AUSTRALIAN PRODUCT INFORMATION

RILAST TURBUHALER®
(budesonide/formoterol fumarate dihydrate)
powder for inhalation

1 NAME OF THE MEDICINE

Budesonide

Formoterol fumarate dihydrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Rilast Turbuhaler is available in a multidose inspiratory flow driven, metered dose dry powder inhaler (Turbuhaler).

The following strengths are registered:

- Rilast Turbuhaler 100/6: Each delivered dose (the dose that leaves the mouthpiece) contains as active constituents: budesonide 80 µg/inhalation and formoterol 4.5 µg/inhalation.
- Rilast Turbuhaler 200/6: Each delivered dose (the dose that leaves the mouthpiece) contains as active constituents: budesonide 160 µg/inhalation and formoterol 4.5 µg/inhalation.
- Rilast Turbuhaler 400/12: Each delivered dose (the dose that leaves the mouthpiece) contains as active constituents: budesonide 320 µg/inhalation and formoterol 9 µg/inhalation.

To avoid confusion budesonide/formoterol Turbuhaler presentations have historically been labelled as the metered dose of the corresponding initially registered budesonide Turbuhaler and formoterol Turbuhaler (M2 version) monoproducts. The following table provides the corresponding Rilast Turbuhaler dose delivered to the patient.

Table 1

Rilast Turbuhaler	Metered dose* (µg)		Corresponding dose delivered to patient (µg)**	
	Budesonide Turbuhaler	Formoterol^ Turbuhaler	Budesonide	Formoterol^
100/6	100	6	80	4.5
200/6	200	6	160	4.5
400/12	400	12	320	9

* not possible to measure metered dose for Rilast Turbuhaler – metered doses of the corresponding monoproduct Turbuhalers; ** doses referred to in budesonide/formoterol fixed dose combination publications; ^ M2 version

Excipient(s) with known effect: Lactose monohydrate

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

3 PHARMACEUTICAL FORM

Powder for inhalation

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Asthma

Rilast Turbuhaler is indicated in adults and adolescents (12 years and older), for the treatment of asthma, to achieve overall asthma control, including the relief of symptoms and the reduction of the risk of exacerbations (see Section 4.2 Dose and method of administration).

Chronic obstructive pulmonary disease (COPD)

Rilast Turbuhaler is indicated for the symptomatic treatment of moderate to severe COPD ($FEV_1 \leq 50\%$ predicted normal) in adults with frequent symptoms despite long-acting bronchodilator use, and/or a history of recurrent exacerbations. Rilast Turbuhaler is not indicated for the initiation of bronchodilator therapy in COPD.

4.2 DOSE AND METHOD OF ADMINISTRATION

Asthma

Rilast Turbuhaler 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)

Rilast Turbuhaler 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 Rilast Turbuhaler 200/6 available for relief of symptoms.

Preventative use of Rilast Turbuhaler 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 and adolescents (12 years and older)

Patients should take 1 inhalation of Rilast Turbuhaler 200/6 as needed in response to symptoms. If symptoms persist after a few minutes, 1 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 3-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 β_2 agonist (LABA) is required, patients take *anti-inflammatory reliever therapy* and in addition take a daily maintenance dose of Rilast Turbuhaler. . The as-needed inhalations provide both rapid relief of symptoms and improved overall asthma control. Patients should be advised to have Rilast Turbuhaler available for relief of symptoms at all times.

Preventative use of Rilast Turbuhaler 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 and adolescents (12 years and older)

Patients should take 1 inhalation of Rilast Turbuhaler 100/6 or 200/6 as needed in response to symptoms to control asthma. If symptoms persist after a few minutes, 1 additional inhalation should be taken. No more than 6 inhalations should be taken on any single occasion.

