down by one. Patients should be advised not to drop the inhaler as this may cause the counter to count down.

Testing the inhaler:
Before using the inhaler for the first time or if the inhaler has not been used for 14 days or more, the patient should release one actuation into the air in order to ensure that the inhaler is working properly. After testing the inhaler for the first time, the counter should read 120.

Whenever possible patients should stand or sit in an upright position when inhaling from their inhaler.

Use of the inhaler:
1. Patients should remove the protective cap from the mouthpiece and check that the mouthpiece is clean and free from dust and dirt or any other foreign objects.
2. Patients should breathe out as slowly and deeply as possible.
3. Patients should hold the canister vertically with its body upwards and put the lips around the mouthpiece without biting the mouthpiece
4. At the same time, patients should breathe in slowly and deeply through the mouth. After starting to breathe in, they should press down on the top of the inhaler to release one puff.
5. Patients should hold the breath for as long as possible and, finally, they should remove the inhaler from the mouth and breathe out slowly. Patients should not breathe out into the inhaler.

To inhale a further puff, patients should keep the inhaler in a vertical position for about half a minute and repeat steps 2 to 5.

IMPORTANT: patients should not perform steps 2 to 5 too quickly.

After use, patients should close the inhaler with protective cap and check the dose counter.

Patients should be advised to get a new inhaler when the dose counter or indicator shows the number 20. They should stop using the inhaler when the counter shows 0 as any puffs left in the device may not be enough to release a full dose.

If mist appears following inhalation, either from the inhaler or from the sides of the mouth, the procedure should be repeated from step 2.

For patients with weak hands it may be easier to hold the inhaler with both hands. Therefore the index fingers should be placed on the top of the inhaler canister and both thumbs on the base of the inhaler.

Patients should rinse their mouth or gargle with water or brush the teeth after inhaling (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Cleaning:
Patients should be advised to read the Patient Information Leaflet carefully for cleaning instructions. For the regular cleaning of the inhaler, patients should remove the cap from the mouthpiece and wipe

the outside and inside of the mouthpiece with a dry cloth. They should not remove the canister from the actuator and should not use water or other liquids to clean the mouthpiece.

Patients who find it difficult to synchronise aerosol actuation with inspiration of breath, may use a suitable spacer device. They should be advised by their doctor, pharmacist or a nurse in the proper use and care of their inhaler and spacer and their technique checked to ensure optimum delivery of the inhaled drug to the lungs. This may be obtained by the patients using the spacer by one continuous slow and deep breath through the spacer, without any delay between actuation and inhalation.

4.3 CONTRAINDICATIONS

Hypersensitivity to beclometasone dipropionate, formoterol fumarate dihydrate or any of the excipients listed in section 6.1 LIST OF EXCIPIENTS.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

TREATMENT GUIDELINES

Treatment of asthma or COPD should be in accordance with current national treatment guidelines.

Patients with asthma should have a personal asthma action plan designed in association with their general practitioner. This plan should incorporate a stepwise treatment regime which can be instituted if the patient's asthma improves or deteriorates.

IDENTIFIED PRECAUTIONS

Use of FOSTAIR

Use of ICS/LABA is not the recommended 'preventer' treatment for mild asthma, and should be considered only when patients have not responded to ICS alone.

For treatment of acute asthma attacks patients should be advised to have their rapid-acting bronchodilator available at all times, either FOSTAIR (for patients using FOSTAIR as maintenance and reliever therapy) or a separate rapid-acting bronchodilator (for patients using FOSTAIR as maintenance therapy only).

Patients with heart conditions

FOSTAIR should be used with caution (which may include monitoring) in patients with cardiac arrhythmias, especially third degree atrioventricular block and tachyarrhythmias (accelerated and/or irregular heart beat), idiopathic subvalvular aortic stenosis, hypertrophic obstructive cardiomyopathy, severe heart disease, particularly acute myocardial infarction, ischaemic heart disease, congestive heart failure, occlusive vascular diseases, particularly arteriosclerosis, arterial hypertension and aneurysm.

QTc interval

Caution should also be observed when treating patients with known or suspected prolongation of the QTc interval, either congenital or drug induced (QTc > 0.44 seconds). Formoterol itself may induce prolongation of the QTc interval.

Use with anaesthesia

If anaesthesia with halogenated anaesthetics is planned, it should be ensured that FOSTAIR is not administered for at least 12 hours before the start of anaesthesia as there is a risk of cardiac arrhythmias.

