

SYMBICORT RAPIHALER®

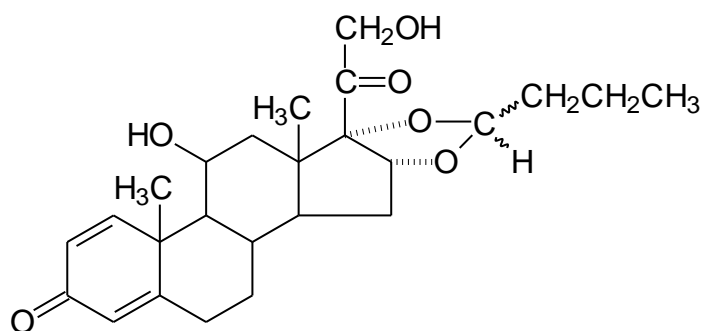
(budesonide/eformoterol fumarate dihydrate)

PRODUCT INFORMATION

NAME OF THE MEDICINE

Budesonide

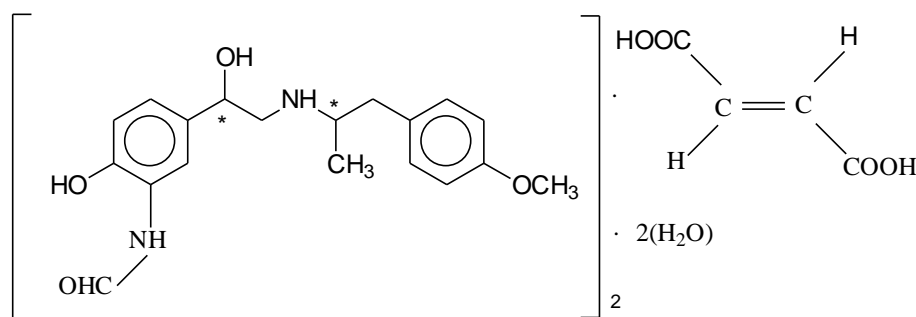
Budesonide is a non-halogenated glucocorticosteroid (GCS) structurally related to 16 α hydroxyprednisolone. The chemical name is 16 α , 17 α -22 R, S-propylmethylenedioxypregna-1, 4-diene-1 β , 21-diol-3, 20-dione. The chemical structure of budesonide is:



CAS number: 51333-22-3.

Eformoterol fumarate dihydrate

The chemical name is (R*R*)-(\pm)-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 eformoterol fumarate dihydrate is:



CAS number: 43229-80-7.

DESCRIPTION

Symbicort Rapihaler contains budesonide and eformoterol fumarate dihydrate (hereafter referred to as eformoterol) as the active ingredients. Symbicort Rapihaler also contains the inactive ingredients povidone (polyvinylpyrrolidone K25), macrogol (polyethylene glycol) 1000 and apaflurane (known as hydrofluroalkane (HFA)-227).

PHARMACOLOGY

Symbicort contains budesonide and eformoterol, which 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 eformoterol allow the combination to be used as regular maintenance and reliever therapy 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 hyper-reactive 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.

Eformoterol

Eformoterol is a potent selective β_2 -adrenergic agonist that produces relaxation of bronchial smooth muscle. Therefore it has a bronchodilating effect in patients with reversible airways obstruction and in patients with bronchospasm induced by direct (methacholine) and indirect (eg, exercise) stimuli. The bronchodilating effect is dose dependent with an onset of effect within 1 to 3 minutes after inhalation. The duration of effect is at least 12 hours after a single dose.

Pharmacokinetics

The budesonide and eformoterol bioavailability of Symbicort Rapihaler and Symbicort Turbuhaler® were similar after single doses containing 1280 μg budesonide and 36 μg eformoterol (8 inhalations) in healthy adult volunteers. The budesonide and eformoterol bioavailability from Symbicort Rapihaler was also comparable with that from similar doses of the component products, Pulmicort® (budesonide) Turbuhaler, Oxis® (eformoterol) Turbuhaler and a specially prepared budesonide HFA pressurised inhalation suspension.