Patients also take the recommended maintenance dose of Rilast Turbuhaler 100/6 or Rilast Turbuhaler 200/6, which is 2 inhalations per day, given as either 1 inhalation in the morning and evening or as 2 inhalations in either the morning or evening. For some patients, a maintenance dose of Rilast Turbuhaler 200/6 2 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 3-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 is required, Rilast Turbuhaler 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 Rilast Turbuhaler 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 and adolescents (12 years and older)

Rilast Turbuhaler 100/6

1or 2 inhalations of Rilast Turbuhaler 100/6 twice daily. The maximum recommended daily maintenance dose is 4 inhalations (2 inhalations twice daily corresponding to 400 µg budesonide/24 µg formoterol).

Rilast Turbuhaler 200/6

1or 2 inhalations of Rilast Turbuhaler 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):

Rilast Turbuhaler 400/12

2 inhalations of Rilast Turbuhaler 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.

COPD

Adults

Rilast Turbuhaler 200/6

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

Rilast Turbuhaler 400/12

1 inhalation of Rilast Turbuhaler 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 Rilast Turbuhaler 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 Rilast Turbuhaler as a maintenance therapy, they should be instructed that Rilast Turbuhaler must be used even when asymptomatic for optimal benefit.

Special patient populations

Renal impairment

There are no data available for use of Rilast Turbuhaler in patients with renal impairment.

Hepatic impairment

There are no data available for use of Rilast Turbuhaler 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.

Use in the elderly

There are no special dosing requirements for elderly patients.

Use in paediatric patients

Rilast Turbuhaler is not recommended for children below 12 years of age.

Instruction for correct use of Rilast Turbuhaler

Turbuhaler is inspiratory flow-driven which means that, when the patient inhales through the mouthpiece, the substance will follow the inspired air into the airways.

NOTE: It is important to instruct the patient to:

- Check the expiry date
- Carefully read the instructions for use in the patient information leaflet that are provided with each pack of Rilast Turbuhaler
- Breathe in forcefully and deeply through the mouthpiece to ensure that an optimal dose is delivered to the lungs
- Never to breathe out through the mouthpiece
- Replace the cover of Rilast Turbuhaler after use
- Rinse their mouth out with water after inhaling the maintenance dose to minimise the risk of oropharyngeal thrush.

The patient may not taste or feel any medication when using Rilast Turbuhaler due to the small amount of drug delivered.

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 patient's asthma improves or deteriorates.

Patients should be advised to have their reliever available at all times, either Rilast Turbuhaler (for asthma patients on *anti-inflammatory reliever therapy* and *anti-inflammatory reliever therapy plus maintenance therapy*) or a separate short-acting bronchodilator (for other asthma patients using Rilast Turbuhaler 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 (eg 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 Rilast Turbuhaler.

It is recommended that the maintenance dose be 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

Rilast Turbuhaler should not be used to initiate treatment with inhaled steroids in patients being transferred from oral steroids. Care should be taken when commencing Rilast Turbuhaler 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 and glaucoma, and retardation of growth rate in children and adolescents. These effects are much less likely to occur with ICS treatments than with oral corticosteroids. 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-dependent 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 Rilast Turbuhaler 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 corticosteroid treatment should be considered during periods of stress, a severe asthma attack or elective surgery.

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 Turbuhaler 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 1cm) 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 lowest dose at which effective control of symptoms is maintained (see Section 4.2 Dose and method of administration).

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.

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 (eg inadequately controlled hyperthyroidism), formoterol should be used with caution.

Cardiovascular disorders

β_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 β_2-adrenoceptor agonists.

Patients with pre-existing cardiovascular conditions may be at greater risk of developing adverse cardiovascular effects following administration of β_2-adrenoreceptor agonists. Caution is advised when formoterol is administered to patients with severe cardiovascular disorders such as ischaemic heart disease, tachyarrhythmias or severe heart failure.

Hypokalaemia

High doses of β_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 β_2-stimulants extra blood glucose controls are initially recommended when diabetic patients are commenced on formoterol.

Pneumonia

Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbations frequently overlap. Pneumonia has been reported following the administration of inhaled corticosteroids. See Section 4.8 Adverse effects (Undesirable effects).