Patients with pulmonary infections

As with all inhaled medication containing corticosteroids, FOSTAIR should be administered with caution in patients with active or quiescent pulmonary tuberculosis, fungal and viral infections in the airways.

It is recommended that treatment with FOSTAIR should not be stopped abruptly.

Ineffective Treatment

If patients find the treatment ineffective medical attention must be sought. Increasing use of rescue bronchodilators indicates a worsening of the underlying condition and warrants a reassessment of the asthma therapy. Sudden and progressive deterioration in control of asthma or COPD is potentially life-threatening and the patient should undergo urgent medical assessment. Consideration should be given to the need for increased treatment with corticosteroids, either inhaled or oral therapy, or antibiotic treatment if an infection is suspected.

Exacerbations

Patients should not be initiated on FOSTAIR 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 FOSTAIR. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on FOSTAIR.

As with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing and rapidness of breath after dosing. This should be treated immediately with a fast-acting inhaled bronchodilator. FOSTAIR should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

Reliever inhalations

Patients should be reminded to take FOSTAIR daily as prescribed even when asymptomatic. The reliever inhalations of FOSTAIR should be taken in response to asthma symptoms but are not intended for regular prophylactic use, e.g. before exercise. For such use, a separate rapid-acting bronchodilator should be considered.

The lowest effective dose of inhaled steroid should be used (see section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Systemic effects

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods . These effects are much less likely to occur with inhaled than with oral corticosteroids. Possible systemic effects include: Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, growth retardation in children and adolescents, cataract and

glaucoma and more rarely, a range of psycological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).

Therefore, it is important 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.

Use with spacers

Single dose pharmacokinetic data (see section 5.2 PHARMACOKINETIC PROPERTIES) have demonstrated that the use of FOSTAIR with AEROCHAMBER PLUS spacer device in comparison to the use of standard actuator, does not increase the total systemic exposure to formoterol and reduces the systemic exposure to beclometasone-17-monopropionate, while there is an increase for unchanged beclometasone dipropionate that reaches systemic circulation from the lung. However taking into account that unchanged beclometasone diproprionate is 30 times less potent compared to beclometasone-17-monopropionate in terms of glucocorticoid receptor activity, the observed increase in beclometasone diproprionate levels is not expected to have any clinically relevant impact on beclometasone diproprionate systemic effects.

Prolonged treatment

Prolonged treatment of patients with high doses of inhaled corticosteroids may result in adrenal suppression. Acute adrenal crisis may occur if the ICS are ceased or reduced in dose or during an intercurrent illness. 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.

Pneumonia in patients with COPD

An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, has been observed in patients with COPD receiving inhaled corticosteroids. There is some evidence of an increased risk of pneumonia with increasing steroid dose but this has not been demonstrated conclusively across all studies. There is no conclusive clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products. Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations. Risk factors for pneumonia in patients with COPD include current smoking, older age, low body mass index (BMI) and severe COPD.

Patients should be advised that FOSTAIR contains a small amount of ethanol (approximately 7 mg per actuation); however at normal doses the amount of ethanol is negligible and does not pose a risk to patients.

Patients should be advised to rinse the mouth or gargle with water or brush the teeth after inhaling the prescribed dose to minimise the risk of oropharyngeal candida infection.

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.

Use in the elderly

No data available.

Paediatric use

The safety and efficacy of FOSTAIR in children and adolescents under 18 years of age have not been established yet. No data are available with FOSTAIR in children under 12 years of age. Only limited data are available in adolescents between 12 and 17 years of age. Therefore FOSTAIR is not recommended for children and adolescents under 18 years until further data become available.

Effects on laboratory tests

Caution is also required when FOSTAIR is used by patients with thyrotoxicosis, diabetes mellitus, phaeochromocytoma and untreated hypokalaemia.

Potentially serious hypokalaemia may result from beta$_2$-agonist therapy. Particular caution is advised in severe asthma as this effect may be potentiated by hypoxia. Hypokalaemia may also be potentiated by concomitant treatment with other drugs which can induce hypokalaemia, such as xanthine derivatives, steroids and diuretics (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). Caution is also recommended in unstable asthma when a number of "rescue" bronchodilators may be used. It is recommended that serum potassium levels are monitored in such situations.

The inhalation of formoterol may cause a rise in blood glucose levels. Therefore blood glucose should be closely monitored in patients with diabetes.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Pharmacokinetic interactions

Beclometasone dipropionate undergoes a very rapid metabolism via esterase enzymes. Beclometasone is less dependent on CYP3A metabolism than some other corticosteroids, and in general interactions are unlikely; however the possibility of systemic effects with concomitant use of strong CYP3A inhibitors (e.g. ritonavir, cobicistat) cannot be excluded, and therefore caution and appropriate monitoring is advised with the use of such agents.

