# AUSTRALIAN PRODUCT INFORMATION – DUORESP® SPIROMAX® (BUDESONIDE/FORMOTEROL (EFORMOTEROL) FUMARATE DIHYDRATE) DRY POWDER INHALER

## 1 NAME OF THE MEDICINE

Budesonide

Formoterol (eformoterol) fumarate dihydrate (hereafter referred to as formoterol).

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

DuoResp Spiromax is available as a multidose inspiratory flow driven, metered dose dry powder inhaler (Spiromax). To avoid confusion, DuoResp Spiromax is labelled as the metered dose of the corresponding monotherapy products budesonide and formoterol dry powders for inhalation. The monotherapy products are also labelled as metered doses. The following table gives the corresponding dose delivered to the patient.

**Table 1**

| Budesonide/ Formoterol | Metered dose (µg) | | Corresponding dose deliver to patient (µg) | |
|---|---|---|---|---|
| | Budesonide | Formoterol | Budesonide | Formoterol |
| 200 / 6 | 200 | 6 | 160 | 4.5 |
| 400 / 12 | 400 | 12 | 320 | 9 |

*Excipient(s) with known effect:* lactose monohydrate

For full list of excipients, see Section 6.1 List of excipients.

## 3 PHARMACEUTICAL FORM

White or off-white powder in a multi-dose dry powder inhaler.

## 4 CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

**Asthma**

DuoResp Spiromax is indicated in adults (18 years and older) for the treatment of asthma, to achieve overall asthma control, including the relief of symptoms and the reduction of the risk and exacerbations (see Section 4.2 Dose and method of administration).

DuoResp Spiromax is not indicated in children and adolescents under the age of 18 years as the 100/6 dose is not available.

**Chronic obstructive pulmonary disease (COPD)**

DuoResp Spiromax is indicated for the symptomatic treatment of moderate to severe COPD ($FEV_1$ ≤50% predicted normal) in adults with frequent symptoms despite long-acting

bronchodilator use, and/or a history of recurrent exacerbations. DuoResp Spiromax is not indicated for the initiation of bronchodilator therapy in COPD.

## 4.2 DOSE AND METHOD OF ADMINISTRATION

**Asthma**
DuoResp Spiromax can be used according to different treatment approaches:

A. Anti-inflammatory reliever therapy (patients with mild disease).
B. Anti-inflammatory reliever plus maintenance therapy.
C. Maintenance therapy (fixed dose).

**Anti-inflammatory reliever therapy (patients with mild disease)**

DuoResp Spiromax 200/6 is taken as needed for the relief of asthma symptoms when they occur, and as a preventative treatment of symptoms in those circumstances recognised by the patient to precipitate an asthma attack. Patients should be advised to always have DuoResp Spiromax 200/6 available for relief of symptoms.

Preventative use of DuoResp Spiromax 200/6 for allergen- or exercise-induced bronchoconstriction (AIB/EIB) should be discussed between physician and patient; the recommended dose frequency should take into consideration both allergen exposure and exercise patterns.

**Adults (18 years and older)**

Patients should take 1 inhalation of DuoResp Spiromax 200/6 as needed in response to symptoms. If symptoms persist after a few minutes, an additional inhalation should be taken. No more than 6 inhalations should be taken on any single occasion.

A total daily dose of more than 8 inhalations is normally not needed, however a total daily dose of up to 12 inhalations can be used temporarily. If the patient experiences a three-day period of deteriorating symptoms after taking additional as needed inhalations, the patient should be reassessed for alternative explanations of persisting symptoms.

**Anti-inflammatory reliever plus maintenance therapy**

When maintenance treatment with a combination of inhaled corticosteroid (ICS) and long acting $\beta_2$ agonist (LABA) is required, patients take anti-inflammatory reliever therapy and in addition take a daily maintenance dose of DuoResp Spiromax. The as-needed inhalations provide both rapid relief of symptoms and improved overall asthma control. Patients should be advised to have DuoResp Spiromax available for relief of symptoms at all times.

Preventative use of DuoResp Spiromax 200/6 for AIB/EIB should be discussed between physician and patient; the recommended dose frequency should take into consideration both allergen exposure and exercise patterns.

**The 400/12 strength should not be used for the anti-inflammatory reliever plus maintenance therapy regimen.**

**Adults (18 years and older)**

Patients should take 1 inhalation of DuoResp Spiromax 200/6 as needed in response to symptoms to control asthma. If symptoms persist after a few minutes, another inhalation should be taken. No more than 6 inhalations should be taken on any single occasion.

Patients also take the recommended maintenance dose of DuoResp Spiromax 200/6, which is two inhalations per day, given as either one inhalation in the morning and evening or as two inhalations in either the morning or evening. For some patients, a maintenance dose of DuoResp Spiromax 200/6 two inhalations twice daily may be appropriate. The maintenance dose should be titrated to the lowest dose at which effective control of asthma is maintained.

A total daily dose of more than 8 inhalations is normally not needed, however a total daily dose of up to 12 inhalations can be used temporarily. If the patient experiences a three day period of deteriorating symptoms after taking the appropriate maintenance therapy and additional as needed inhalations, the patient should be reassessed for alternative explanations of persisting symptoms.

**Maintenance therapy (fixed dose)**

When maintenance treatment with a combination of ICS and LABA s required, DuoResp Spiromax is taken as a fixed daily dose treatment, with a separate short-acting bronchodilator for relief of symptoms. Patients should be advised to have their separate short-acting bronchodilator available for relief of symptoms at all times.

Increasing use of short-acting bronchodilators indicates a worsening of the underlying condition and warrants reassessment of the asthma therapy. The dosage of DuoResp Spiromax should be individualised according to disease severity. When control of asthma has been achieved, the maintenance dose should be titrated to the lowest dose at which effective asthma control is maintained.

**Adults (18 years and older)**

DuoResp Spiromax 200/6

1-2 inhalations of DuoResp Spiromax 200/6 twice daily. The maximum recommended daily maintenance dose is 4 inhalations (2 inhalations twice daily corresponding to 800 µg budesonide/24 µg formoterol).

## Adults (18 years and over) who require a higher daily maintenance dose (1600/48):

DuoResp Spiromax 400/12

2 inhalations of DuoResp Spiromax 400/12 twice daily. The maximum recommended daily maintenance dose is 4 inhalations (corresponding to 1600 µg budesonide/48 µg formoterol). When control of asthma has been achieved, the dose can be decreased to 1 inhalation twice daily.

**DuoResp Spiromax is not indicated in children and adolescents under the age of 18 years. Lower strength of 100/6 µg for children and adolescents under the age of 18 years can be available from other brands.**

**COPD**
**Adults**

DuoResp Spiromax 200/6

2 inhalations of DuoResp Spiromax 200/6 twice daily. The maximum recommended daily dose is 4 inhalations (corresponding to 800 µg budesonide/24 µg formoterol).

DuoResp Spiromax 400/12

1 inhalation of DuoResp Spiromax 400/12 twice daily. The maximum recommended daily dose is 2 inhalations (corresponding to 800 µg budesonide/24 µg formoterol).

**General Information**
If patients take DuoResp Spiromax as an anti-inflammatory reliever (either alone or in combination with maintenance therapy) physicians should discuss allergen exposure and exercise patterns with the patients and take these into consideration when recommending the dose frequency for asthma treatment.

If patients take DuoResp Spiromax as a maintenance therapy, they should be instructed to take the maintenance dose of budesonide/formoterol combination therapy even when asymptomatic for optimal benefit.

**Renal impairment**
There are no data available for use of budesonide and formoterol in combination in patients with renal impairment.

**Hepatic impairment**
There are no data available for use of budesonide and formoterol in combination in patients with hepatic impairment. As budesonide and formoterol are primarily eliminated via hepatic metabolism an increased systemic availability can be expected in patients with severe liver disease.

**Elderly**
There are no special dosing requirements for elderly patients.

**Instruction for correct use of Spiromax**
Spiromax is a reservoir type, breath actuated, inspiratory flow-driven inhaler, which means that the active substances are delivered into the airways when the patient inhales through the mouthpiece. Moderate and severe asthmatic patients were shown to be able to generate a sufficient inspiratory flow rate for Spiromax to deliver the therapeutic dose (See Section Clinical trials *Peak Inspiratory Flow Rate through the Spiromax Device*).

DuoResp Spiromax should be used correctly in order to achieve effective treatment. Patients should be advised to read the patient information leaflet carefully and follow the instructions for use as detailed in the leaflet.

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

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

**Breathe:** Place the mouthpiece between the teeth with the lips closed around the mouthpiece. Do not bite the mouthpiece of the inhaler. Inhale forcefully and deeply through the mouthpiece. Remove the Spiromax from the mouth and hold the breath for 10 seconds, or as long as comfortable.

**Close:** Breathe out gently and close the mouthpiece cover.

It is important to advise patients not to shake the inhaler before use and to not exhale through the Spiromax. Patients should not block the air vents during preparation for the "Breathe" step.

Patients should rinse their mouth with water after inhaling.

The patient may notice a taste when using DuoResp Spiromax due to the lactose excipient.

## 4.3 CONTRAINDICATIONS

Hypersensitivity to budesonide, formoterol or lactose.

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

Patients with asthma should have a personal asthma action plan designed in association with their healthcare professional. This plan should incorporate a stepwise treatment regime which can be instituted if the patients asthma improves or deteriorates.

Patients should be advised to have their reliever available at all times, either budesonide/formoterol dry powder for inhalation (for asthma patients on anti-inflammatory reliever plus maintenance therapy) or a separate short-acting bronchodilator (for other asthma patients using budesonide/formoterol dry powder for inhalation as fixed dose maintenance therapy only and for COPD patients).

Sudden and progressive deterioration in control of asthma or COPD is potentially life threatening and the patient should undergo urgent medical assessment. In this situation, consideration should be given to the need for increased therapy with corticosteroids (e.g. a course of oral corticosteroids), or antibiotic treatment if a bacterial infection is present. For treatment of severe exacerbations, a combination product of ICS and LABA alone is not sufficient. Patients should be advised to seek medical attention if they find the treatment ineffective or they have exceeded the prescribed dose of budesonide/formoterol dry powder for inhalation.

It is recommended that the maintenance dose is tapered when long-term treatment is discontinued, and the dosing should not be stopped abruptly. Complete withdrawal of ICS

should not be considered unless it is temporarily required to confirm the diagnosis of asthma.

**Oral corticosteroid usage**
Budesonide/formoterol dry powder for inhalation should not be used to initiate treatment with inhaled steroids in patients being transferred from oral steroids. Care should be taken when commencing budesonide/formoterol fixed combination treatment, particularly if there is any reason to suspect that adrenal function is impaired from previous systemic steroid therapy.

