AUSTRALIAN PRODUCT INFORMATION
FOSTAIR 100/6 and 200/6
(beclometasone dipropionate, formoterol fumarate dihydrate) pressurised inhalation

1. NAME OF THE MEDICINE

Beclometasone dipropionate and formoterol fumarate dihydrate.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

FOSTAIR 100/6

Each metered dose (the dose leaving the valve) contains 100 micrograms of beclometasone dipropionate and 6 micrograms of formoterol fumarate dihydrate.

Each delivered dose (the dose leaving the mouthpiece) contains 84.6 micrograms of beclometasone dipropionate and 5.0 micrograms of formoterol fumarate dihydrate.

FOSTAIR 200/6

Each metered dose (the dose leaving the valve) contains 200 micrograms of beclometasone dipropionate and 6 micrograms of formoterol fumarate dihydrate.

Each delivered dose (the dose leaving the mouthpiece) contains 177.7 micrograms of beclometasone dipropionate and 5.1 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.

Colourless to yellowish solution.

The inhalation solution is contained in a pressurised aluminium container sealed with a metering valve (pressurised metered dose inhaler (pMDI)). 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 (FOSTAIR 100/6) or dark green cap (FOSTAIR 200/6). 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 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). (See section 4.2 DOSE AND METHOD OF ADMINISTRATION for treatment approaches).

COPD (FOSTAIR 100/6 only)

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

Dosage

FOSTAIR is only for use in adults 18 years and above.

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 100/6 or FOSTAIR 200/6 is taken as regular maintenance treatment with a separate as needed rapid-acting bronchodilator.

B. Maintenance and reliever therapy: FOSTAIR 100/6 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.

FOSTAIR 100/6

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

The starting dose is 1 inhalation taken twice daily for patients who are inadequately controlled with an ICS and SABA or adequately controlled with an ICS and LABA. The dose should be increased to 2 inhalations taken twice daily if the patient's asthma is poorly controlled. FOSTAIR 100/6 should be discontinued if the patient is commenced on FOSTAIR 200/6 for maintenance therapy.

FOSTAIR 200/6

Two inhalations twice daily. The maximum daily dose is 4 inhalations.

FOSTAIR 200/6 should be used as maintenance therapy only.

Increasing use of short-acting bronchodilators can indicate worsening of the underlying condition and warrants the reassessment of the patient and therapy (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

B. Maintenance and reliever therapy for FOSTAIR 100/6 only

Patients take their daily maintenance dose of FOSTAIR 100/6 and in addition take FOSTAIR 100/6 as needed in response to asthma symptoms. The as-needed inhalations provide both rapid relief of symptoms and improved overall asthma control. Patients should be advised to always have FOSTAIR 100/6 available for rescue use.

FOSTAIR 100/6 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.

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. FOSTAIR 100/6 should be discontinued if the patient is commenced on FOSTAIR 200/6 for maintenance therapy.

Patients should be regularly reassessed by a doctor, so that the dosage of FOSTAIR 100/6 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 100/6 every day even when asymptomatic.

COPD for FOSTAIR 100/6 only

Two inhalations twice daily.

Special patient groups

Elderly

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

FOSTAIR is for inhalation use.

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, who should also regularly check the patient's inhalation technique (see Instructions for use).

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. For the 180 doses presentation, each time the patient presses the canister the counter rotates by a small amount and the number of actuations remaining is displayed in intervals of 20. Patients should be advised not to drop the inhaler as this may cause the counter to count down.

Instructions for use

Priming 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 (primed for use). After priming the inhaler for the first time, the counter should read 120 or 180.

Use of the inhaler

Whenever possible patients should stand or sit in an upright position when inhaling from their inhaler. IMPORTANT: patients should not perform steps 2 to 5 too quickly.

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 as deeply as possible, in order to empty their lungs.
3. Patients should hold the inhaler vertically with its body upwards and place the mouthpiece between their teeth without biting. Their lips should then be placed around the mouthpiece, with the tongue flat under it.
4. At the same time, patients should breathe in slowly and deeply through the mouth until the lungs are full of air (this should take approximately 4-5 seconds). Immediately after starting to breathe in, patients should firmly press down on the top of the pressurised container to release one puff.
5. Patients should hold the breath for as long as comfortably possible, then remove the inhaler from the mouth and breathe out slowly. Patients should not breathe out into the inhaler.
6. Patients should then check the dose counter or dose indicator to ensure it has moved accordingly.