Pharmacodynamic interactions

Beta-blockers (including eye drops) should be avoided in asthmatic patients. If beta-blockers are administered for compelling reasons, the effect of formoterol will be reduced or abolished.

On the other hand, concomitant use of other beta-adrenergic drugs can have potentially additive effects, therefore caution is required when theophylline or other beta-adrenergic drugs are prescribed concomitantly with formoterol.

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

In addition, L-dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards $beta_2$-sympathomimetics.

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

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

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate a possible hypokalaemic effect of $beta_2$-agonists (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Hypokalaemia may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides.

FOSTAIR contains a small amount of ethanol. There is a theoretical potential for interaction in particularly sensitive patients taking disulfiram or metronidazole.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no relevant clinical data on the effect of FOSTAIR on fertility.
Disruption of normal oestrus cycling was observed in female rats treated with beclometasone dipropionate and formoterol fumarate dihydrate in combination at an oral dose of 18.9/1.1 mg/kg/day, yielding almost 600 times the systemic exposure to beclometasone and 6 times the exposure to formoterol compared to patients at the maximum recommended clinical dose of 8 actuations per day (based on plasma AUC). Fertility was unaffected in male rats at this dose level, and female fertility was unaffected at a dose of 1.89/0.11 mg/kg/day, yielding approximately 120 times the systemic exposure to beclometasone and 0.2 times the exposure to formoterol compared to patients at the maximum recommended clinical dose. The effects on female fertility observed in animals are likely to be due to the beclometasone dipropionate (corticosteroid) component of FOSTAIR. Given the magnitude of the exposure multiples, impairment of fertility is not expected in patients.

Use in pregnancy (Category B3)

There are no relevant clinical data on the use of FOSTAIR in pregnant women. Because of the tocolytic actions of formoterol as a $beta_2$-adrenergic agonist particular care should be exercised in the run up to delivery. FOSTAIR should not be recommended for use during pregnancy and particularly at the end of pregnancy or during labour unless there is no other (safer) established alternative.

In pregnant rats, administration of beclometasone dipropionate and formoterol fumarate dihydrate in combination was not teratogenic with oral administration at up to 18.9/1.13 mg/kg/day, yielding almost 600 times the systemic exposure to beclometasone and 6 times the exposure to formoterol compared to patients at the maximum recommended clinical dose of 8 actuations per day (based on plasma AUC). Dystocia and litter loss, decreased fetal weight, increased fetal visceral variations, and impaired fetal ossification were observed in pregnant rats treated at ≥1.89/0.11 mg/kg/day (yielding approximately 120 times the systemic exposure to beclometasone and 0.2 times the exposure to formoterol compared to patients at the maximum recommended clinical dose).

FOSTAIR should only be used during pregnancy if the expected benefits outweigh the potential risks.

Use in lactation

There are no relevant clinical data on the use of FOSTAIR in lactation in humans.

Although no data from animal experiments are available, it is reasonable to assume that beclometasone dipropionate is secreted in milk, like other corticosteroids. While it is not known whether formoterol passes into human breast milk, it has been detected in the milk of lactating animals.

Administration of FOSTAIR to women who are breast-feeding should only be considered if the expected benefits outweigh the potential risks.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

FOSTAIR is unlikely to have any effect on the ability to drive and operate machinery.

However, adverse effects of FOSTAIR include dizziness and visual disturbances such as blurred vision which could affect the ability to drive or use machines (see section 4.8 ADVERSE EFFECT (UNDESIRABLE EFFECTS)).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

As FOSTAIR contains beclometasone dipropionate and formoterol fumarate dihydrate, the type and severity of adverse reactions associated with each of the compounds may be expected. There is no incidence of additional adverse events following concurrent administration of the two compounds.

Undesirable effects which have been associated with beclometasone dipropionate and formoterol administered as a fixed combination (FOSTAIR) and as single agents are given below, listed by system organ class. 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 < 1/1,000) and very rare (≤1/10,000).

Common and uncommon ADRs were derived from clinical trials in asthmatic and COPD patients.

*One related non-serious case of pneumonia was reported by one patient treated with FOSTAIR in a pivotal clinical trial in COPD patients. Other adverse reactions observed with FOSTAIR in COPD clinical trials were: reduction of blood cortisol and atrial fibrillation.