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

Budesonide

Inhaled budesonide is rapidly absorbed and the maximum plasma concentration is reached within 30 minutes after inhalation.

Plasma protein binding is approximately 90% for budesonide and volume of distribution is 3 L/kg. Budesonide undergoes an extensive degree (approximately 90%) of biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6 β -hydroxy-budesonide and 16 α -hydroxy-prednisolone is less than 1% of that of budesonide.

Budesonide is eliminated via metabolism mainly catalysed by the enzyme CYP3A4. The metabolites of budesonide are excreted in urine as such or in conjugated form. Only negligible amounts of unchanged budesonide have been 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.

Eformoterol

Inhaled eformoterol is rapidly absorbed and the maximum plasma concentration is reached within 10 minutes after inhalation. Plasma protein binding is approximately 50% for eformoterol and volume of distribution is about 4 L/kg.

Eformoterol is inactivated via conjugation reactions (active-O-demethylated and deformedylated metabolites are formed, but they are seen mainly as inactivated conjugates).

The major part of a dose of eformoterol is eliminated by metabolism in the liver followed by renal excretion. After inhalation of eformoterol via a Turbuhaler, 8% to 13% of the delivered dose of eformoterol is excreted unmetabolised in the urine. Eformoterol has a high systemic clearance (approximately 1.4 L/min) and terminal elimination half-life averages 17 hours.

The pharmacokinetics of budesonide or eformoterol in children, elderly patients, and patients with renal failure is unknown. The systemic availability of budesonide and eformoterol may be increased in patients with liver disease.

CLINICAL TRIALS

Asthma

Therapeutic equivalence between Symbicort Rapihaler and Symbicort Turbuhaler was demonstrated in three clinical efficacy and safety studies in adults and adolescents with asthma. They included two randomised, double-blind, active controlled, parallel-group studies, Studies 681 (12 weeks duration) and 003 (6 weeks duration); and one randomised, open-label, parallel group, long-term (12 months) study, Study 715.

No clinical studies have been conducted to directly compare the efficacy and safety of Symbicort Rapihaler 100/3 with Symbicort Turbuhaler 200/6.

In Study 681, Symbicort Rapihaler 200/6 (2 inhalations twice daily) was compared with the corresponding dose of budesonide pressurised metered dose inhaler (pMDI) (200 µg; 2 inhalations twice daily), or Symbicort Turbuhaler (200/6; 2 inhalations twice daily) in adults and adolescents (≥12 years) with moderate to severe asthma [eg mean forced expiratory volume during the first second (FEV₁) ≥50% and ≤90% of predicted normal (PN) and FEV₁ reversibility ≥12%]. Symbicort Rapihaler was shown to significantly improve morning peak expiratory flow rate (primary efficacy variable), other lung function parameters, symptom scores and use of rescue medication compared to budesonide and was equivalent to Symbicort Turbuhaler (see Table 1).

Table 1 Study 681 - Estimated treatment means and treatment contrasts: effects of 12 weeks of treatment with twice daily Symbicort Rapihaler 200/6, budesonide pMDI 200 and Symbicort Turbuhaler 200/6