Lactose

Rilast Turbuhaler contains lactose (<1 mg/inhalation) which may contain milk protein residue. This amount does not normally cause problems in lactose intolerant people.

Use in hepatic impairment

The effect of decreased liver function on the pharmacokinetics of formoterol and budesonide are 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 are not known.

Use in the elderly

See Section 5.1 Pharmacodynamic properties - *Clinical trials*.

Paediatric use

Rilast Turbuhaler is not recommended for children below 12 years of age.

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 CYP3A4 inhibitors may therefore increase systemic exposure to budesonide. This is of limited clinical importance for short-term (1-2 weeks) treatment with potent CYP3A4 inhibitors but should be taken into consideration during long-term treatment.

If a patient requires long-term concomitant treatment with Rilast and a potent CYP3A4 inhibitor, the benefit should be weighed against the increased risk of systemic corticosteroid side effects, patients should be monitored for corticosteroid side effects and/or a reduction of the ICS dose could be considered.

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, especially those that are non-selective, may partially or totally inhibit the effect of β_2-agonists. 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 should not be given concomitantly with formoterol, since the 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 β_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*).

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).

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 – Category B3

For Rilast Turbuhaler or the concomitant treatment with budesonide and formoterol, no clinical data on exposed pregnancies are available. Animal studies with respect to the reproductive toxicity of the combination have not been performed.

Rilast Turbuhaler should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Only after special consideration should Rilast Turbuhaler 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, Rilast Turbuhaler 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 corticosteroids 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 Rilast Turbuhaler in nursing mothers. Administration of Rilast Turbuhaler 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 Rilast Turbuhaler on the individual is established. Rilast Turbuhaler does not generally affect the ability to drive or use machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Since Rilast Turbuhaler contains both budesonide and formoterol, the same adverse effects as reported for these substances may be expected. 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 β_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 Rilast Turbuhaler therapy. 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 Turbuhaler and Rapihaler combination products, are given in Table 2.

Table 2 Tabulation of adverse reactions

Frequency	System Organ Class	Event
Common (≥1% - <10%)	Cardiac disorders	Palpitations
	Infections & 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 (≥0.1% - <1%)	Cardiac disorders	Tachycardia
	Eye disorders	Vision blurred
	Gastrointestinal disorders	Nausea, diarrhoea
	Metabolism & nutrition disorders	Weight gain
	Musculoskeletal & connective tissue disorders	Muscle cramps
	Nervous system disorders	Dizziness, bad taste, thirst, tiredness
	Psychiatric disorders	Agitation, restlessness, nervousness, sleep disturbances
Rare (≥0.01% - <0.1%)	Immune system disorders	Immediate & delayed hypersensitivity reactions including dermatitis, exanthema, urticaria, pruritis, angioedema & 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 (<0.01%)	Cardiac disorders	Angina pectoris
	Endocrine disorders	Signs or symptoms of systemic glucocorticosteroid effects, eg hypofunction of the adrenal gland
	Metabolism & nutrition disorders	Hyperglycaemia
	Psychiatric disorders	Depression, behavioural disturbances
	Vascular disorders	Variations in blood pressure

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 (as Turbuhaler or Rapihaler 200/6) and comparative placebo arms.

Table 3 Pneumonia incidence (%) – budesonide/formoterol (Turbuhaler and Rapihaler) pivotal Phase III COPD studies (6 months or 12 months duration)

Budesonide/formoterol Turbuhaler				**Budesonide/formoterol Rapihaler**			
Study 629 [a]		**Study 670 [a]**		**Study 001 [a]**		**Study 002 [a]**	
Turbuhaler 200/6	**Placebo**	**Turbuhaler 200/6**	**Placebo**	**Rapihaler 200/6**	**Placebo**	**Rapihaler 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 budesonide/formoterol 200/6 and placebo arms are presented in this table, not all treatment arms within the clinical studies

[b] Includes budesonide/formoterol 200/6 arm (n=277) + the free combination budesonide 200 + formoterol 6 arm (n=287)

n – number of patients in the safety analysis

In these placebo-controlled studies, the incidence of pneumonia was low.