System Organ Class	Adverse Reaction	Frequency
Infections and Infestations	Pharyngitis, oral candidiasis, pneumonia* (in COPD patients)	Common
	Influenza, oral fungal infection, oropharyngeal candidiasis, oesophageal candidiasis, vulvovaginal candidiasis, gastroenteritis, sinusitis, rhinitis,	Uncommon
Blood and lymphatic system disorders	Granulocytopenia	Uncommon
	Thrombocytopenia	Very rare
Immune system disorders	Dermatitis allergic	Uncommon
	Hypersensitivity reactions, including erythema, lips, face, eye and pharyngeal oedema	Very rare
Endocrine disorders	Adrenal suppression	Very rare
Metabolism and nutrition disorders	Hypokalaemia, hyperglycaemia	Uncommon
Psychiatric disorders	Restlessness	Uncommon
	Psychomotor hyperactivity, sleep disorders, anxiety, depression, aggression, behavioural changes (predominantly in children)	unknown
Nervous system disorders	Headache	Common
	Tremor, dizziness	Uncommon
Eye disorders	Glaucoma, cataract	Very rare
	Vision, blurred (see also section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)	Unknown
Ear and labyrinth disorders	Otosalpingitis	Uncommon
Cardiac disorders	Palpitations, electrocardiogram QT corrected interval prolonged, electrocardiogram change, tachycardia, tachyarrhythmia, atrial fibrillation*,	Uncommon
	Ventricular extrasystoles, angina pectoris	Rare
Vascular disorders	Hyperaemia, flushing	Uncommon

Respiratory, thoracic and mediastinal disorders	Dysphonia	Common
	Cough, productive cough, throat irritation, asthmatic crisis	Uncommon
	Bronchospasm paradoxical	Rare
	Dyspnoea, exacerbation of asthma	Very rare
Gastrointestinal disorders	Diarrhoea, dry mouth, dyspepsia, dysphagia, burning sensation of the lips, nausea, dysgeusia	Uncommon
Skin and subcutaneous tissue disorders	Pruritus, rash, hyperhidrosis, urticaria	Uncommon
	Angioedema	Rare
Musculoskeletal and connective tissue disorders	Muscle spasms, myalgia	Uncommon
	Growth retardation in children and adolescents	Very rare
Renal and urinary disorders	Nephritis	Rare
General disorders and administration site conditions	Oedema peripheral	Very rare
Investigations	C-reactive protein increased, platelet count increased, free fatty acids increased, blood insulin increased, blood ketone body increased, blood cortisol decrease*	Uncommon
	Blood pressure increased, blood pressure decreased	Rare
	Bone density decreased	Very rare

As with other inhalation therapy, paradoxical bronchospasm may occur (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Among the observed adverse reactions those typically associated with formoterol are: hypokalaemia, headache, tremor, palpitations, cough, muscle spasms and prolongation of QTc interval. Adverse reactions typically associated with the administration of beclometasone dipropionate are: oral fungal infections, oral candidiasis, dysphonia, throat irritation.

Dysphonia and candidiasis may be relieved by gargling or rinsing the mouth with water or brushing the teeth after using the product. Symptomatic candidiasis can be treated with topical anti-fungal therapy whilst continuing the treatment with FOSTAIR.

Systemic effects of inhaled corticosteroids (e.g. beclometasone dipropionate) may occur particularly when administered at high doses prescribed for prolonged periods, these may include adrenal suppression, decrease in bone mineral density, growth retardation in children and adolescents, cataract and glaucoma (see also section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Hypersensitivity reactions including rash, urticaria pruritus, erhythema and oedema of the eyes, face, lips and throat may also occur.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Inhaled doses of FOSTAIR up to twelve cumulative actuations (total beclometasone dipropionate 1200 micrograms, formoterol 72 micrograms) have been studied in asthmatic patients. The cumulative treatments did not cause abnormal effect on vital signs and neither serious nor severe adverse events were observed.

Excessive doses of formoterol may lead to effects that are typical of beta$_2$-adrenergic agonists: nausea, vomiting, headache, tremor, somnolence, palpitations, tachycardia, ventricular arrhythmias, prolongation of QTc interval, metabolic acidosis, hypokalaemia, hyperglycaemia.

In case of overdose of formoterol, supportive and symptomatic treatment is indicated. Serious cases should be hospitalised. Use of cardioselective beta-adrenergic blockers may be considered, but only subject to extreme caution since the use of beta-adrenergic blocker medication may provoke bronchospasm. Serum potassium should be monitored.