**Potential systemic effects of ICS**
ICS are designed to direct glucocorticoid delivery to the lungs in order to reduce overall systemic glucocorticoid exposure and side effects. However, in higher than recommended doses, ICS may have adverse effects; possible systemic effects of ICS include Cushing's syndrome, Cushingoid features, depression of the HPA axis, reduction of bone density, cataract, glaucoma and blurred vision, and retardation of growth rate in children and adolescents. Increased susceptibility to infections and impairment of the ability to adapt to stress may also occur.

In steroid-dependent patients, prior systemic steroid usage may be a contributing factor, but such effects may occur amongst patients who use only ICS regularly.

**HPA axis suppression and adrenal insufficiency**
Dose-dependant HPA axis suppression (as indicated by 24 hour urinary and/or plasma cortisol AUC) has been observed with inhaled budesonide, although the physiological circadian rhythms of plasma cortisol were preserved. This indicates that the HPA axis suppression represents a physiological adaption in response to inhaled budesonide, not necessarily adrenal insufficiency. The lowest dose that results in clinically relevant adrenal insufficiency has not been established. Very rare cases of clinically relevant adrenal dysfunction have been reported in patients using inhaled budesonide at recommended doses.

Clinically important disturbances of the HPA axis and/or adrenal insufficiency induced by severe stress (eg trauma, surgery, infection in particular gastroenteritis or other conditions associated with severe electrolyte loss) may be related to inhaled budesonide in specific patient populations. These are patients with prolonged treatment at the highest recommended dose of budesonide/formoterol fixed combination and patients administered concomitant CYP3A4-inhibitors (see Section 4.5 Interactions with other medicines and other forms of interactions). Monitoring for signs of adrenal dysfunction is advisable in these patient groups. For these patients additional systemic glucocorticosteroid treatment should be considered during periods of stress, a severe asthma attack or elective surgery.

A fixed-dose combination of budesonide and formoterol fumarate dihydrate should be administered with caution in patients with phaeochromocytoma.

**Bone density**
Whilst corticosteroids may have an effect on bone mass at high doses, long term follow up (3-6 years) studies of budesonide treatment in adults at recommended doses, have not demonstrated a negative effect on bone mass compared to placebo, including one study conducted in patients with a high risk of osteoporosis. The lowest dose that does effect bone mass has not been established.

Bone mineral density measurements in children should be interpreted with caution as an increase in bone area in growing children may reflect an increase in bone volume. In three large medium to long term (12 months-6 years) studies in children (5-16 years), no effects on bone mineral density were observed after treatment with budesonide (189-1322 µg/day) compared to nedocromil, placebo or age matched controls. However, in a randomised 18 month paediatric study (n=176; 5-10 years), bone mineral density was significantly decreased by 0.11 g/cm$^2$ (p=0.023) in the group treated with inhaled budesonide via dry powder inhaler compared with the group treated with inhaled disodium cromoglycate. The dose of budesonide was 400 µg twice-daily for 1 month, 200 µg twice-daily for 5 months and 100 µg twice-daily for 12 months and the dose of disodium cromoglycate 10 mg three times daily. The clinical significance of this result remains uncertain.

**Growth**
Limited data from long-term studies suggest that most children and adolescents treated with inhaled budesonide will ultimately achieve their adult target height. However, an initial small but transient reduction in growth (approximately 1 cm) has been observed. This generally occurs within the first year of treatment.

Rare individuals may be exceptionally sensitive to ICS. Height measurements should be performed to identify patients with increased sensitivity. The potential growth effects of prolonged treatment should be weighed against the clinical benefit. To minimise the systemic effects of ICS, each patient should be titrated to his/her dose at which control of symptoms is maintained (see Section 4.2 Dose and method of administration).

**Visual disturbances**
Visual disturbances 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.

**Infections/tuberculosis**
Signs of existing infection may be masked by the use of high doses of glucocorticosteroids and new infections may appear during their use. Special care is needed in patients with active or quiescent pulmonary tuberculosis or fungal, bacterial or viral infections of the respiratory system.

**Sensitivity to sympathomimetic amines**
In patients with increased susceptibility to sympathomimetic amines (e.g. inadequately controlled hyperthyroidism), formoterol should be used with caution.

**Cardiovascular disorders**
$\beta_2$-agonists have an arrhythmogenic potential that must be considered before commencing treatment for bronchospasm.

The effects of formoterol in acute as well as chronic toxicity studies were seen mainly on the cardiovascular system and consisted of hyperaemia, tachycardia, arrhythmias and myocardial lesions. These are known pharmacological manifestations seen after administration of high doses of $\beta_2$-adrenoceptor agonists.

Patients with pre-existing cardiovascular conditions may be at greater risk of developing adverse cardiovascular effects following administration of $\beta_2$-adrenoreceptor agonists. Caution is advised when formoterol is administered to patients with severe cardiovascular disorders such as ischaemic heart disease, tachyarrythmias, hypertrophic obstructive cardiomyopathy, idiopathic subvalvular aortic stenosis, severe hypertension, aneurysm or severe heart failure.

Caution should be observed when treating patients with prolongation of the QTc-interval. Formoterol itself may induce prolongation of the QTc-interval.

**Hypokalaemia**
High doses of $\beta_2$-agonists can lower serum potassium by inducing a redistribution of potassium from the extracellular to the intracellular compartment, via stimulation of Na+/K+-ATPase in muscle cells.

Potentially serious hypokalaemia may result. Particular caution is advised in acute exacerbation as the associated risk may be augmented by hypoxia. The hypokalaemic effect may be potentiated by concomitant treatments (see Section 4.5 Interactions with other medicines and other forms of interactions). Patients receiving digoxin are particularly sensitive to hypokalaemia. Serum potassium levels should therefore be monitored in such situations.

**Diabetes**
Due to the blood-glucose increasing effects of $\beta_2$-stimulants extra blood glucose controls are initially recommended when diabetic patients are commenced on formoterol.

**Lactose**
Budesonide/formoterol combination powder for inhalation contains lactose which may contain milk protein residue. This amount does not normally cause problems in lactose intolerant people.

**Other**
As with other inhalation therapy, paradoxical bronchospasm may occur in very rare cases, with an immediate increase in wheezing and shortness of breath, after dosing. If the patient experiences paradoxical bronchospasm; budesonide + formoterol fumerate should be discontinued immediately, the patient should be assessed and an alternative therapy instituted, if necessary

**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.

**Use in hepatic impairment**
The effect of decreased liver function on the pharmacokinetics of formoterol and budesonide is not known. As budesonide and formoterol are primarily eliminated via hepatic metabolism an increased exposure can be expected in patients with severe liver disease.

**Use in renal impairment**
The effect of decreased kidney function on the pharmacokinetics of formoterol and budesonide is not known.

**Use in the elderly**
See Section 5.1 Pharmacodynamic properties - Clinical trials.

**Paediatric use**
This medicinal product is not for use in children and adolescents under the age of 18 years.

**Effects on laboratory tests**
No data available.

## 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

**Pharmacokinetic interactions**
The metabolism of budesonide is primarily mediated by the enzyme CYP3A4. Potent inhibitors of this enzyme, eg ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, nefazodone, ritonavir and HIV protease inhibitors} may therefore increase systemic exposure to budesonide. This is of limited clinical importance for short-term (1-2 weeks) treatment but should be taken into consideration during long-term treatment with potent CYP3A4 inhibitors.

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

Use of DuoResp Spiromax 200 mcg/6 mcg inhalation powder as a maintenance and reliever therapy is not recommended in patients using potent CYP3A4 inhibitors.

**Pharmacodynamic interactions**
Neither budesonide nor formoterol have been observed to interact with any other drug used in the treatment of asthma or COPD.

**β-receptor blocking agents**

β-receptor blocking agents (including eye drops), especially those that are non-selective, may partially or totally inhibit the effect of $\beta_2$-agonists (such as formoterol). These drugs may also increase airway resistance, therefore the use of these drugs in asthma patients is not recommended.

**Other sympathomimetic agents**

Other β-adrenergic stimulants or sympathomimetic amines such as ephedrine and anticholinergics should not be given concomitantly with formoterol, since the bronchodilating effects will be cumulative. Patients who have already received large doses of sympathomimetic amines should not be given formoterol.

**Xanthine derivatives, mineralocorticosteroids and diuretics**

Hypokalaemia may result from $\beta_2$-agonist therapy and may be potentiated by concomitant treatment with xanthine derivatives, mineralocorticosteroids, and diuretics (see Section 4.4 Special warnings and precautions for use -Hypokalaemia).

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

**Monoamine oxidase inhibitors, tricyclic antidepressants, quinidine, disopyramide, procainamide, phenothiazines and antihistamines**

The adverse cardiovascular effects of formoterol may be exacerbated by concurrent administration of drugs associated with QT interval prolongation and increased risk of ventricular arrhythmia. For this reason caution is advised when formoterol is administered to patients already taking monoamine oxidase inhibitors, tricyclic antidepressants, quinidine, disopyramide, procainamide, phenothiazines or antihistamines associated with QT interval prolongation (eg terfenadine, astemizole).

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

L-Dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards $\beta_2$ sympathomimetics.

**Halogenated hydrocarbons**

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

## 4.6 FERTILITY, PREGNANCY AND LACTATION

**Effects on fertility**
There are no animal studies on the effect of the budesonide/formoterol combination on fertility.

Long-term treatment of female mice and rats with formoterol fumarate causes ovarian stimulation, the development of ovarian cysts and hyperplasia of granulosa/theca cells as a result of the β-agonist properties of the compound. A study by another company showed no effect on fertility of female rats dosed orally with formoterol fumarate at 60 mg/kg/day for two weeks. This finding was repeated in an AstraZeneca study where no effect was seen on the fertility of female rats dosed orally with formoterol fumarate at 15 mg/kg/day for two weeks.

Testicular atrophy was observed in mice given formoterol fumarate in the diet at 0.2 to 50 mg/kg/day for two years, but no effect on male fertility was observed in rats dosed orally at 60 mg/kg/day for nine weeks, in studies undertaken by another company.

**Use in pregnancy – Pregnancy Category B3**
For budesonide and formoterol in combination powder for inhalation or the concomitant treatment with budesonide or formoterol, no clinical data on exposed pregnancies are available. Animal studies with respect to the reproductive toxicity of the combination have not been performed.

Budesonide and formoterol powder for inhalation, alone or in combination, should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Only after special consideration should budesonide and formoterol be used during the first 3 months and shortly before delivery.

Because β-agonists, including formoterol, may potentially interfere with uterine contractility, due to a relaxant effect on uterine smooth muscle, budesonide and formoterol powder for inhalation in combination should be used during labour only if the potential benefit justifies the potential risk.