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 Rilast Turbuhaler 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 β_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 corticosteroid effects, such as hypercorticism and adrenal suppression, may appear.

Withdrawing Rilast Turbuhaler 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 Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Rilast Turbuhaler contains budesonide and formoterol, which have different modes of action and show additive effects in terms of reduction of asthma and 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 non-halogenated glucocorticoid structurally related to 16α hydroxyprednisolone 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 β_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

Rilast Turbuhaler 100/6 and 200/6 refers to the metered dose of the corresponding monoproducts (budesonide/formoterol) ie 100 μg of budesonide and 6 μg formoterol and 200 μg of budesonide and 6 μg formoterol respectively. Similarly, Rilast Turbuhaler 400/12 refers to the metered dose of the corresponding monoproducts ie 400 μg of budesonide and 12 μg formoterol. See also Table 1 in Section 2 Qualitative and quantitative composition.

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 Turbuhaler *anti-inflammatory reliever therapy* for 12 months. Patients were required to be uncontrolled on only short-acting β_2 agonist (SABA) as needed or controlled on low dose ICS or leukotriene receptor agonist plus SABA as needed.

Both studies compared *anti-inflammatory reliever therapy* (budesonide/formoterol Turbuhaler 200/6 used as needed in response to symptoms) to budesonide Turbuhaler 200 μg (1 inhalation twice daily) given with as needed SABA. SYGMA 1 also compared *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, *anti-inflammatory reliever therapy* was comparable to a maintenance dose of budesonide Turbuhaler 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 *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, *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 *anti-inflammatory reliever therapy* compared to a maintenance dose of budesonide Turbuhaler 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 *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 *anti-inflammatory reliever therapy* compared to a maintenance dose of budesonide Turbuhaler 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 FEV_1) were statistically significantly larger for patients on *anti-inflammatory reliever therapy* compared to patients on as needed SABA alone. Statistically significantly smaller increases were observed for *anti-inflammatory reliever therapy* compared to a maintenance dose of budesonide Turbuhaler 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 *anti-inflammatory reliever therapy* is a more effective treatment than SABA as needed in patients with mild asthma. In addition, these studies suggest that *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 Turbuhaler 200/6 as needed	1277	77	0.07
	Terbutaline Turbuhaler 0.4 mg as needed	1277	188	0.20[c]
	Budesonide Turbuhaler 200 µg twice daily + terbutaline Turbuhaler 0.4 mg as needed	1282	89	0.09[d]
SYGMA 2	Budesonide/formoterol Turbuhaler 200/6 as needed	2084	217	0.11
	Budesonide Turbuhaler 200 µg twice daily + terbutaline Turbuhaler 0.4 mg as needed	2083	221	0.12[e]

[a] Budesonide Turbuhaler 200 µg (metered dose); Terbutaline Turbuhaler 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 Turbuhaler 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 Turbuhaler as needed vs budesonide 200 µg twice daily + terbutaline 0.4 mg as needed in SYGMA 1.

[e] Budesonide/formoterol Turbuhaler 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 *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 *anti-inflammatory reliever therapy* and a maintenance dose of budesonide given with SABA as needed.