Acute inhalation of beclometasone dipropionate doses in excess of those recommended may lead to temporary suppression of adrenal function. This does not need emergency action as adrenal function recovers in a few days, as verified by plasma cortisol measurements. In these patients treatment should be continued at a dose sufficient to control asthma.

Chronic overdose of inhaled beclometasone dipropionate: risk of adrenal suppression (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Monitoring of adrenal reserve may be necessary. Treatment should be continued at a dose sufficient to control asthma.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Drugs for obstructive airway diseases: Adrenergics, Inhalants

ATC-code: R03 AK08

MECHANISM OF ACTION

FOSTAIR contains beclometasone dipropionate and formoterol. These two drugs have different modes of action. In common with other inhaled corticosteroids and beta$_2$-adrenergic agonist combinations, additive effects are seen in respect of reduction in asthma exacerbations.

Beclometasone dipropionate (BDP)

Beclometasone dipropionate 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.

Formoterol

Formoterol is a selective beta$_2$-adrenergic agonist that produces relaxation of bronchial smooth muscle in patients with reversible airways obstruction. The bronchodilating effect sets in rapidly, within 1-3 minutes after inhalation, and has a duration of 12 hours after a single dose.

CLINICAL TRIALS

ASTHMA

Maintenance therapy:

The efficacy of FOSTAIR as maintenance treatment for asthma was evaluated in randomized double blind, multicentre trials in patients with different degree of asthma severity. The efficacy of FOSTAIR fixed combination was first evaluated in patients with mild to moderate asthma who were still symptomatic despite receiving low-dose ICS. FOSTAIR given at one inhalation twice daily proved to be more effective at improving lung function than a double equipotent dosage of BDP non-extrafine. A second investigation was carried out in patients with more severe asthma. In this setting, FOSTAIR given as two inhalations twice daily was as effective as non-extrafine BDP and formoterol administered via separate inhalers, and superior to non-extrafine BDP alone in improving lung function.

A third study showed that after 24-weeks of treatment extrafine FOSTAIR delivered by an HFApMDI was superior in improving asthma control to the combination of the same drugs formulated as larger non-extrafine agents at equipotent doses.

Two head-to-head clinical trials assessed the efficacy and tolerability of FOSTAIR vs budesonide/formoterol and fluticasone propionate/salmeterol. The two studies shared a similar study design. Subjects were allowed to enter the studies only if they had asthma symptoms and impaired lung function despite receiving ICS. In the first trial, patients given FOSTAIR as 2 inhalations twice daily showed improvement in lung function, measured by morning pre-dose Peak Expiratory Flow (PEF), which was comparable with an equipotent regimen of budesonide/formoterol administered as 2 inhalations twice daily. In the second trial, FOSTAIR was compared with fluticasone propionate/salmeterol, both administered as 2 inhalations twice daily. FOSTAIR demonstrated improvement in lung function comparable to that of fluticasone propionate/salmeterol.

Maintenance and reliever therapy:
In a 48-week parallel group study involving 1701 asthma patients, the efficacy of FOSTAIR administered as maintenance (1 inhalation BID) and reliever therapy (up to a total of 8 puffs per day) was compared to FOSTAIR administered as maintenance therapy (1 inhalation BID) plus as needed salbutamol, in adult patients with un-controlled moderate to severe asthma. The results demonstrated that FOSTAIR used as maintenance and reliever therapy significantly prolonged the time to first severe exacerbation (*) when compared with FOSTAIR used as maintenance plus as needed salbutamol ($p< 0.001$ for both ITT and PP population). The rate of severe asthma exacerbations per patients/year, was significantly reduced in the maintenance and reliever therapy group compared to salbutamol group: 0,1476 vs 0,2239 respectively (statistically significant reduction: $p<0.001$). Patients in the FOSTAIR maintenance and reliever group achieved a clinically meaningful improvement in asthma control. The mean number of inhalations/day of reliever medication and the proportion of patients using reliever medication decreased similarly in both groups.

Note*: severe exacerbations were defined as deterioration in asthma resulting in hospitalisation or emergency room treatment or resulting in the need for systemic steroids for more than 3 days.
In another clinical study, a single dose of FOSTAIR 100/6 mcg provided a quick bronchodilation effect and a rapid relief from dyspnea symptoms similar to that of salbutamol 200 mcg/dose in asthmatic patients when metacholine challenge is used to induce bronchocostriction.

COPD
In two 48-weeks studies, the effects on lung function and the rate of exacerbation (defined as courses of oral steroids and/or course of antibiotics and/or hospitalisations) in patients with severe COPD ($30\% <FEV_1\%<50\%$) was evaluated.