**Budesonide**

Results from a large prospective epidemiological study and from worldwide post marketing experience indicate no adverse effects of inhaled budesonide during pregnancy on the health of the fetus or newborn child.

If treatment with glucocorticosteroids during pregnancy is unavoidable, ICS such as budesonide should be considered due to their lower systemic effect. The lowest effective dose of budesonide to maintain asthma control should be used.

**Formoterol**

No teratogenic effects were observed in rats receiving formoterol fumarate at doses up to 60 mg/kg/day orally or 1.2 mg/kg/day by inhalation. Fetal cardiovascular malformations were observed in one study in which pregnant rabbits were dosed orally at 125 or 500 mg/kg/day during the period of organogenesis, but similar results were not obtained in another study at the same dose range. In a third study, an increased incidence of subcapsular hepatic cysts was observed in fetuses from rabbits dosed orally at 60 mg/kg/day. Decreased birth weight and increased perinatal/postnatal mortality were observed when formoterol fumarate was given to rats at oral doses of 0.2 mg/kg/day or greater during late gestation.

**Use in lactation.**
Budesonide is excreted in breast milk. However, due to the relatively low doses used via the inhalational route the amount of drug present in the breast milk, if any, is likely to be low.

It is not known whether formoterol is excreted in human milk. In reproductive studies in rats formoterol was excreted into breast milk. There are no well-controlled human studies of the use of budesonide/formoterol fixed combination powder for inhalation in nursing mothers. Administration of budesonide/formoterol fixed combination powder for inhalation to women

who are breastfeeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Driving or using machinery should be undertaken with caution until the effect of budesonide/formoterol fixed combination on the individual is established. Budesonide/formoterol in combination powder for inhalation does not generally affect the ability to drive or use machinery. However, adverse effects of this medicine include dizziness and blurred vision/visual disturbances which could affect the ability to drive or use machines (see Section 4.8 Adverse effects (Undesirable effects)).

## 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The same adverse effects may be expected for DuoResp Spiromax fixed combination as those reported for the respective monotherapies, budesonide and formoterol. No increased incidence of adverse reactions has been seen following concurrent administration of the two compounds. The most common drug related adverse reactions are pharmacologically predictable side-effects of $\beta_2$-agonist therapy, such as tremor and palpitations. These tend to be mild and usually disappear within a few days of commencing treatment.

If oropharyngeal candidiasis develops, it may be treated with appropriate anti-fungal therapy whilst still continuing with DuoResp Spiromax. The incidence of candidiasis can generally be held to a minimum by having patients rinse their mouth out with water after inhaling their maintenance dose.

Adverse reactions, which have been associated with budesonide, formoterol and budesonide/formoterol in combination, are given in Table 2.

**Table 2 Tabulation of adverse reactions**

| Frequency | System Order Class | Event |
|---|---|---|
| Common | Cardiac disorders | Palpitations |
| 1 to 10% | Infections and infestations | Candida infections in the oropharynx, pneumonia (in COPD patients) |
| | Nervous system disorders | Headache, tremor |
| | Respiratory; thoracic & mediastinal disorders | Mild irritation in the throat, coughing, hoarseness |
| Uncommon | Cardiac disorders | Tachycardia |
| 0.1 to 1% | Eye Disorders | Blurred vision |
| | Gastrointestinal disorders | Nausea, diarrhea |
| | Metabolism and nutrition disorders | Weight gain |
| | Musculoskeletal & connective tissue disorders | Muscle cramps |
| | Nervous system disorders | Dizziness, bad taste, thirst, tiredness |
| | Psychiatric disorders | Agitation, restlessness, nervousness, anxiety, sleep disturbances |
| | Skin and subcutaneous disorders | Bruises |
| Rare | Immune system disorders | Immediate and delayed hypersensitivity reactions including dermatitis, exanthema, |

| Frequency | System Order Class | Event |
|---|---|---|
| 0.01 to 0.1% | | urticaria, pruritis, angioedema and anaphylactic reaction |
| | Cardiac disorders | Cardiac arrhythmias eg atrial fibrillation, supraventricular tachycardia, extrasystoles |
| | Respiratory, thoracic & mediastinal disorders | Bronchospasm |
| | Skin & subcutaneous tissue disorders | Skin bruising |
| | Metabolism & nutrition disorders | Hypokalaemia |
| Very Rare | Cardiac disorders | Angina pectoris, Prolongation of QTc-interval |
| < 0.01% | Eye Disorders | Cataract and Glaucoma |
| | Endocrine disorders | Cushing's syndrome, growth retardation, decrease in bone mineral density Signs or symptoms of systemic glucocorticosteroid effects, eg hypofunction of the adrenal gland |
| | Metabolism & nutrition disorders | Hyperglycaemia |
| | Psychiatric disorders | Depression, behavioural disturbances |
| | Respiratory; thoracic & mediastinal disorders | Paradoxical bronchospasm |
| | Vascular disorders | Variations in blood pressure |
| Not Known | Eye Disorders | Central serous retinopathy |

As with other inhalation therapy, paradoxical bronchospasm may occur in very rare cases.

Treatment with β-sympathomimetics may result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies.

**Pneumonia**

The following table provides the incidence of pneumonia observed in the four pivotal phase III COPD studies (see Section 5.1 Pharmacodynamic properties - Clinical trials/COPD) for budesonide + formoterol 200/6 and comparative placebo arms.

**Table 3 Pneumonia incidence (%) – Budesonide + formoterol pivotal Phase III COPD studies (6 months or 12 months duration)**

| Dry Powder inhaler (DPI) | | | | Metered Dose inhaler | | | |
|---|---|---|---|---|---|---|---|
| ***Study 629*** [a] | | ***Study 670*** [a] | | ***Study 001*** [a] | | ***Study 002*** [a] | |
| Budesonide + formoterol DPI 200/6 | Placebo | Budesonide + formoterol DPI 200/6 | Placebo | Budesonide + formoterol MDI 200/6 | Placebo | Budesonide + formoterol MDI 200/6 | Placebo |
| n=208 | n=205 | n=254 | n=256 | n=494 | n=481 | n=564[b] | n=300 |
| 5.3% | 5.4% | 3.5% | 0.8% | 4.5% | 5.2% | 1.8% | 1.7% |

[a] Only the fixed dose combination 200/6 and placebo arms are presented in this table, not all treatment arms within the clinical studies

[b] Includes fixed dose combination 200/6 arm (n=277) + the free combination budesonide 200 + eformoterol 6 arm (n=287) n – number of patients in the safety analysis

In these placebo-controlled studies, the incidence of pneumonia was low, with no consistent evidence of increased risk of pneumonia for budesonide +formoterol treated patients compared to patients on placebo.

**Anti-inflammatory reliever therapy (SYGMA 1 and 2)**

Overall, anti-inflammatory reliever therapy is generally well tolerated, based on the frequency and nature of adverse effects. No new safety concerns were identified for the use of budesonide/formoterol 200/6 as needed in a mild asthma population.

**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

An overdose of formoterol may lead to effects that are typical for $\beta_2$-adrenergic agonists: tremor, headache, palpitations, and tachycardia. Monitoring of serum potassium concentrations may be warranted. Hypotension, metabolic acidosis, hypokalaemia and hyperglycaemia may also occur. Supportive and symptomatic treatment may be indicated. β-blockers should be used with care because of the possibility of inducing bronchospasm in sensitive individuals. A metered dose of 120 µg administered during three hours in patients with acute bronchial obstruction raised no safety concerns.

Acute overdosage with budesonide, even in excessive doses, is not expected to be a clinical problem. However, the plasma cortisol level will decrease and number and percentage of circulating neutrophils will increase. The number and percentage of lymphocytes and eosinophils will decrease concurrently. When used chronically in excessive doses, systemic glucocorticosteroid effects, such as hypercorticism and adrenal suppression, may appear.

Withdrawing budesonide/formoterol or decreasing the dose of budesonide will abolish these effects, although the normalisation of the HPA-axis may be a slow process.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMIC PROPERTIES

**Mechanism of action**
Budesonide and formoterol have different modes of action and show additive effects in terms of reduction of asthma and chronic obstructive pulmonary disease (COPD) exacerbations. The specific properties of budesonide and formoterol allow the combination to be used either as an anti-inflammatory reliever or as maintenance treatment for asthma, and for symptomatic treatment of patients with moderate to severe COPD.

**Budesonide**

Budesonide is a glucocorticosteroid with a high local anti-inflammatory effect. Budesonide has shown anti-anaphylactic and anti-inflammatory effects in provocation studies in animals and humans, manifested as decreased bronchial obstruction in the immediate as well as the late phase of an allergic reaction. Budesonide has also been shown to decrease airway reactivity to both direct (histamine, methacholine) and indirect (exercise) challenge in hyperreactive patients. Budesonide, when inhaled, has a rapid (within hours) and dose-dependent anti-inflammatory action in the airways, resulting in reduced symptoms and fewer exacerbations. Inhaled budesonide has less severe adverse effects than systemic corticosteroids. The exact mechanism responsible for the anti-inflammatory effect of glucocorticosteroids is unknown.

**Formoterol**

Formoterol is a potent selective $\beta_2$-adrenergic agonist that when inhaled results in rapid and long acting relaxation of bronchial smooth muscles in patients with reversible airways obstruction. The bronchodilating effect is dose dependent with an onset of effect within 1-3 minutes after inhalation. The duration of effect is at least 12 hours after a single dose.

**Clinical trials**

The reported clinical studies are those of the innovator reference product being compared against the respective monotherapies and alternative treatments for asthma and COPD. Bioequivalence has been demonstrated between DuoResp Spiromax dry powder inhaler and the innovator reference dry powder inhaler for the 200/6 and 400/12 doses. Additionally, an investigation was conducted to assess inspiratory flow rates achieved using the Spiromax device as this device is different to the innovator dry powder inhaler device.

***Peak Inspiratory Flow rate through the Spiromax device***

A randomised, open label placebo study was performed in children and adolescents with asthma (aged 6 -17 years), adults with asthma (18-45 years), adults with chronic obstructive pulmonary disease (COPD aged >50 years) and healthy volunteers (aged 18-45 years) to evaluate the peak inspiratory flow rate (PIFR) and other related inhalation parameters following inhalation from a Spiromax device (containing placebo) compared with inhalation from an already marketed multi dose dry powder inhaler device (containing placebo). The impact of enhanced training in dry powder inhalation technique on inhalation speed and volume was also assessed in these subject groups. The data from the study indicated that regardless of age and underlying disease severity, children, adolescents and adults with asthma as well as patients with COPD were able to achieve inspiratory flow rates through the Spiromax device that were similar to those generated through the marketed multi dose dry powder inhaler device. The mean PIFR achieved by patients with asthma or COPD was over 60 L/min, a flow rate at which both devices studied are known to deliver comparable amounts of drug to the lungs. Very few patients had PIFRs below 40 L/min; when PIFRs were less than 40 L/min there appeared to be no clustering by age or disease severity.