Anti-inflammatory reliever plus maintenance therapy

The safety and efficacy of budesonide/formoterol Turbuhaler in the *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 Turbuhaler in patients with asthma. A total of 14219 patients (1134 elderly, 11144 adults, 1595 adolescents and 345 children) were randomised into the studies, of which 5514 were treated with *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 COPD 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 inhaled corticosteroids (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 *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 MART[a] vs budesonide/formoterol maintenance + formoterol prn	0.73	0.59, 0.90
2. Budesonide/formoterol MART vs budesonide/formoterol maintenance + terbutaline prn	0.55	0.45, 0.68
3. Budesonide/formoterol maintenance + formoterol prn vs budesonide/formoterol maintenance + terbutaline prn	0.76	0.63, 0.92
COMPASS 735		
1. Budesonide/formoterol MART vs budesonide/formoterol maintenance + terbutaline prn	0.74	0.56, 0.96
2. Budesonide/formoterol MART vs fluticasone/salmeterol + terbutaline prn	0.67	0.52, 0.87
3. Budesonide/formoterol maintenance + terbutaline prn vs fluticasone/salmeterol + terbutaline prn	0.91	0.72, 1.16
STAY 673		
1. Budesonide/formoterol MART vs budesonide/formoterol Maintenance + terbutaline prn	0.55	0.44, 0.67
2. Budesonide/formoterol MART vs budesonide + terbutaline prn	0.53	0.43, 0.65
3. Budesonide/formoterol maintenance + terbutaline prn vs budesonide + terbutaline prn	0.97	0.82, 1.16
STEP 668		
Budesonide/formoterol MART vs budesonide + terbutaline prn	0.61	0.50, 0.74
COSMOS 691		
Budesonide/formoterol MART vs fluticasone/salmeterol + salbutamol prn	0.75	0.61, 0.93
Morning peak flow (L/min)		
STEAM 667		
Budesonide/formoterol MART vs budesonide + terbutaline prn	Mean diff 25 L/min	19, 31

[a] *Anti-inflammatory reliever plus maintenance therapy*, previously known as *maintenance & reliever therapy (MART)*.

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 MART[a]	194	143/1107 (13%)
2. Budesonide/formoterol maintenance + formoterol prn	296	195/1137 (17%)
3. Budesonide/formoterol maintenance + terbutaline prn	377	245/1138 (22%)
COMPASS 735 (6 months)		
1. Budesonide/formoterol MART	125	94/1103 (9%)
2. Budesonide/formoterol maintenance + terbutaline prn	173	126/1099 (11%)
3. Fluticasone/salmeterol + terbutaline prn	208	138/1119 (12%)
STAY 673 (12 months)		
1. Budesonide/formoterol MART	303	148/922 (16%)
2. Budesonide/formoterol maintenance+ terbutaline prn	553	248/906 (27%)
3. Budesonide + terbutaline prn	564	256/925 (28%)

Treatment	No. of exacerbations	No. of patients with exacerbations / total patients (%)
STEP 668 (12 months)		
1. Budesonide/formoterol MART	331	170/947 (18%)
2. Budesonide + terbutaline prn	546	259/943 (27%)
STEAM 667 (6 months)		
1. Budesonide/formoterol MART	43	27/354 (8%)
2. Budesonide + terbutaline prn	94	54/342 (16%)
COSMOS 691 (12 months)		
1. Budesonide/formoterol MART	255	159/1064 (15%)
2. Fluticasone/salmeterol + salbutamol prn	329	204/1071 (19%)

[a] *Anti-inflammatory reliever plus maintenance therapy*, previously known as *maintenance & reliever therapy (MART)*.

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 Turbuhaler 200/6, 1 inhalation twice daily plus additional inhalations as needed

2 Budesonide/formoterol maintenance - budesonide/formoterol Turbuhaler 200/6, 1 inhalation twice daily with formoterol Turbuhaler as needed

3 Budesonide/formoterol maintenance - budesonide/formoterol Turbuhaler 200/6, 1 inhalation twice daily with terbutaline Turbuhaler 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 maintenance plus formoterol and budesonide/formoterol maintenance 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 maintenance plus formoterol and budesonide/formoterol maintenance 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 variables for Study 734

Variable†	Bud/form MART[a]	Bud/form maint + form prn	Bud/form maint + terb prn	Comparison (mean difference & 95% confidence interval)	
				Bud/form MART v bud/form maint + form prn	Bud/form MART v bud/form maint + 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$^{\Delta}$ (% 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	-0.64	-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. Bud/form – budesonide/formoterol; form – formoterol; maint – maintenance; terb – terbutaline; prn – as needed use; MART – maintenance and reliever therapy

[a] *anti-inflammatory reliever plus maintenance therapy*, previously known as *maintenance & reliever therapy* (MART)