One pivotal trial showed a significant improvement in lung function (primary endpoint change in pre-dose FEV_1) compared to formoterol after 12 weeks of treatment (adjusted mean difference between FOSTAIR and formoterol: 69 ml) as well as at each clinic visit during the whole treatment period (48 weeks). The study demonstrated that the mean number of exacerbations per patient/year (exacerbation rate, co-primary endpoint) was statistically significantly reduced with FOSTAIR as compared with formoterol treatment (adjusted mean rate 0.80 compared with 1.12 in the formoterol group, adjusted ratio 0.72, $p<0.001$) over 48 weeks treatment period in a total of 1199 patients with severe COPD. In addition, FOSTAIR statistically significantly prolonged the time to first exacerbation compared to formoterol. The superiority of FOSTAIR versus formoterol was also confirmed in terms of exacerbation rate in subgroups of patients taking (around 50% in each treatment arm) or not Tiotropium Bromide as concomitant medication.

The other pivotal study, which was a three arm, randomised, parallel group study in 718 patients, confirmed the superiority of FOSTAIR versus formoterol treatment in terms of change in pre-dose FEV_1 at the end of treatment (48 weeks) and demonstrated the non-inferiority of FOSTAIR compared to budesonide/formoterol fixed dose combination on the same parameter.

5.2 PHARMACOKINETIC PROPERTIES
The systemic exposure to the active substances beclometasone dipropionate and formoterol in the fixed combination FOSTAIR have been compared to the single components.

In a pharmacokinetic study conducted in healthy subjects treated with a single dose of FOSTAIR fixed combination (4 puffs of 100/6 micrograms) or a single dose of beclometasone dipropionate CFC (4 puffs of 250 micrograms) and Formoterol HFA (4 puffs of 6 micrograms), the AUC of beclometasone dipropionate main active metabolite (beclometasone-17-monopropionate) and its maximal plasma concentration were, respectively, 35% and 19% lower with the fixed combination than with non-extrafine beclometasone dipropionate CFC formulation, in contrast, the rate of absorption was more rapid (0.5 vs 2h) with the fixed combination compared to non-extrafine beclometasone dipropionate CFC formulation alone.

For formoterol, maximal plasma concentration was similar after administration of the fixed or the extemporary combination and the systemic exposure was slightly higher after administration of FOSTAIR than with the extemporary combination.

There was no evidence of pharmacokinetic or pharmacodynamic (systemic) interactions between beclometasone dipropionate and formoterol.

In another pharmacokinetic study 12 healty volunteers were treated with a single dose of FOSTAIR fixed combination (4 puffs of 100/6 micrograms) or a single dose of Beclometasone dipropionate HFA, QVAR (4 puffs of 100 micrograms) and Formoterol HFA, ATIMOS (2 puffs of 12 micrograms). The results showed similar formoterol PK parameters and a rapid systemic absorption and metabolisation of BDP to the active metabolite B17MP. Systemic exposure and peak concentration of BDP were lower after administration of the fixed combination than after administration of the free combination. B17MP total systemic exposure was comparable and peak B17MP was slightly lower. Administration of formoterol and BDP as a free combination or as a fixed combination were both safe and well tolerated.

The use of AEROCHAMBER PLUS spacer increased the lung delivery of beclometasone dipropionate active metabolite beclometasone 17-monopropionate and formoterol by 41% and 45% respectively, in comparison to the use of standard actuator in a study conducted in healthy volunteers. The total systemic exposure was unchanged for formoterol, reduced by 10% for beclometasone 17-monopropionate and increased for unchanged beclometasone dipropionate.

A lung deposition study conducted in stable COPD patients, healthy volunteers and asthmatic patients, demonstrated that on average 33% of the nominal dose is deposited into the lung of COPD patients compared to 34% in healthy subjects and 31% in asthmatic patients. Beclometasone 17-monopropionate and formoterol plasma exposures were comparable across the three groups during the 24 hours following the inhalation. The total exposure of beclometasone dipropionate was higher in COPD patients compared to the exposure in asthmatic patients and healthy volunters.

BECLOMETASONE DIPROPIONATE

Beclometasone dipropionate is a pro-drug with weak glucocorticoid receptor binding affinity that is hydrolysed via esterase enzymes to an active metabolite beclometasone-17-monopropionate which has a more potent topical anti-inflammatory activity compared with the pro-drug beclometasone dipropionate.