**Asthma**
**Anti-inflammatory reliever therapy**

A total of 8064 patients aged 12 and above with mild asthma were included in 2 double-blind efficacy and safety studies (SYGMA 1 and SYGMA 2), of which 3384 patients were randomised to *budesonide/formoterol anti-inflammatory reliever therapy* for 12 months. Patients were required to be uncontrolled on only short-acting $\beta_2$ agonist (SABA) as needed or controlled on low dose ICS or leukotriene receptor agonist plus SABA as needed.

Both studies compared *budesonide/formoterol anti-inflammatory reliever therapy* (budesonide/formorterol dry powder for inhalation 200/6 used as needed in response to symptoms) to budesonide dry powder for inhalation 200 µg (1 inhalation twice daily) given with as needed SABA. SYGMA 1 also compared *budesonide/formoterol anti-inflammatory reliever therapy* to as needed SABA alone.

In SYGMA 1 and SYGMA 2, respectively, based on physician assessment before enrolment, 44.5% and 46.3% of patients were uncontrolled on SABA as needed, and 55.5% and 53.7% of patients were controlled on low dose ICS or leukotriene receptor antagonists plus SABA as needed. At baseline, patients in SYGMA 1 and SYGMA 2, respectively, had a median age of 40 and 41 years (overall range across both studies 12 to 85 years), 12.5% and 9.8% of patients were adolescents (≥12 to <18 years) and approximately 7% and 9% of patients were over 65 years of age, 87.0% and 84.3% had never smoked, 10.3% and 13.1% were former smokers, 2.7% and 2.6% were current smokers, and 19.7% and 22.0% of patients had experienced a severe exacerbation within the 12 months prior to study enrolment.

In SYGMA 2, *budesonide/formoterol anti-inflammatory reliever therapy* was comparable to a maintenance dose of budesonide dry powder for inhalation given with as-needed SABA in terms of the rate of severe exacerbations (Table 4). Protection against severe exacerbation was achieved with a 75% reduction in median ICS load and without requiring adherence to maintenance ICS treatment. SYGMA 1 showed that *budesonide/formoterol anti-inflammatory reliever therapy* provided a statistically significant and clinically meaningful reduction in the rate of annual severe exacerbations by 64% compared with SABA as- needed alone (Table 4). Reduction in the annual rate of moderate to severe exacerbations was consistent (60%) with that observed for severe exacerbations (Risk Ratio (RR): 0.40 (95% Confidence Interval (CI): 0.32, 0.49); p<0.001).

In SYGMA 1, *budesonide/formoterol anti-inflammatory reliever therapy* provided superior daily asthma symptom control compared to as-needed SABA alone (Odds Ratio (OR): 1.14 (1.00 to 1.30); p=0.046), showing a mean percentage of weeks with well-controlled asthma of 34.4% and 31.1%, respectively. Asthma symptom control was inferior for *budesonide/formoterol anti-inflammatory reliever therapy* compared to a maintenance dose of budesonide dry powder for inhalation given with as-needed SABA (OR: 0.64 (2-sided 95% CI 0.57, 0.73; lower limit of the CI ≥0.8 for non-inferiority), showing a mean percentage of well-controlled asthma weeks of 34.4% and 44.4%, respectively. Improvements in asthma control (as defined by Asthma Control Questionnaire (ACQ-5)) in patients using *budesonide/formoterol anti-inflammatory reliever therapy* were superior to improvements in patients using as needed SABA alone (estimate for difference: -0.15 (-0.20, -0.11); p<0.001). In accordance with the pre-specified hierarchical testing strategy, apart from well-controlled asthma weeks, all other efficacy results from this study were considered of nominal

statistical significance. Improvements in asthma control were lower for *budesonide/formoterol anti-inflammatory reliever therapy* compared to a maintenance dose of budesonide dry powder for inhalation given with SABA as needed (SYGMA 1 estimate for difference: 0.15 (0.10, 0.20); SYGMA 2: 0.11 (0.07, 0.15); both $p < 0.001$). For both comparisons, mean differences in treatments' effect upon ACQ-5 are not clinically meaningful (as assessed by a difference of greater than or equal to 0.5). These results were observed in a clinical study setting with considerably higher adherence to budesonide maintenance dosing than expected in real life.

In the SYGMA studies, increases in lung function compared to baseline (mean pre-bronchodilator FEV1) were statistically significantly larger for patients on *budesonide/formoterol anti-inflammatory reliever therapy* compared to patients on as needed SABA alone. Statistically significantly smaller increases were observed for *budesonide/formoterol anti-inflammatory reliever therapy* compared to a maintenance dose of budesonide dry powder for inhalation given with SABA as needed. For both comparisons, mean differences in treatments' effect were small (approximately 30 to 55 mL, equating to approximately 2% of the baseline mean).

Overall, the results of the SYGMA studies show that *budesonide/formoterol anti-inflammatory reliever therapy* is a more effective treatment than SABA as needed in patients with mild asthma. In addition, these studies suggest that *budesonide/formoterol anti-inflammatory reliever therapy* may be considered an alternative treatment option for patients with mild asthma who are eligible for ICS treatment.

**Table 4 Overview of severe exacerbations in SYGMA 1 and 2**

| Study | Treatment groups [a] | N | Severe exacerbations [b] | |
|---|---|---|---|---|
| | | | Number of events | Exacerbations/ patient-year |
| SYGMA 1 | Budesonide/formoterol dry powder for inhalation 200/6 as needed | 1277 | 77 | 0.07 |
| | Terbutaline dry powder for inhalation 0.4 mg as needed | 1277 | 188 | 0.20[c] |
| | Budesonide dry powder for inhalation 200 µg twice daily + terbutaline dry powder for inhalation 0.4 mg as needed | 1282 | 89 | 0.09[d] |
| SYGMA 2 | Budesonide/formoterol dry powder for inhalation 200/6 as needed | 2084 | 217 | 0.11 |
| | Budesonide dry powder for inhalation 200 µg twice daily + terbutaline dry powder for inhalation 0.4 mg as needed | 2083 | 221 | 0.12[e] |

a Budesonide 200 µg (metered dose; Budesonide dry powder for inhalation); Terbutaline dry powder for inhalation 0.4 mg (delivered dose; M3 version).

b Defined as hospitalisation/emergency room treatment or treatment with oral steroids due to asthma.

c Reduction in exacerbation rate is statistically significant ($p<0.001$) for the comparison of budesonide/formoterol dry powder for inhalation as needed vs terbutaline 0.4 mg as needed.

d Reduction in exacerbation rate is not statistically significantly different ($p=0.279$) when comparing budesonide/formoterol dry powder for inhalation as needed vs budesonide 200 µg twice daily + terbutaline 0.4 mg as needed in SYGMA 1.

e Budesonide/formoterol dry powder for inhalation as needed was non-inferior to budesonide 200 µg twice daily + terbutaline 0.4 mg as needed in reducing the severe exacerbation rate in SYGMA 2. The upper limit (1.16) of the 95% CI for the rate ratio was below the pre-specified non-inferiority limit (1.20).

Analysis of time to first severe exacerbation in SYGMA 1 showed that the likelihood of experiencing a severe exacerbation was statistically significantly higher for SABA as needed use compared to *budesonide/formoterol anti-inflammatory reliever therapy* over the 1 year treatment period, with a risk reduction of 56% (Hazard Ratio (HR): 0.44 (0.33, 0.58); p<0.001). There were no differences in the probability of experiencing a severe exacerbation between *budesonide/formoterol anti-inflammatory reliever therapy* and a maintenance dose of budesonide given with SABA as needed.

**Budesonide/formoterol anti-inflammatory reliever plus maintenance therapy**

The safety and efficacy of budesonide/formoterol in the *budesonide/formoterol anti-inflammatory reliever plus maintenance therapy* regimen have been investigated in six clinical trials using two dose strengths (100/6 and 200/6) of budesonide/formoterol dry powder for inhalation in patients with asthma. A total of 14218 patients (1134 elderly, 11144 adults, 1595 adolescents and 345 children) were randomised into the studies, of which 5514 were treated with budesonide/formoterol anti-inflammatory reliever plus maintenance therapy. Of the overall patient population 7% were smokers. In comparison with the usual patient proportions seen in practice, smokers and the elderly were under-represented in the trials. However, the results for these subgroups were generally consistent with the results for the whole study population. Patients with chronic obstructive pulmonary disease were excluded.

The studies showed that *anti-inflammatory reliever plus maintenance therapy* was significantly superior compared with fixed dose combination products or higher doses of ICS with a separate short acting or long acting β-agonist used as reliever (see Table 5 and Table 6). In the 5 double-blind long-term studies, patients receiving *budesonide/formoterol anti-inflammatory reliever plus maintenance therapy* used no reliever inhalations on 57% of treatment days and 0-2 reliever inhalations on 87% of treatment days.

**Table 5 Summary of primary efficacy variable**

| Treatment | Hazard Ratio | 95% confidence interval |
|---|---|---|
| **Time to first severe asthma exacerbation** | | |
| *SMILE 734* | | |
| 1. Budesonide/formoterol maintenance & reliever therapy[a] vs budesonide/formoterol + formoterol prn | 0.73 | 0.59, 0.90 |
| 2. Budesonide/formoterol maintenance & reliever therapy vs budesonide/formoterol + terbutaline prn | 0.55 | 0.45, 0.68 |
| 3. Budesonide/formoterol + formoterol prn vs budesonide/formoterol + terbutaline prn | 0.76 | 0.63, 0.92 |
| *COMPASS 735* | | |
| 1. Budesonide/formoterol maintenance & reliever therapy vs budesonide/formoterol + terbutaline prn | 0.74 | 0.56, 0.96 |
| 2. Budesonide/formoterol maintenance & reliever therapy vs fluticasone/salmeterol + terbutaline prn | 0.67 | 0.52, 0.87 |
| 3. Budesonide/formoterol + terbutaline prn vs fluticasone/salmeterol + terbutaline prn | 0.91 | 0.72, 1.16 |

| Treatment | Hazard Ratio | 95% confidence interval |
|---|---|---|
| *STAY 673* | | |
| 1. Budesonide/formoterol maintenance & reliever therapy vs budesonide/formoterol + terbutaline prn | 0.55 | 0.44, 0.67 |
| 2. Budesonide/formoterol maintenance & reliever therapy vs budesonide + terbutaline prn | 0.53 | 0.43, 0.65 |
| 3. Budesonide/formoterol + terbutaline prn vs budesonide + terbutaline prn | 0.97 | 0.82, 1.16 |
| *STEP 668* | | |
| 1. Budesonide/formoterol maintenance & reliever therapy vs budesonide + terbutaline prn | 0.61 | 0.50, 0.74 |
| *COSMOS 691* | | |
| 1. Budesonide/formoterol maintenance & reliever therapy vs fluticasone/salmeterol + salbutamol prn | 0.75 | 0.61, 0.93 |
| **Morning peak flow (L/min)** | | |
| *STEAM 667* | | |
| Budesonide/formoterol maintenance & reliever therapy vs budesonide + terbutaline prn | Mean diff 25 L/min | 19, 31 |

[a] Budesonide/formoterol anti-inflammatory reliever plus maintenance therapy, previously known as budesonide/formoterol maintenance & reliever therapy.