The study specifically demonstrates that both the budesonide and the formoterol components of budesonide/formoterol Turbuhaler contribute to improved asthma control achieved through the as-needed dosing of budesonide/formoterol Turbuhaler 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 Turbuhaler 200/6, 1 inhalation twice daily plus additional inhalation as needed

2 Fluticasone/salmeterol Inhaler 125/25, 2 inhalations twice daily with terbutaline Turbuhaler as needed

3 Budesonide/formoterol maintenance - budesonide/formoterol Turbuhaler 400/12, 1 inhalation twice daily with terbutaline Turbuhaler 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 Turbuhaler 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 maintenance 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 maintenance 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 Turbuhaler 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 variables for Study 673

Variable†	Bud/form MART[a]	Bud/form maint + terb prn	Bud + terb prn	Comparison (mean difference & 95% confidence interval)	
				Bud/form MART v bud/form maint + terb prn	Bud/form MART 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$^{\Delta}$ (% 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; $^{\Delta}$ day and night with no symptoms and a night with no awakenings. Bud/form – budesonide/formoterol; Bud - budesonide; maint – maintenance; terb – terbutaline; prn – as needed use; MART – maintenance and reliever therapy

[a] *anti-inflammatory reliever plus maintenance therapy*, previously known as *maintenance & reliever therapy* (MART)

Table 9 Secondary efficacy variables for Study 668

Variable†	Bud/form MART[a]	Bud + terb prn	Comparison (mean difference & 95% confidence interval)
			Bud/form MART 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)

Variable†	Bud/form MART[a]	Bud + terb prn	Comparison (mean difference & 95% confidence interval)
			Bud/form MART v Bud + terb prn
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. Bud/form – budesonide/formoterol; Bud - budesonide; terb – terbutaline; prn – as needed use; MART – maintenance and reliever therapy

[a] *anti-inflammatory reliever plus maintenance therapy*, previously known as *maintenance & reliever therapy* (MART)

Table 10 Secondary efficacy variables for Study 667

Variable†	Bud/form MART[a]	Bud + terb prn	Comparison (mean difference & 95% confidence interval)
			Bud/form MART 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. Bud/form – budesonide/formoterol; Bud - budesonide; terb – terbutaline; prn – as needed use; MART – maintenance and reliever therapy

[a] *anti-inflammatory reliever plus maintenance therapy*, previously known as *maintenance & reliever therapy* (MART)

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 MART[a]	fluticasone/salmeterol + salbutamol
Fixed dose period (4 weeks)	budesonide/formoterol Turbuhaler 200/6, 2 inhalations twice daily with additional inhalations as needed	fluticasone/salmeterol 250/50, 1 inhalation twice daily + salbutamol as needed

	Budesonide/formoterol MART[a]	fluticasone/salmeterol + salbutamol
Dose adjustment period (11 months)	budesonide/formoterol Turbuhaler 200/6 either • 2 inhalations twice daily + as needed, or • 1 inhalation twice daily + as needed, or • 2 inhalations once daily + as needed	Either • fluticasone/salmeterol 500/50, 1 inhalation twice daily + salbutamol as needed • fluticasone/salmeterol 250/50, 1 inhalation twice daily + salbutamol as needed, or • fluticasone/salmeterol 100/50, 1 inhalation twice daily + salbutamol as needed

[a] *anti-inflammatory reliever plus maintenance therapy*, previously known as *maintenance & reliever therapy* (MART)

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 only therapy with a decrease in asthma-related adverse events.

Exercise-induced and allergen-induced bronchoconstriction

The use of budesonide/formoterol Turbuhaler 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 Turbuhaler 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 Turbuhaler 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 Turbuhaler 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 FEV_1) methacholine (MCh) during each treatment period. This study showed that when administered 30 minutes after a low-dose allergen challenge, budesonide/formoterol Turbuhaler 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 Turbuhaler 200/6 than with formoterol.