Absorption, distribution and metabolism

Inhaled beclometasone dipropionate is rapidly absorbed through the lungs; prior to absorption there is extensive conversion to its active metabolite beclometasone-17-monopropionate via esterase enzymes that are found in most tissues. The systemic availability of the active metabolite arises from lung (36 %) and from gastrointestinal absorption of the swallowed dose. The bioavailability of swallowed beclometasone dipropionate is negligible however, pre-systemic conversion to beclometasone-17-monopropionate results in 41% of the dose being absorbed as the active metabolite.

There is an approximately linear increase in systemic exposure with increasing inhaled dose.

The absolute bioavailability following inhalation is approximately 2% and 62% of the nominal dose for unchanged beclometasone dipropionate and beclometasone-17-monopropionate respectively.

Following intravenous dosing, the disposition of beclometasone dipropionate and its active metabolite are characterised by high plasma clearance (150 and 120L/h respectively), with a small volume of distribution at steady state for beclometasone dipropionate (20L) and larger tissue distribution for its active metabolite (424L).

Plasma protein binding is moderately high.

Elimination

Faecal excretion is the major route of beclometasone dipropionate elimination mainly as polar metabolites. The renal excretion of beclometasone dipropionate and its metabolites is negligible. The terminal elimination half-lives are 0.5 h and 2.7 h for beclometasone dipropionate and beclometasone-17-monopropionate respectively.

Special populations

The pharmacokinetics of beclometasone dipropionate in patients with renal or hepatic impairment has not been studied; however, as beclometasone dipropionate undergoes a very rapid metabolism via esterase enzymes present in intestinal fluid, serum, lungs and liver, to originate the more polar products beclometasone-21-monopropionate, beclometasone-17-monopropionate and beclometasone, hepatic impairment is not expected to modify the pharmacokinetics and safety profile of beclometasone dipropionate.

As beclometasone dipropionate or its metabolites were not traced in the urine, an increase in systemic exposure is not envisaged in patients with renal impairment.

FORMOTEROL

Absorption and distribution

Following inhalation, formoterol is absorbed both from the lung and from the gastrointestinal tract. The fraction of an inhaled dose that is swallowed after administration with a metered dose inhaler (MDI) may range between 60% and 90%. At least 65% of the fraction that is swallowed is absorbed from the gastrointestinal tract. Peak plasma concentrations of unchanged drug occur within 0.5 to 1 hours after oral administration. Plasma protein binding of formoterol is 61-64% with 34% bound to albumin.

There was no saturation of binding in the concentration range attained with therapeutic doses. The elimination half-life determined after oral administration is 2-3 hours. Absorption of formoterol is linear following inhalation of 12 to 96 μg of formoterol fumarate.

Metabolism
Formoterol is widely metabolised and the prominent pathway involves direct conjugation at the phenolic hydroxyl group. Glucuronide acid conjugate is inactive. The second major pathway involves O-demethylation followed by conjugation at the phenolic 2'-hydroxyl group. Cytochrome P450 isoenzymes CYP2D6, CYP2C19 and CYP2C9 are involved in the O-demethylation of formoterol. Liver appears to be the primary site of metabolism. Formoterol does not inhibit CYP450 enzymes at therapeutically relevant concentrations.

Elimination
The cumulative urinary excretion of formoterol after single inhalation from a dry powder inhaler increased linearly in the 12 – 96 μg dose range. On average, 8% and 25% of the dose was excreted as unchanged and total formoterol, respectively. Based on plasma concentrations measured following inhalation of a single 120 μg dose by 12 healthy subjects, the mean terminal elimination half-life was determined to be 10 hours. The (R,R)- and (S,S)-enantiomers represented about 40% and 60% of unchanged drug excreted in the urine, respectively. The relative proportion of the two enantiomers remained constant over the dose range studied and there was no evidence of relative accumulation of one enantiomer over the other after repeated dosing.

After oral administration (40 to 80 μg), 6% to 10% of the dose was recovered in urine as unchanged drug in healthy subjects; up to 8% of the dose was recovered as the glucuronide.

A total 67% of an oral dose of formoterol is excreted in urine (mainly as metabolites) and the remainder in the faeces. The renal clearance of formoterol is 150 ml/min.

Special populations
The pharmacokinetics of formoterol has not been studied in patients with hepatic or renal impairment however, as formoterol is primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe liver cirrhosis.

5.3 PRECLINICAL SAFETY DATA

GENOTOXICITY
Beclometasone dipropionate and formoterol fumarate dihydrate, tested in combination, were not mutagenic in bacterial reverse mutation assays, and not clastogenic *in vitro* in human lymphocytes or i*n vivo* in the rat bone marrow micronucleus test.