**Table 6 Summary of the number of severe asthma exacerbations**

| Treatment | No. of exacerbations | No. of patients with exacerbations / total patients (%) |
|---|---|---|
| *SMILE 734 (12 months)* | | |
| 1. Budesonide/formoterol maintenance & reliever therapy[a] | 194 | 143/1107 (13%) |
| 2. Budesonide/formoterol + formoterol prn | 296 | 195/1137 (17%) |
| 3. Budesonide/formoterol + terbutaline prn | 377 | 245/1138 (22%) |
| *COMPASS 735 (6 months)* | | |
| 1. Budesonide/formoterol maintenance & reliever therapy | 125 | 94/1103 (9%) |
| 2. Budesonide/formoterol + terbutaline prn | 173 | 126/1066 (11%) |
| 3. Fluticasone/salmeterol + terbutaline prn | 208 | 138/1119 (12%) |
| *STAY 673 (12 months)* | | |
| 1. Budesonide/formoterol maintenance & reliever therapy | 303 | 148/922 (16%) |
| 2. Budesonide/formoterol + terbutaline prn | 553 | 248/906 (27%) |
| 3. Budesonide + terbutaline prn | 564 | 256/925 (28%) |
| *STEP 668 (12 months)* | | |
| 1. Budesonide/formoterol maintenance & reliever therapy | 331 | 170/947 (18%) |
| 2. Budesonide + terbutaline prn | 546 | 259/943 (27%) |
| *STEAM 667 (6 months)* | | |
| 1. Budesonide/formoterol maintenance & reliever therapy | 43 | 27/354 (8%) |
| 2. Budesonide + terbutaline prn | 94 | 54/342 (27%) |

| | | |
|---|---|---|
| *COSMOS 691 (12 months)* | | |
| 1. Budesonide/formoterol maintenance & reliever therapy | 255 | 159/1064 (15%) |
| 2. Fluticasone/salmeterol + Salbutamol prn | 329 | 204/1071 (19%) |

[a] Budesonide/formoterol Anti-inflammatory reliever plus maintenance therapy, previously known as budesonide/formoterol maintenance & reliever therapy.

**Study 734 (SMILE)**

A 12 month randomised, double-blind, parallel-group, trial in 3394 adult and adolescent patients aged 12 to 89 years with moderate to severe asthma. The study comprised of the following three arms:

1. *Budesonide/formoterol anti-inflammatory reliever plus maintenance therapy* - budesonide/formoterol dry powder for inhalation 200/6, 1 inhalation twice daily plus additional inhalations as needed

2. Budesonide/formoterol 200/6, 1 inhalation twice daily with formoterol dry powder inhaler as needed

3. Budesonide/formoterol dry powder for inhalation 200/6, 1 inhalation twice daily with terbutaline dry powder inhaler as needed

The primary efficacy variable, time to first severe exacerbation, was significantly increased with *budesonide/formoterol anti-inflammatory reliever plus maintenance therapy* compared with budesonide/formoterol plus formoterol and budesonide/formoterol plus terbutaline (see Table 5).

Use of oral steroids due to exacerbations was lower in the budesonide/formoterol *anti-inflammatory reliever plus maintenance therapy* group (1204 days total vs 2063 and 2755 days in the budesonide/formoterol plus formoterol and budesonide/formoterol plus terbutaline groups, respectively).

The majority of secondary variables supported the superiority of budesonide/formoterol *anti-inflammatory reliever plus maintenance therapy* over both comparators (see Table 7). The average daily as-needed use in the *budesonide/formoterol anti-inflammatory reliever plus maintenance therapy* group was 1.02 inhalations/day and the frequency of high as-needed use was lower for budesonide/formoterol *anti-inflammatory reliever plus maintenance therapy* compared to both comparators.

**Table 7 Secondary efficacy variable for Study 734**

| Variable[†] | Bud/For maintenance & reliever[a] | Bud/For + For prn | Bud/For + terb prn | Comparison (mean difference & 95% confidence interval) | |
|---|---|---|---|---|---|
| | | | | Bud/For maintenance & reliever v Bud/For + For prn | Bud/For maintenance & reliever v Bud/For + terb prn |
| mPEF (L/min) | 15.3 | 10.6 | 7.9 | 4.8 (1.5, 8.0) | 7.5 (4.2, 10.7) |
| ePEF (L/min) | 13.8 | 8.5 | 7.5 | 5.4 (2.1, 8.6) | 6.3 (3.1, 9.5 |
| $FEV_1$ (L) | 0.060 | 0.011 | -0.016 | 0.049 (0.024, 0.075) | 0.076 (0.050, 0.101) |
| Total asthma symptom score (0-6) | -0.69 | -0.57 | -0.58 | -0.12 (-0.18, -0.06) | -0.11 (-0.17, -0.05) |
| Nocturnal awakenings due to asthma (% nights) | -16.0 | -14.0 | -13.5 | -2.0 (-3.7, -0.4) | -2.6 (-4.3, -0.9) |
| Symptom free days[Δ] (% days) | 31.3 | 28.9 | 29.4 | 2.4 (-0.3, 5.0) | 1.9 (-0.8, 4.6) |
| Rescue medication use (inhalations/24 hours) | -0.84 | -0.67 | -0.67 | -0.17 (-0.25, -0.08) | -0.20 (-0.28, -0.11) |

[†] Mean change from mean of run-in to mean of the treatment period; mPEF – morning peak expiratory flow; ePEF – evening peak expiratory flow; $FEV_1$ – forced expiratory volume in 1 second; [Δ] day and night with no symptoms and a night with no awakenings.

[a] Budesonide/formoterol anti-inflammatory reliever plus maintenance therapy, previously known as budesonide/formoterol maintenance & reliever therapy.

The study specifically demonstrates that both the budesonide and the formoterol components of budesonide/formoterol contribute to improved asthma control achieved through the as-needed dosing of budesonide/formoterol within the *budesonide/formoterol anti-inflammatory reliever plus maintenance therapy* concept.

**Study 735 (COMPASS)**

A 6 month randomised, double-blind, parallel-group trial in 3335 adult and adolescent patients aged 11 to 83 years. The study compared the following three arms:

1. *Budesonide/formoterol anti-inflammatory reliever plus maintenance therapy* - budesonide/formoterol dry powder for inhalation 200/6, 1 inhalation twice daily plus additional inhalation as needed

2. Fluticasone/salmeterol Inhaler 125/25, 2 inhalations twice daily with terbutaline dry powder inhaler as needed

3. Budesonide/formoterol dry powder for inhalation 400/12, 1 inhalation twice daily with terbutaline dry powder inhaler as needed

The primary efficacy variable, time to first severe exacerbation, was significantly increased with *budesonide/formoterol anti-inflammatory reliever plus maintenance therapy* compared with both Fluticasone/salmeterol plus terbutaline and budesonide/formoterol at a higher maintenance dose plus terbutaline (see Table 5).

Use of oral steroids due to exacerbations was lower in the *budesonide/formoterol anti-inflammatory reliever plus maintenance therapy* group compared to Fluticasone/salmeterol plus terbutaline and budesonide/formoterol plus terbutaline (619 days total use vs. 1132 and 1044 days, respectively).

Results for secondary variables, including lung function, mean use of as-needed medication and symptom variables, were not significantly different between *budesonide/formoterol anti-inflammatory reliever plus maintenance therapy* and the other two groups. The average daily as-needed use in the *budesonide/formoterol anti-inflammatory reliever plus maintenance therapy* group was 1.02 inhalations/day.

Since the mean daily dose in the *budesonide/formoterol anti-inflammatory reliever plus maintenance therapy* group remained lower than in the budesonide/formoterol plus terbutaline group, the study specifically confirms the benefit of as-needed administration of part of the budesonide/formoterol dose.

**Study 673 (STAY), Study 668 (STEP) and Study 667 (STEAM)**

In Studies 673, 668 and 667, *budesonide/formoterol anti-inflammatory reliever plus maintenance therapy* prolonged the time to the first exacerbation compared to budesonide/formoterol at the same maintenance dose with terbutaline as reliever and compared to a 2 to 4-fold higher maintenance dose of budesonide with terbutaline as reliever (see Table 5). Symptoms and reliever use were reduced and lung function improved compared with all other treatments (see Table 8, Table 9 and Table 10).

**Table 8 Secondary efficacy variable for Study 673**

| | **Bud/For maintenance & reliever[a]** | **Bud/For + terb prn** | **Bud + terb prn** | **Comparison (mean difference & 95% confidence interval)** | |
|---|---|---|---|---|---|
| **Variable[†]** | | | | **Bud/For maintenance & reliever v Symb + terb prn** | **Bud/For maintenance & reliever v Bud + terb prn** |
| mPEF (L/min) | 29.9 | 22.0 | 13.0 | 7.9 (4.2, 11.7) | 16.9 (13.2, 20.7) |
| ePEF (L/min) | 26.5 | 18.3 | 9.2 | 8.3 (4.5, 12.0) | 17.4 (13.7, 21.1) |
| $FEV_1$ (L) | 0.22 | 0.15 | 0.12 | 0.075 (0.044, 0.106) | 0.102 (0.071, 0.132) |
| Total asthma symptom score (0-6) | -0.68 | -0.59 | -0.46 | -0.09 (-0.16, -0.02) | -0.21 (-0.28, -0.15) |
| Nocturnal awakenings due to asthma (% nights) | -12.7 | -8.8 | -8.4 | -3.9 (-5.4, -2.3) | -4.3 (-5.9, -2.7) |
| Symptom free days[Δ] (% days) | 29.1 | 28.2 | 21.6 | 0.9 (-1.9, 3.8) | 7.5 (4.6, 10.3) |

| | | | | | |
|---|---|---|---|---|---|
| Rescue medication use (inhalations/24 hours) | -1.40 | -1.18 | -0.93 | -0.22 (-0.33, -0.11) | -0.46 (-0.57, -0.35) |

† Mean change from mean of run-in to mean of the treatment period; mPEF – morning peak expiratory flow; ePEF – evening peak expiratory flow; $FEV_1$ – forced expiratory volume in 1 second; Δ day and night with no symptoms and a night with no awakenings.