Maintenance therapy

The efficacy and safety of budesonide/formoterol Turbuhaler 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 Turbuhaler.

Budesonide/formoterol Turbuhaler 100/6 and 200/6

In one study the maximum recommended maintenance dose of budesonide/formoterol Turbuhaler 200/6 (2 inhalations twice daily) was compared to corresponding doses of the free combination (budesonide Turbuhaler 200 µg + formoterol Turbuhaler 6 µg (M2 version), two inhalations twice daily) and budesonide Turbuhaler 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 Turbuhaler 200/6, budesonide 200 µg alone and the free combination of the monoproducts

Variable	Bud/form	Bud	Free comb	Comparison p values	
				Bud/form v bud	Bud/form 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	11.09	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. Bud/form – budesonide/formoterol; Bud - budesonide; comb - combination

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

In a study in adults with milder asthma (mean FEV_1 81.7% predicted normal and reversibility 22.2%) budesonide/formoterol Turbuhaler 100/6 (1 inhalation twice daily) was compared with budesonide Turbuhaler 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 Turbuhaler 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 Turbuhaler 100/6 than with a doubled dose of budesonide.

Budesonide/formoterol Turbuhaler 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 Turbuhaler 400/12 (2 inhalations twice daily) was compared to corresponding doses of the free combination (formoterol Turbuhaler 12 µg (M2 version) + budesonide Turbuhaler 400 µg, two inhalations twice daily) and budesonide Turbuhaler 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 Turbuhaler 400/12, budesonide 400 µg alone and the free combination of the monoproducts

Variable†	Bud/form	Bud	Free comb	Comparison p values	
				Bud/form v bud	Bud/form v free comb
mPEF§ (L/min)	37.4	4.5	36.2	<0.001	ns
ePEF (L/min)	30.7	-0.1	31.3	<0.001	ns
FEV_1 ‡ (L)	0.303	0.143	0.280	<0.001	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	<0.001	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
Symptom free days$^{\Delta}$ (% patients)	31.2	15.6	32.2	<0.001	ns
Rescue medication use (inhalations/24 hours)	-1.08	-0.50	-1.20	<0.001	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; Δ day and night with no symptoms and a night with no awakenings. Bud/form – budesonide/formoterol; Bud - budesonide; comb – combination

When administered twice daily, budesonide/formoterol Turbuhaler 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 as a fixed dose combination in the treatment of patients with moderate to severe COPD (pre-bronchodilator $FEV_1 \leq 50\%$ 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 Turbuhaler (Studies 629 and 670), and one 12-month and one 6-month study were performed with the pressurised metered dose inhaler (pMDI) budesonide/formoterol Rapihaler (Studies 001 and 002, respectively).

- Studies 629 and 670 - In both studies, budesonide/formoterol Turbuhaler 200/6 was compared with placebo and the corresponding monoproducts (budesonide Turbuhaler 200 µg and formoterol Turbuhaler 6 µg (M2 version)), 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 Turbuhaler. Patients in both studies had a mean age of 64 years and FEV_1 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 Rapihaler.

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 Rapihaler 200/6, fixed combination of 200 µg budesonide and 6 µg formoterol per actuation, administered as 2 actuations twice daily;

2 Budesonide/formoterol Rapihaler 100/6, fixed combination of 100 µg budesonide and 6 µg formoterol per actuation, administered as 2 actuations twice daily;