To inhale a further puff, patients should keep the inhaler in a vertical position for approximately 30 seconds and repeat steps 2 to 6.

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

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

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).

When to get a new inhaler

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 actuations left in the device may not be enough to release a full dose.

Additional instructions for specific groups of patients

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

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.

Cleaning

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.

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 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 100/6 (for patients using FOSTAIR 100/6 as maintenance and reliever therapy) or a separate rapid-acting bronchodilator (for patients using FOSTAIR 200/6 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

Sudden and progressive worsening in the control of asthma or COPD is potentially life threatening. In such cases, patients should receive urgent medical assessment with consideration given to increased corticosteroid therapy (such as a course of oral corticosteroids) or antibiotic treatment in the presence of a bacterial infection.

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 100/6 (for patients using FOSTAIR 100/6 for maintenance and reliever therapy) 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.

Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of beclometasone dipropionate and formoterol fumarate dihydrate. Regular review of patients as treatment is stepped down is important. 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 a suitable 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 dipropionate is 30 times less potent compared to beclometasone-17-monopropionate in terms of glucocorticoid receptor activity, the observed increase in beclometasone dipropionate levels is not expected to have any clinically relevant impact on beclometasone dipropionate 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.

Prevention of oropharyngeal infections

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.

Excipients

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

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 systemic exposure to formoterol in patients at the maximum recommended clinical dose (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 in 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 systemic exposure to formoterol in patients at the maximum recommended clinical dose (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 systemic exposure to formoterol in 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), very rare (≤1/10,000) and not known (cannot be estimated from available data).

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

Table 1. Adverse reactions with FOSTAIR

System Organ Class	Frequency	Adverse Reaction
Infections and Infestations	Common	Pharyngitis, oral candidiasis, pneumonia* (in COPD patients)
	Uncommon	Influenza, oral fungal infection, oropharyngeal candidiasis, oesophageal candidiasis, vulvovaginal candidiasis, gastroenteritis, sinusitis, rhinitis
Blood and lymphatic system disorders	Uncommon	Granulocytopenia
	Very rare	Thrombocytopenia
Immune system disorders	Uncommon	Dermatitis allergic
	Very rare	Hypersensitivity reactions, including erythema, lips, face, eye and pharyngeal oedema
Endocrine disorders	Very rare	Adrenal suppression
Metabolism and nutrition disorders	Uncommon	Hypokalaemia, hyperglycaemia
Psychiatric disorders	Uncommon	Restlessness
	Not known	Psychomotor hyperactivity, sleep disorders, anxiety, depression, aggression, behavioural changes (predominantly in children)
Nervous system disorders	Common	Headache
	Uncommon	Tremor, dizziness
Eye disorders	Very rare	Glaucoma, cataract
	Not known	Vision, blurred (see also section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)
Ear and labyrinth disorders	Uncommon	Otosalpingitis
Cardiac disorders	Uncommon	Palpitations, electrocardiogram QT corrected interval prolonged, electrocardiogram change, tachycardia, tachyarrhythmia, atrial fibrillation*
	Rare	Ventricular extrasystoles, angina pectoris
Vascular disorders	Uncommon	Hyperaemia, flushing
Respiratory, thoracic and mediastinal disorders	Common	Dysphonia
	Uncommon	Cough, productive cough, throat irritation, asthmatic crisis, pharyngeal erythema
	Rare	Bronchospasm paradoxical
	Very rare	Dyspnoea, exacerbation of asthma
Gastrointestinal disorders	Uncommon	Diarrhoea, dry mouth, dyspepsia, dysphagia, burning sensation of the lips, nausea, dysgeusia
Skin and subcutaneous tissue disorders	Uncommon	Pruritus, rash, hyperhidrosis, urticaria
	Rare	Angioedema
Musculoskeletal and connective tissue disorders	Uncommon	Muscle spasms, myalgia
	Very rare	Growth retardation in children and adolescents
Renal and urinary disorders	Rare	Nephritis
General disorders and administration site conditions	Very rare	Oedema peripheral

System Organ Class	Frequency	Adverse Reaction
Investigations	Uncommon	C-reactive protein increased, platelet count increased, free fatty acids increased, blood insulin increased, blood ketone body increased, blood cortisol decrease*
	Rare	Blood pressure increased, blood pressure decreased
	Very rare	Bone density decreased

*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.