[a] Budesonide/formoterol anti-inflammatory reliever plus maintenance therapy, previously known as budesonide/formoterol maintenance & reliever therapy.

**Table 9 Secondary efficacy variable for Study 668**

| Variable† | Bud/For maintenance + reliever[a] | Bud. + terb prn | Comparison (mean difference & 95% confidence interval) Bud/For maintenance & reliever v Bud + terb prn |
|---|---|---|---|
| mPEF (L/min) | 34.2 | 13.9 | 20.3 (16.5, 24.1) |
| ePEF (L/min) | 21.8 | 7.9 | 14.0 (10.4, 17.5) |
| $FEV_1$ (L) | 0.19 | 0.09 | 0.100 (0.071, 0.130) |
| Total asthma symptom score (0-6) | -0.81 | -0.61 | -0.21 (-0.28, -0.13) |
| Nocturnal awakenings due to asthma (% nights) | -13.8 | -10.6 | -3.3 (-4.8, -1.7) |
| Symptom free days[Δ] (% days) | 33.1 | 25.7 | 7.5 (4.5, 10.4) |
| Rescue medication use (inhalations/24 hours) | -0.99 | -0.55 | -0.44 (-0.54, -0.34) |

† Mean change from mean of run-in to mean of the treatment period; mPEF – morning peak expiratory flow; ePEF – evening peak expiratory flow; $FEV_1$ – forced expiratory volume in 1 second; Δ day and night with no symptoms and a night with no awakenings.

[a] Budesonide/formoterol anti-inflammatory reliever plus maintenance therapy, previously known as budesonide/formoterol maintenance & reliever therapy.

**Table 10 Secondary efficacy variable for Study 667**

| Variable† | Bud/For maintenance + reliever[a] | Bud. + terb prn | Comparison (mean difference & 95% confidence interval) Bud/For maintenance & reliever v Bud + terb prn |
|---|---|---|---|
| ePEF (L/min) | 25.4 | 6.6 | 18.8 (13.3, 24.3) |
| $FEV_1$ (L) | 0.21 | 0.06 | 0.148 (0.103, 0.193) |
| Total asthma symptom score (0-6) | -0.55 | -0.38 | -0.17 (-0.26, -0.07) |
| Nocturnal awakenings due to asthma (% nights) | -8.3 | -6.1 | -2.2 (-4.5, 0.01) |
| Symptom free days[Δ] (% days) | 26.8 | 20.2 | 6.5 (2.0, 11.0) |
| Rescue medication use (inhalations/24 hours) | -0.68 | -0.34 | -0.34 (-0.51, -0.17) |

† Mean change from mean of run-in to mean of the treatment period; ePEF – evening peak expiratory flow; $FEV_1$ – forced expiratory volume in 1 second; Δ day and night with no symptoms and a night with no awakenings.

[a] Budesonide/formoterol anti-inflammatory reliever plus maintenance therapy, previously known as budesonide/formoterol maintenance & reliever therapy.

**Study 691 (COSMOS)**

A 12-month, randomised, open, parallel group trial that compared the effectiveness of *budesonide/formoterol anti-inflammatory reliever plus maintenance therapy* with Fluticasone/salmeterol plus Salbutamol in steroid-treated adult and adolescent patients (N=2143) aged 12 to 84 years with asthma. Randomised treatment started with a 4-week period during which the maintenance doses were fixed, followed by 11 months where the maintenance dose was adjusted to the lowest dose required for symptom control (see Table 11).

**Table 11 Treatments in the COSMOS (691) study**

| | **Budesonide/formoterol maintenance & reliever therapy[a]** | **Fluticasone/salmeterol plus salbutamol** |
|---|---|---|
| Fixed dose period (4 weeks) | Budesonide/formoterol 200/6, 2 inhalations twice daily with additional inhalations as needed | Fluticasone/salmeterol 250/50, 1 inhalation twice daily + Salbutamol as needed |
| Dose adjustment period (11 months) | Budesonide/formoterol 200/6 either<br>- 2 inhalations twice daily + as needed,<br>or<br>- 1 inhalation twice daily + as needed,<br>or<br>- 2 inhalations once daily + as needed | Either<br>- Fluticasone/salmeterol 500/50, 1 inhalation twice daily + Salbutamol as needed<br>- Fluticasone/salmeterol 250/50, 1 inhalation twice daily + Salbutamol as needed, or<br>- Fluticasone/salmeterol 100/50, 1 inhalation twice daily + Salbutamol as needed |

[a] Budesonide/formoterol anti-inflammatory reliever plus maintenance therapy, previously known as budesonide/formoterol maintenance & reliever therapy.

This study showed that *budesonide/formoterol anti-inflammatory reliever plus maintenance therapy* treatment is more effective than adjustable therapy with Fluticasone/salmeterol plus Salbutamol in controlling asthma in adults and adolescents.

*Budesonide/formoterol anti-inflammatory reliever plus maintenance therapy* increased the time to first severe asthma exacerbations, reduced the total number of severe asthma exacerbations (see Table 5 and Table 6), reduced use of oral steroids for severe asthma exacerbations, and reduced use of as needed medications as compared with fluticasone/salmeterol at a similar daily ICS dose.

**Safety in the combined studies**

*Budesonide/formoterol anti-inflammatory reliever plus maintenance therapy* treatment has a safety profile that is similar to budesonide and budesonide/formoterol maintenance therapy with a decrease in asthma-related adverse events.

**Exercise-induced and allergen-induced bronchoconstriction**

The use of budesonide/formoterol dry powder for inhalation 200/6 in relation to exercise-induced and allergen-induced bronchoconstriction has been studied in three clinical trials for patients with mild / intermittent asthma.

Study D5890L00032 was a 6-week, 3-arm study in 66 adults and adolescents with mild asthma and episodic exercise-induced bronchoconstriction, in which the primary variable was change in maximum decrease in post-exercise $FEV_1$ calculated before and after 6 weeks of treatment. This study demonstrated that budesonide/formoterol dry powder for inhalation 200/6, taken as 1 inhalation before exercise plus additional inhalations as needed in response to symptoms, improved asthma control by reducing exercise-induced bronchoconstriction to the same order of magnitude as regular maintenance treatment with budesonide 400 µg plus terbutaline 0.5 mg as needed, despite a substantially lower steroid dose. Both treatments were superior to terbutaline as needed when taken alone.

Study AF-039-0001 was a 6-month, 2-arm study in 92 adult and adolescents with mild intermittent asthma who used SABA for symptom relief, in which the primary variable of efficacy was the change in level of fractional exhaled nitric oxide (FENO) in the two treatment groups over the duration of the study. This study demonstrated that the budesonide component in budesonide/formoterol dry powder for inhalation 200/6 taken before exercise and as needed, reduced airway inflammation and improved airway function, and showed the beneficial effect of the budesonide component when taken as needed together with formoterol (for symptom relief) as budesonide/formoterol dry powder for inhalation 200/6.

Study D5890L00007 was a 3-arm, placebo-controlled, cross-over study in 15 adult patients with mild allergic asthma, in which the primary efficacy variable was change in PD20 (the provocative dose causing a 20% fall in FEV1) methacholine (MCh) during each treatment period. This study showed that when administered 30 minutes after a low-dose allergen challenge, budesonide/formoterol dry powder for inhalation 200/6 abolished allergen-induced components of asthma deterioration whilst improving baseline pulmonary function, whereas, formoterol 6 ug alone inhibited the rise in symptoms but did not protect against allergen-induced airway inflammation. This study indicated that deteriorating asthma, provoked by low-dose allergen, is managed more effectively with budesonide/formoterol dry powder for inhalation 200/6 than with formoterol.

**Budesonide/formoterol maintenance therapy**

The efficacy and safety of budesonide/formoterol for maintenance therapy has been evaluated in seven randomised, double-blind, double dummy, active controlled, parallel group studies. All treatment arms in these studies used a SABA for relief of symptoms. Six studies were conducted for 12 weeks (100/6 and 200/6 presentations) while the 400/12 presentation study was conducted for 24 weeks (12 weeks efficacy and additional 12 weeks

safety). Efficacy and safety data were collected for 3340 mild to moderate/severe asthmatic patients (2411 adults, 128 adolescents, 801 children aged 4 to 11 years old); 1704 were treated with budesonide/formoterol.

*Budesonide/formoterol 100/6 and 200/6*

In one study the maximum recommended maintenance dose of budesonide/formoterol 200/6 (2 inhalations twice daily) was compared to corresponding doses of the free combination (budesonide dry powder inhaler 200 µg + formoterol dry powder inhaler 6µg, two inhalations twice daily) and budesonide dry powder inhaler 200 µg (2 inhalations twice daily) only in adults with moderate asthma (mean $FEV_1$ 73.8% predicted normal and reversibility 22.5%). Table 12 details the efficacy results after 12 weeks treatment.

**Table 12 Estimated treatment means and treatment contrasts: effects of 12 weeks treatment with twice daily budesonide/formoterol 200/6, budesonide 200 µg alone and the free combination of the monoproducts**

| Variable | Bud/ For | Bud | Free comb | Comparison p values | |
|---|---|---|---|---|---|
| | | | | Bud/For v Bud | Bud/For v free comb |
| Change† in mPEF§ (L/min) | 35.7 | 0.2 | 32 | <0.0001 | ns |
| Change† in ePEF (L/min) | 24.8 | -3.7 | 22.3 | <0.0001 | ns |
| $FEV_1$+ (L) | 2.47 | 2.35 | 2.50 | 0.0128 | ns |
| Total asthma symptom score# (0-6) | 0.75 | 1.08 | 0.84 | 0.0002 | ns |
| Nocturnal awakenings due to asthma# (% patients) | 8.31 | 10.94 | 10.09 | ns | ns |
| Symptom free days$^{\Delta\#}$ (% days) | 57.16 | 40.15 | 54.43 | <0.0001 | ns |
| Change† in rescue medication use (inhalations/24 hours) | -0.99 | -0.44 | -1.13 | 0.006 | ns |

† Mean change from mean of baseline to mean of the 12 week treatment period; §Primary efficacy variable; mPEF – morning peak expiratory flow; ePEF – evening peak expiratory flow; $FEV_1$ – forced expiratory volume in 1 second; +mean of the last value during treatment; #mean of the treatment average value; Δ day and night with no symptoms and a night with no awakenings.

When administered twice daily, budesonide/formoterol 200/6 is a more effective treatment than budesonide, at corresponding budesonide doses.

In a study in adults with milder asthma (mean FEV1 81.7% predicted normal and reversibility 22.2%) budesonide/formoterol 100/6 (1 inhalation twice daily) was compared with budesonide dry powder inhaler 200 µg (1 inhalation twice daily). Table 13 details the efficacy results after 12 weeks treatment.