3 Formoterol Turbuhaler (M2 version), 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 Turbuhaler 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 Rapihaler 200/6. The study populations had a mean age of 63 years and mean FEV_1 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 Turbuhaler significantly improved mean FEV_1 compared with placebo and budesonide by 15% ($p<0.001$) and 9% ($p<0.001$), respectively.
- Budesonide/formoterol Turbuhaler 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 Turbuhaler 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 Turbuhaler 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 Turbuhaler 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 Turbuhaler 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 Rapihaler 100/6 produced a significantly greater change in post-dose FEV_1 compared to placebo (LS mean = 0.16 L; $p<0.001$); however, the change in pre-dose FEV_1 was not significantly different to formoterol 6 µg (LS mean = 0.02 L; p=0.161).
- Budesonide/formoterol Rapihaler 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 Rapihaler 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 Rapihaler 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 Rapihaler 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 Rapihaler 200/6, 30.8%; Budesonide/formoterol Rapihaler 100/6, 32.6%; placebo 37.2%. The majority of exacerbations were treated with oral glucocorticosteroids. Budesonide/formoterol Rapihaler 200/6, 96.5% of exacerbations; Budesonide/formoterol Rapihaler 100/6, 94.1%; placebo 97.4%. Treatment comparisons were by means of rate ratios estimates, CIs and p-values derived from a Poisson regression adjusted for treatment, country and differential treatment exposure. Budesonide/formoterol Rapihaler 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 Rapihaler 100/6 reduced the exacerbation rate by 41% compared with placebo ($p<0.001$).

Budesonide/formoterol Rapihaler 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 NNT to prevent one severe COPD exacerbation in a year for budesonide/formoterol Rapihaler 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 Rapihaler 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 Rapihaler 100/6 caused a significantly greater change from baseline compared to budesonide (LS mean = 0.16; $p<0.001$). Pre-dose 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 pre-dose FEV_1 was not statistically significant (LS mean = 0.02 (-0.02, 0.05; $p=0.335$)).
- Budesonide/formoterol Rapihaler 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 Rapihaler 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 Rapihaler 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

Budesonide/formoterol Turbuhaler and the corresponding monoproduct (budesonide Turbuhaler and formoterol Turbuhaler (M2 version) as per Table 1 in Section 2 Qualitative and quantitative composition) 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 (via Turbuhaler) or as the fixed dose combination budesonide/formoterol (via Turbuhaler).

Absorption

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

In studies the mean lung deposition of formoterol after inhalation via Turbuhaler 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 (approximately 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 of formoterol via a Turbuhaler 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 in patients with renal failure is unknown. The systemic availability of budesonide and formoterol may be increased in patients with liver disease.

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 β_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 (also see Section 2 Qualitative and quantitative composition).

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

Do not store above 30°C. Replace cap firmly after use.

6.5 NATURE AND CONTENTS OF CONTAINER

The following pack sizes are registered^ for Rilast Turbuhaler:

- 100/6: 120 inhalations
- 200/6: 120 inhalations
- 400/12: 60 inhalations of single or double Turbuhaler pack.

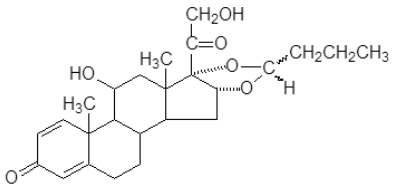
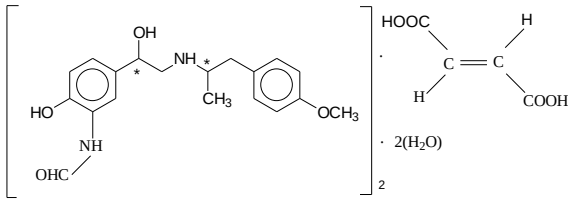
^not all pack sizes may be supplied in Australia.

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

Chemical structure

	Budesonide	**Formoterol fumarate dihydrate**
Chemical structure:		
Chemical name:	16α, 17α-22 R, S-propylmethylenedioxypregna-1, 4-diene-1β, 21-diol-3, 20-dione	(R*R*)-(±)-N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide, (E)-2-butendioate(2:1), dihydrate

CAS number

Budesonide	**Formoterol fumarate dihydrate**
51333-22-3	183814-30-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4)

8 SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
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MACQUARIE PARK NSW 2113

Telephone: 1800 805 342

9 DATE OF FIRST APPROVAL

22 December 2017

10 DATE OF REVISION

23 September 2024

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Addition of Cushing's syndrome and Cushingoid features

Rilast Turbuhaler, Rapihaler and Turbuhaler are trade marks of the AstraZeneca group of companies

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