CARCINOGENICITY
No carcinogenicity studies have been performed with beclometasone dipropionate and formoterol fumarate dihydrate in combination. Data for the individual active components are described below.

Beclometasone dipropionate: The potential carcinogenicity of beclometasone dipropionate has not been adequately investigated in animal studies. Other glucocorticoids (budesonide, prednisolone and triamcinolone acetate) have been shown to increase the incidence of hepatocellular tumours in rats by a non-genotoxic mechanism.

Formoterol fumarate: In 2-year studies in mice and rats, treatment with formoterol fumarate, given via the diet or drinking water at very high doses, was associated with increases in several tumour types. In mice, these included hepatocellular adenoma and carcinomas (≥ 2 mg/kg/day), leiomyomas and leiomyosarcomas in the female reproductive tract (≥2 mg/kg/day) and adrenal subcapsular cell tumours (≥ 66 mg/kg/day). In rats, treatment was associated with benign granulosa/theca cell tumours in the ovaries (≥ 0.5 mg/kg/day), mesovarian leiomyomas (≥ 18 mg/kg/day), mammary adenocarcinomas (≥ 36 mg/kg/day) and thyroid C-cell neoplasms (46 mg/kg/day). A mesovarian leiomyoma was also observed in a female rat dosed by inhalation at 130 µg/kg/day for two years (approximately 30 times the maximum recommended human dose for FOSTAIR, adjusted for body surface area).

Mammary adenocarcinomas, smooth muscle tumours in the female reproductive tract and effects on the ovary have been reported in rats and mice treated with other β_2-adrenergic agonists and are likely to be secondary to prolonged stimulation of β_2-adrenoceptors in these tissues.

Pre-clinical data on the CFC-free propellant HFA-134a reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Norflurane
Ethanol absolute
Hydrochloric acid

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Prior to dispensing to the patient:
Store in a refrigerator (2-8°C) (for a maximum of 15 months). Do not freeze.

After dispensing:
Store below 30°C (for a maximum of 2 months).

The canister contains a pressurised liquid. Do not expose to temperatures higher than 50°C. Do not pierce the canister.

6.5 NATURE AND CONTENTS OF CONTAINER

The inhalation solution is contained in a pressurised aluminium container sealed with a metering valve.

The canister is inserted into a polypropylene plastic actuator which incorporates a mouthpiece and is fitted with a plastic protective cap.

The actuator is light purplish-red with a dark purplish-red cap. The actuator has a dose counter. The dose counter will show number of actuations left in the canister through a window in the plastic actuator.

Each pack contains one pressurised container which provides 120 actuations.

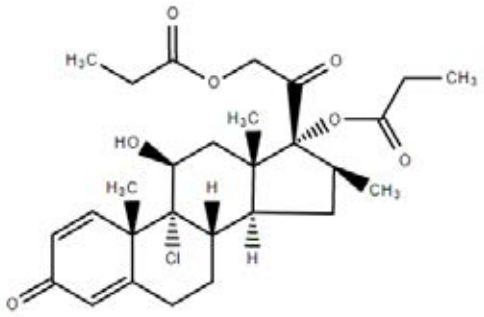
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

For pharmacies:
Enter the date of dispensing to the patient on the pack.
Ensure that there is a period of at least 2 months between the date of dispensing and the expiry date printed on the pack.

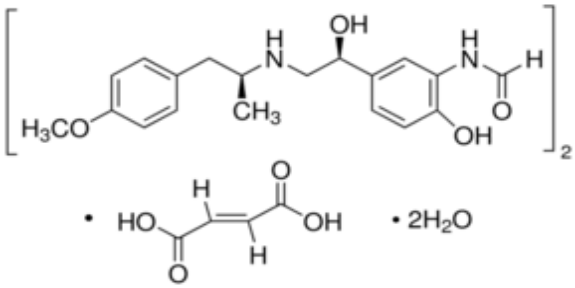
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Beclometasone dipropionate



Formoterol fumarate dihydrate

CAS number

Beclometasone dipropionate: 5534-09-8
Formoterol fumarate dihydrate: 183814-30-4

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8. SPONSOR

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9. DATE OF FIRST APPROVAL

12 February 2020

10. DATE OF FIRST REVISION

2 April 2020

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.2	Deletion of strikethrough text which mistakenly remained from the final PI negotiation stage of submission PM-2018-03998-1-5.