**Table 13 Estimated treatment means and treatment contrasts: effects of 12 weeks treatment with twice daily Budesonide/formoterol 100/6 and budesonide 200 µg alone**

| Variable† | Budesonide/ formoterol | Budesonide | Comparison p values |
|---|---|---|---|
| Change† in mPEF§ (L/min) | 16.47 | 7.32 | 0.002 |
| Change† in ePEF (L/min) | 13.65 | 4.16 | <0.001 |
| $FEV_1$+ (L) | 2.63 | 2.64 | ns |
| Total asthma symptom score# (0-6) | 0.84 | 0.94 | ns |
| Nocturnal awakenings due to asthma# (% patients) | 11.57 | 13.82 | ns |
| Symptom free days$^{\Delta\#}$ (% days) | 55.31 | 48.86 | 0.007 |
| Change† in rescue medication use (inhalations/24 hours) | -0.33 | -0.14 | 0.025 |

† Mean change from mean of baseline to mean of the 12 week treatment period; §Primary efficacy variable; mPEF – morning peak expiratory flow; ePEF – evening peak expiratory flow; $FEV_1$ – forced expiratory volume in 1 second; +mean of the last value during treatment; #mean of the treatment average value; $^{\Delta}$ day and night with no symptoms and a night with no awakenings.

In conclusion, there was a greater improvement in lung function and asthma control with budesonide/formoterol 100/6 than with a doubled dose of budesonide.

**Budesonide/formoterol 400/12**

In a study in predominantly adult patients (<3% of patients were adolescents) with moderate to severe asthma (mean $FEV_1$ 66% predicted normal and reversibility 28%) budesonide/formoterol 400/12 (2 inhalations twice daily) was compared to corresponding doses of the free combination (formoterol dry powder inhaler 12 µg+budesonide dry powder inhaler 400 µg, two inhalations twice daily) and budesonide dry powder inhaler 400 µg (2 inhalations twice daily) only. Table 14 details the efficacy results after 12 weeks treatment.

**Table 14 Mean change from baseline in efficacy variables: effects of 12 weeks treatment with twice daily budesonide/formoterol 400/12, budesonide 400 µg alone and the free combination of the monoproducts**

| Variable† | Bud/ For | Bud | Free comb | Comparison p values | |
|---|---|---|---|---|---|
| | | | | Bud/For v Bud | Bud/For v free comb |
| mPEF§ (L/min) | 37.4 | 4.5 | 36.2 | <0.0001 | ns |
| ePEF (L/min) | 30.7 | -0.1 | 31.3 | <0.0001 | ns |
| $FEV_1$‡ (L) | 0.303 | 0.143 | 0.280 | <0.0001 | ns |
| Total asthma symptom score (0-6) | -0.62 | -0.36 | -0.66 | 0.0051 | ns |
| Daytime symptom score (0-3) | -0.39 | -0.19 | -0.43 | <0.0001 | ns |
| Night-time symptom score (0-3) | -0.23 | -0.18 | -0.23 | ns | ns |
| Nocturnal awakenings due to asthma (% patients) | -14.4 | -11.8 | -13.1 | ns | ns |

| Variable† | Bud/ For | Bud | Free comb | Comparison p values | |
|---|---|---|---|---|---|
| | | | | Bud/For v Bud | Bud/For v free comb |
| Symptom free days$^{\Delta}$ (% patients) | 31.2 | 15.6 | 32.2 | <0.0001 | ns |
| Rescue medication use (inhalations/24 hours) | -1.08 | -0.50 | -1.20 | <0.0001 | ns |

† Adjusted mean change from mean of baseline to mean of the 12 week treatment period; §Primary efficacy variable; mPEF – morning peak expiratory flow; ePEF – evening peak expiratory flow; ‡mean from visit 3 to 5; $FEV_1$ – forced expiratory volume in 1 second; $^{\Delta}$ day and night with no symptoms and a night with no awakenings.

When administered twice daily, budesonide/formoterol 400/12 is a more effective treatment for the majority of clinical endpoints than the corresponding budesonide dose.

**COPD**

The efficacy and safety of budesonide/formoterol in the treatment of patients with moderate to severe COPD (pre-bronchodilator $FEV_1$ ≤50% predicted normal) has been evaluated in four randomised, double-blind, placebo and active controlled, parallel-group, multi-centre clinical studies. Two 12-month studies were performed with the dry powder inhaler budesonide/formoterol dry powder for inhalation (studies 629 and 670), and one 12-month and one 6-month study were performed with the pressurised metered dose inhaler (pMDI) budesonide/formoterol pressurised metered dose inhaler (studies 001 and 002, respectively).

- Studies 629 and 670 - In both studies, budesonide/formoterol dry powder for inhalation 200/6 was compared with placebo and the corresponding mono-products (budesonide dry powder inhaler 200 µg and formoterol dry powder inhaler 6 µg), all taken as two inhalations twice daily. A total of 812 and 1022 patients with moderate to severe COPD were randomised, of which 208 and 254 were treated with Budesonide/formoterol dry powder for inhalation. Patients in both studies had a mean age of 64 years and FEV1 of 0.99 L or 36% of predicted normal at baseline.
- Studies 001 and 002 - The study plans were similar. Both studies used budesonide/formoterol pMDI.

  For Study 001, after a screening visit (visit 1), subjects entered a two weeks run-in period after which they were randomly assigned (visit 2) to one of the four following treatments:

  1. Budesonide/formoterol pMDI 200/6, fixed combination of 200 µg budesonide and 6 µg formoterol per actuation, administered as 2 actuations twice daily;
  2. Budesonide/formoterol pMDI 100/6, fixed combination of 100 µg budesonide and 6 µg formoterol per actuation, administered as 2 actuations twice daily;
  3. Formoterol dry powder inhaler, 6 µg per inhalation, administered as 2 actuations twice daily;
  4. Placebo.

  Study 002 had two additional treatment groups:

  5. Budesonide pMDI 200 µg per actuation, administered as 2 actuations twice daily;

6. Free combination of budesonide pMDI 200 µg per actuation plus formoterol dry powder inhaler 6 µg per actuation, administered as 2 actuations of each twice daily

A total of 1964 (Study 001) and 1704 (Study 002) patients with moderate to severe COPD were randomised, of which 494 and 277 were treated with budesonide/formoterol pMDI 200/6. The study populations had a mean age of 63 years and mean FEV1 of 1.04-1.05 L or 34% of predicted normal at baseline.

**Study 629**

In Study 629, efficacy was evaluated over 12 months using the co-primary endpoints of post-dose $FEV_1$ and number of severe COPD exacerbations (defined as intake of a course of oral steroids and/or antibiotics and/or hospitalisation due to respiratory symptoms).

- Budesonide/formoterol dry powder for inhalation significantly improved mean $FEV_1$ compared with placebo and budesonide by 15% ($p<0.001$) and 9% ($p<0.001$), respectively.

- Budesonide/formoterol dry powder for inhalation significantly reduced the number of severe exacerbations compared with placebo and formoterol by 24% (p=0.035) and 23% (p=0.043), respectively. The number needed to treat (NNT) to prevent one severe COPD exacerbation in a year for budesonide/formoterol dry powder for inhalation compared with formoterol was 2.4.

**Study 670**

In Study 670, efficacy was evaluated over 12 months using the co-primary endpoints of post dose- $FEV_1$ and time to first severe COPD exacerbation (defined as intake of a course of oral steroids and/or antibiotics and/or hospitalisation due to respiratory symptoms).

- Budesonide/formoterol dry powder for inhalation significantly improved mean $FEV_1$ compared with placebo, budesonide, and formoterol by 14% ($p<0.001$), 11% ($p<0.001$), and 5% (p=0.002), respectively.

- Budesonide/formoterol dry powder for inhalation significantly prolonged the time to first severe COPD exacerbation compared to all comparator treatments. The instantaneous risk of experiencing a severe COPD exacerbation compared to placebo, budesonide, and formoterol was reduced by 29% (p=0.006), 23% (p=0.033), and 30% (p=0.003), respectively.

Budesonide/formoterol dry powder for inhalation also significantly reduced the number of severe COPD exacerbations compared to placebo and formoterol by 24% (p=0.029) and 26% (p=0.015), respectively. The NNT to prevent one COPD exacerbation in a year compared to formoterol was 2.1.

**Study 001**

In Study 001, efficacy was evaluated over 12 months using the co-primary efficacy variables of change from baseline in average pre-dose and 1-hour post-dose $FEV_1$ over the treatment period.

*Primary endpoints*

- Budesonide/formoterol pMDI 100/6 produced a significantly greater change in postdose $FEV_1$ compared to placebo (LS mean = 0.16 L; p<0.001); however the change in predose $FEV_1$ was not significantly different to formoterol 6 µg (LS mean = 0.02 L; p=0.161).

- Budesonide/formoterol pMDI 200/6 significantly improved 1-hour pre-dose $FEV_1$ compared with formoterol and placebo by 0.04 L (p=0.008) and 0.09 L (p<0.001), respectively.

- Budesonide/formoterol pMDI 200/6 significantly improved post-dose $FEV_1$ over the treatment period compared with formoterol and placebo by 0.03 L (p=0.023) and 0.18 L (p<0.001), respectively.

Serial $FEV_1$ measures over 12 hours were obtained in a subset of patients (N=491). The median time to onset of bronchodilation (>15% improvement in $FEV_1$) was seen within 5 minutes at the end of treatment time point in patients receiving Budesonide/formoterol pMDI 200/6 (N=121). Maximum improvement in $FEV_1$ occurred at approximately 2 hours post-dose, and post-dose bronchodilator effect was maintained over 12 hours.

*Exacerbations (secondary variable)*

Budesonide/formoterol pMDI reduced the number of severe COPD exacerbations (defined as a worsening of COPD requiring oral steroid use and/or hospitalisation) to a statistically significant degree. Overall 34.1% of subjects experienced 1159 exacerbations: Budesonide/formoterol pMDI 200/6, 30.8%; Budesonide/formoterol pMDI 100/6, 32.6%; placebo 37.2%. The majority of exacerbations were treated with oral glucocorticosteroids: Budesonide/formoterol pMDI 200/6, 96.5% of exacerbations; Budesonide/formoterol pMDI 100/6, 94.1%; placebo 97.4%. Treatment comparisons were by means of rate ratios (RR) estimates, CIs and p-values derived from a Poisson regression adjusted for treatment, country and differential treatment exposure. Budesonide/formoterol pMDI 200/6 demonstrated a statistically significant reduction of 37% (p<0.001) and 25% (p=0.004) in the rate of exacerbations per subject-treatment year compared with placebo and formoterol, respectively. Budesonide/formoterol pMDI 100/6 reduced the exacerbation rate by 41% compared with placebo (p<0.001).