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 13 11 26 (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.

FOSTAIR contains a non-volatile solution formulation and uses a specific actuator orifice geometry (MODULITE® technology) which results in an aerosol with extrafine particles with an average mass median aerodynamic diameter (MMAD) of around 1.3-1.5 micrometres and co-deposition of the two components. The aerosol particles of FOSTAIR are on average much smaller than the particles delivered in non-extrafine formulations. For beclometasone dipropionate, this results in a more potent effect than formulations with a non-extrafine particle size distribution (100 micrograms of beclometasone dipropionate extrafine in FOSTAIR are equivalent to 250 micrograms of beclometasone dipropionate in a non-extrafine formulation).

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 100/6 as maintenance treatment for asthma was evaluated in randomised double blind, multicentre trials in patients with different degrees of asthma severity. The efficacy of FOSTAIR 100/6 fixed combination was first evaluated in patients with mild to moderate asthma who were still symptomatic despite receiving low-dose ICS. FOSTAIR 100/6 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 100/6 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. The study also showed that after 24-weeks of treatment with extrafine FOSTAIR 100/6 delivered by a hydrofluoroalkane propellant (HFA) pMDI, FOSTAIR 100/6 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 100/6 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 100/6 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 100/6 was compared with fluticasone propionate/salmeterol, both administered as 2 inhalations twice daily. FOSTAIR 100/6 demonstrated improvement in lung function comparable to that of fluticasone propionate/salmeterol.

The efficacy of FOSTAIR 200/6, 2 puffs twice a day, was evaluated in a 12-week pivotal FORCE trial comparing the effect on lung function versus treatment with extrafine beclometasone dipriopionate monotherapy BDP 100 micrograms in asthmatic patients not adequately controlled with previous treatment (high dose ICS or medium dose ICS+LABA combinations). The study demonstrated the superiority of FOSTAIR 200/6 micrograms compared to BDP 800 micrograms daily dose in terms of change from baseline in the average pre-dose morning PEF (adjusted mean difference 18.53 L).

In a 24-week pivotal trial the safety profile of FOSTAIR 200/6, 2 puffs twice a day, was comparable to fixed dose combination fluticasone/salmeterol 500/50, 1 puff twice daily. No clinically relevant effect was observed with FOSTAIR 200/6 on the HPA axis after 6 months of treatment. The study showed that both FOSTAIR 200/6 micrograms and fluticasone/salmeterol were not superior to non extrafine beclometasone dipriopionate monotherapy (2000 micrograms/day) on the change in pre-dose morning FEV_1 and percentage of complete days without asthma symptoms.

Maintenance and reliever therapy for FOSTAIR 100/6 only

In a 48-week parallel group study involving 1701 asthma patients, the efficacy of FOSTAIR 100/6 administered as maintenance (1 inhalation BID) and reliever therapy (up to a total of 8 puffs per day) was compared to FOSTAIR 100/6 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 100/6 used as maintenance and reliever therapy significantly prolonged the time to first severe exacerbation (*) when compared with FOSTAIR 100/6 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 100/6 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 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 for FOSTAIR 100/6 only)

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 in 1199 patients with severe COPD 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 100/6 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 100/6 as compared with formoterol treatment (adjusted mean rate 0.80 compared with 1.12 in the formoterol group, adjusted ratio 0.72, $p<0.001$). In addition, FOSTAIR 100/6 statistically significantly prolonged the time to first exacerbation compared to formoterol. The superiority of FOSTAIR 100/6 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 100/6 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 100/6 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 100/6 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 separate combination and the systemic exposure was slightly higher after administration of FOSTAIR 100/6 than with the separate combination.

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

In another pharmacokinetic study 12 healthy volunteers were treated with a single dose of FOSTAIR 100/6 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 separate 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 FOSTAIR 100/6 with Aerochmaber 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.