Budesonide/formoterol pMDI 200/6 significantly prolonged the time to first severe COPD exacerbation compared to placebo, reducing the instantaneous risk of experiencing a severe COPD exacerbation by 26% (p=0.009). The number needed to treat (NNT) to prevent one severe COPD exacerbation in a year for Budesonide/formoterol pMDI compared with formoterol was 5.4.

**Study 002**

In Study 002, efficacy was evaluated over 6 months using the co-primary efficacy variables of change from baseline in average pre-dose and 1-hour post-dose $FEV_1$ over the treatment period.

- Budesonide/formoterol pMDI 100/6: Post-dose $FEV_1$ increased significantly from baseline to the average of the treatment period (LS mean (95% CI) = 0.19 (0.17, 0.22)). Budesonide/formoterol pMDI 100/6 caused a significantly greater change from

baseline compared to budesonide (LS mean = 0.16; p<0.001). Predose $FEV_1$ increased significantly from baseline to the average of the treatment period, LS mean = 0.06 (0.03, 0.08). However, the change from baseline, compared to formoterol, for predose $FEV_1$ was not statistically significant, LS mean = 0.02 (-0.02, 0.05; p=0.335).

- Budesonide/formoterol pMDI 200/6 significantly improved pre-dose $FEV_1$ compared with formoterol by 0.04 L (p=0.026) and compared with placebo and budesonide by 0.08 L (p<0.001) for both comparators.

- Budesonide/formoterol pMDI 200/6 significantly improved 1-hour post-dose $FEV_1$ compared with formoterol by 0.04 L (p=0.039) and compared with placebo and budesonide by 0.17 L (p<0.001) for both comparators.

Study 002 was not powered for showing effect on severe COPD exacerbations.

Serial $FEV_1$ measures over 12 hours were obtained in subsets of patients (n=618). The median time to onset of bronchodilation (>15% improvement in $FEV_1$) was seen within 5 minutes at the end of treatment in patients receiving budesonide/formoterol pMDI 200/6 (N=101). Maximal improvement in $FEV_1$ occurred at approximately 2 hours post-dose, and post-dose bronchodilator effect was generally maintained over 12 hours.

## 5.2 PHARMACOKINETIC PROPERTIES

The fixed-dose combination of budesonide and formoterol, and the corresponding monoproducts have been shown to be bioequivalent with regard to systemic exposure of budesonide and formoterol, respectively.

There was no evidence of pharmacokinetic interactions between budesonide and formoterol.

Pharmacokinetic parameters for the respective substances were comparable after the administration of budesonide and formoterol as monoproducts or as the fixed-dose combination.

### Absorption

After inhalation of budesonide via powder for inhalation device, the mean lung deposition ranged from 26 to 34% of the metered dose. The systemic bioavailability of budesonide inhaled via powder for inhalation device is approximately 40% of the metered dose.

In studies, the mean lung deposition of formoterol after inhalation via Spiromax ranged from 21-37% of the metered dose. The total systemic bioavailability for the higher lung deposition is approximately 46%.

### Distribution

Plasma protein binding of budesonide is approximately 90% with a volume of distribution of approximately 3 L/kg.

Plasma protein binding of formoterol is approximately 50% with a volume of distribution of approximately 4 L/kg.

### Metabolism

Budesonide undergoes an extensive degree (approx. 90%) of biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity.

Formoterol is metabolised by conjugation to inactive glucuronides. Active O-demethylated and deformylated metabolites are formed, however plasma levels of these are low.

**Excretion**
Elimination of budesonide is via metabolism mainly catalysed by the enzyme CYP3A4. The metabolites are excreted in urine as such or in conjugated form with only negligible amounts of unchanged budesonide being detected in the urine. Budesonide has a high systemic clearance (approx. 1.2 L/min) and the plasma elimination half life after i.v. dosing averages 4 hours.

Elimination of formoterol is via metabolism in the liver followed by renal excretion. After inhalation 6-10% of the metered dose is excreted unmetabolised in the urine. Formoterol has a terminal elimination half-life of approximately 17 hours.

**Special patient populations – elderly, hepatic and/or renal impairment**
The pharmacokinetics of budesonide or formoterol in elderly and patients with renal failure is unknown. The systemic availability of budesonide and formoterol may be increased in patients with liver disease.

**DuoResp Spiromax pharmacokinetic profile**

In pharmacokinetic studies with and without a charcoal blockage, DuoResp Spiromax was evaluated by comparing it against the innovator fixed-dose combination inhalation product containing the same active substances. Budesonide and formoterol have been shown to be equivalent in both pulmonary and systemic deposition for the 200/6 and 400/12 doses.

## 5.3 PRECLINICAL SAFETY DATA

**Genotoxicity**
Individually, budesonide and formoterol were not genotoxic in a series of assays for gene mutations (except for a slight increase in reverse mutation frequency in *Salmonella typhimurium* at high concentrations of formoterol fumarate), chromosomal damage and DNA repair. The combination of budesonide and formoterol has not been tested in genotoxicity assays.

**Carcinogenicity**
The carcinogenic potential of the budesonide/formoterol combination has not been investigated in animal studies.

In formoterol carcinogenicity studies performed by AstraZeneca, there was a dose dependent increase in the incidence of uterine leiomyomas in mice dosed orally at 0.1, 0.5 and 2.5 mg/kg/day for two years, and a mesovarian leiomyoma was observed in a female rat dosed by inhalation at 0.13 mg/kg/day for two years. The effects observed are expected findings with high dose exposure to $ß_2$-agonists.

Formoterol carcinogenicity studies performed by other companies used systemic exposure levels 800 to 4800-fold higher than those expected upon clinical use of formoterol (based on an 18 µg daily dose).

Some carcinogenicity activity was observed in rats and mice. However, in view of the dose levels at which these effects were observed and the fact that formoterol is not mutagenic

(except for very weak activity at high concentrations in one test system), it is concluded that the cancer risk in patients treated with formoterol fumarate is no greater than for other beta-adrenoceptor agonists.

The carcinogenic potential of budesonide has been evaluated in the mouse and rat at oral doses up to 200 and 50 µg/kg/day, respectively. In male rats dosed with 10, 25 and 50 µg budesonide/kg/day, those receiving 25 and 50 µg/kg/day showed an increased incidence of primary hepatocellular tumours. In a repeat study this effect was observed in a number of steroid groups (budesonide, prednisolone, triamcinolone acetonide) thus indicating a class effect of corticosteroids.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 LIST OF EXCIPIENTS

Lactose monohydrate.

## 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 below 25°C. Replace cap firmly after use.

Use the product within 6 months of removing from foil wrapping.

## 6.5 NATURE AND CONTENTS OF CONTAINER

DuoResp Spiromax 200/6 is registered* as a 120 dose inhaler in packs of 1, 2 or 3.

DuoResp Spiromax 400/12 is registered* as a 60 dose inhaler in packs of 1, 2 or 3.

*Not all pack sizes are commercially available.

## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

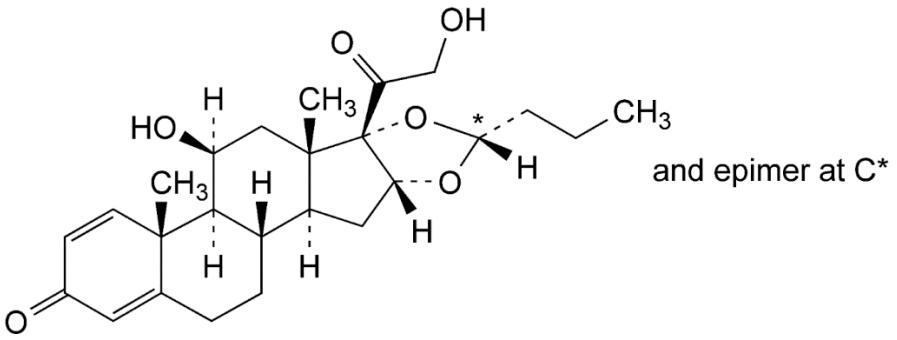
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

## 6.7 PHYSICOCHEMICAL PROPERTIES

Budesonide is a white to off white crystalline powder. It is freely soluble in methylene chloride, sparingly soluble in ethanol and practically insoluble in water.

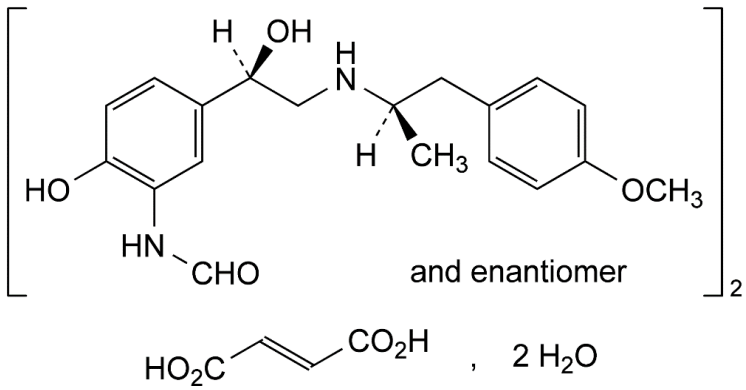
Formoterol (eformoterol) fumarate dihydrate is a white or almost white or slightly yellow powder. It is slightly soluble in water, soluble in methanol, slightly soluble in 2-propanol and practically insoluble in acetonitrile.

**Chemical structure: Budesonide**
Budesonide is a non halogenated glucocorticoid structurally related to 16α hydroxyprednisolone. The chemical name is 16α, 17α - 22 R, S-propylmethylenedioxypregna-1,4-diene-ß, 21-diol-3, 20-dione.




**CAS number**
51333-22-3

**Chemical structure: Formoterol (eformoterol) fumarate dihydrate**
(R*R*)-(±)-N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4 -methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide, (E)-2-butendioate(2:1), dihydrate. The chemical structure of formoterol (eformoterol) fumarate dihydrate is:




**CAS number**
183814-30-4

# 7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4).

# 8 SPONSOR

Teva Pharma Australia Pty Ltd
Level 1, 37 Epping Road

Macquarie Park NSW 2113
Telephone: 1800 288 382

# 9 DATE OF FIRST APPROVAL

19 December 2016

# 10 DATE OF REVISION

7 April 2021

**SUMMARY TABLE OF CHANGES**

| Section Changed | Summary of new information |
|---|---|
| **1** | Editorial correction to active ingredient spelling |
| **2** | Editorial update to correct grammar |
| **4.5** | Modified pharmacokinetic interactions text |
| **4.8** | New ADR included in Table 2 |
| **8** | Address details updated |