A pharmacokinetic study conducted in healthy volunteers with activated charcoal blockade demonstrated that the lung bioavailability of beclometasone-17-monopropionate in the FOSTAIR 200/6 formulation is dose proportional with respect to that of the 100/6 strength for AUC only (mean ratio between systemic bioavailability in the 200/6 formulation and in the 100/6 strength equal to 91.63 (90 % Confidence Interval: 83.79; 100.20)). For formoterol fumarate the mean ratio between systemic bioavailability in the 200/6 formulation and in the 100/6 strength was equal to 86.15 (90% Confidence Interval: 75.94; 97.74).

In another pharmacokinetic study conducted in healthy volunteers without charcoal blockade, the systemic exposure of beclometasone-17-monopropionate in the FOSTAIR 200/6 formulation was shown to be dose proportional with respect to that of the 100/6 strength (mean ratio between systemic bioavailability in the 200/6 formulation and in the 100/6 strength equal to 89.2 (90 % Confidence Interval: 79.8; 99.7)). The total systemic exposure of formoterol fumarate was unchanged (mean ratio between systemic bioavailability in the 200/6 formulation and in the 100/6 strength equal to 102.2 (90% Confidence Interval: 90.4; 115.5)0.

The use of FOSTAIR 200/6 with a suitable spacer increased the lung delivery of beclometasone dipropionate active metabolite beclometasone 17-monopropionate and formoterol in healthy volunteers by 25 % and 32 % respectively, while the total systemic exposure was slightly reduced

for beclometasone 17-monopropionate (by 17%) and formoterol (by 17%) and increased for unchanged beclometasone dipropionate (by 54%).

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 120 L/h respectively), with a small volume of distribution at steady state for beclometasone dipropionate (20 L) and larger tissue distribution for its active metabolite (424 L).

Plasma protein binding is moderately high.

Excretion

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 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 micrograms 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. The liver appears to be the primary site of metabolism. Formoterol does not inhibit CYP450 enzymes at therapeutically relevant concentrations.

Excretion

The cumulative urinary excretion of formoterol after single inhalation from a dry powder inhaler increased linearly in the 12 – 96 micrograms 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 micrograms 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 micrograms), 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 micrograms/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 (CFC-free propellant also known as HFA-134a)
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

Store at 2°C to 8°C (Refrigerate. Do not freeze).

After first use: Store below 30°C (for a maximum of 2 months).
Advise the patient to enter the date of first use on the removable label and affix to the actuator.

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 has a dose counter (120 doses pack) or a dose indicator (180 doses pack). The dose counter/indicator shows the number of actuations left in the canister through a window in the plastic actuator.

FOSTAIR 100/6 pack sizes:

Single inhaler pack containing either 120 or 180 actuations.
Multiple packs containing 2 inhalers each with 120 actuations.

FOSTAIR 200/6 pack sizes:

Single inhaler pack containing 120 actuations.
Multiple pack containing 2 inhalers each with 120 actuations.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

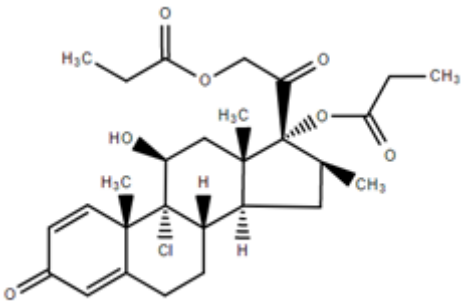
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

The canister contains a pressurised liquid. Do not puncture, expose to heat (temperatures higher than 50°C) or incinerate even when empty.

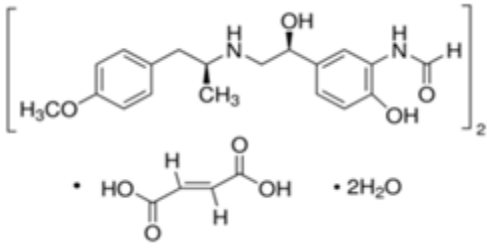
6.7 PHYSICOCHEMICAL PROPERTIES

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 (Prescription Only Medicine)

8. SPONSOR

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9. DATE OF FIRST APPROVAL

12 February 2020

10. DATE OF REVISION

04 September 2024

Summary table of changes

Section changed	Summary of new information
6.4	Clarify storage conditions
6.5	Clarify pack sizes
6.6	Update disposal information
8	Update Sponsor contact details
All	Minor editorial changes including revision of ingredient names to align with AAN