Variable [†]	Symbicort Rapihaler n=234	budesonide pMDI n=217	Symbicort Turbuhaler n=229	Mean difference (95% confidence limits)	
				Symbicort Rapihaler vs budesonide pMDI	Symbicort Rapihaler vs Symbicort Turbuhaler
mPEF [§] (L/min)	29.3	0.6	32.0	28.6 (20.9, 36.4)	-2.8 (-10.4, 4.9)
ePEF (L/min)	24.3	-0.6	25.1	24.9 (17.5, 32.4)	-0.8 (-8.2, 6.6)
FEV ₁ (L)	0.321	0.114	0.291	0.207 (0.135, 0.279)	0.030 (-0.042, 0.101)
Total asthma symptom score (0-6)	-0.70	-0.44	-0.84	-0.26 (-0.41, -0.11)	0.14 (-0.01, 0.29)
Nocturnal awakenings due to asthma (% nights)	-16.5	-9.7	-15.5	-6.7 (-10.6, -2.8)	-1.0 (-4.9, 2.9)
Symptom-free days ^Δ (% days)	28.0	19.1	34.2	8.9 (3.1, 14.8)	-6.2 (-12.0, -0.4)
Asthma control days* (% of days)	26.5	18.3	33.1	8.2 (2.4, 14.0)	-6.5 (-12.3, -0.8)
Rescue medication use (inhalations/24 hours)	-0.94	-0.35	-0.92	-0.59 (-0.81, -0.37)	-0.02 (-0.23, 0.20)

[†] 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; FEV₁ – forced expiratory volume during the first second; ^Δ day and night with no symptoms and a night with no awakenings; * day and night with no symptoms, no rescue medication use and a night with no awakenings.

Study 003 was a 6-week study with similar design to Study 681. In this study, Symbicort Rapihaler 50/3 (2 inhalations twice daily) was compared primarily (as regular therapy) with the corresponding dose of budesonide Turbuhaler 100 µg (1 inhalation twice daily), or and secondarily with Symbicort Turbuhaler 100/6 (1 inhalation twice daily) in adults and adolescents (≥12 years) with asthma (mean FEV₁ 74% PN and FEV₁ reversibility 24%). The primary efficacy variable was the change in morning peak expiratory flow (mPEF) from baseline (mean of the 10 last days of the run-in period) to the treatment period (mean of the 6-week treatment period). The primary objective was to demonstrate that Symbicort Rapihaler 50/3 was more efficacious than budesonide Turbuhaler 100 µg. The adjusted mean mPEF increased by 12.2 L/min with Symbicort Rapihaler 50/3, 4.15 L/min with budesonide Turbuhaler, and 13.1 L/min with Symbicort Turbuhaler 100/6. The results showed that the mean change from baseline in mPEF was greater with Symbicort Rapihaler 50/3 than with budesonide Turbuhaler, and that the mean

difference was statistically significant (mean difference of 8.07 L/min [95% CI: 3.26 to 12.9], $p=0.001$). The secondary objective was to demonstrate therapeutic equivalence of Symbicort Rapihaler 50/3 and Symbicort Turbuhaler 100/6. The results supported equivalence of the two Symbicort formulations as regular treatment in both the ITT and per-protocol analyses. There was no statistically significant difference between the two Symbicort formulations for any outcome variable in this study.

Study 715 investigated primarily the safety of Symbicort Rapihaler 200/6 (2 inhalations twice daily) during 12 months. The reference treatment was the corresponding dose of Symbicort Turbuhaler 200/6 and in a population consisting of adults and adolescents (≥ 12 years) with moderate to severe asthma (eg mean FEV_1 of $\geq 50\%$ of PN and FEV_1 reversibility $\geq 12\%$). The study was of an open-label design.

There was no statistically significant difference between Symbicort Rapihaler and Symbicort Turbuhaler regarding FEV_1 and FVC (forced vital capacity). The percentage of patients experiencing one or more severe asthma exacerbations did not differ between the two Symbicort groups: 11% in the Symbicort Rapihaler group and 13% in the Symbicort Turbuhaler group. The maximum number of severe exacerbations per patient was 6 in the Symbicort Rapihaler group and 4 in the Symbicort Turbuhaler group. There was no statistical significant difference in time to first severe asthma exacerbation between the two treatment groups.

COPD

The efficacy and safety of Symbicort 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 Symbicort Turbuhaler (studies 629 and 670), and one 12-month and one 6-month study were performed with the pressurised metered dose inhaler (pMDI) Symbicort Rapihaler (studies 001 and 002, respectively).

Studies 629 and 670

In both studies, Symbicort Turbuhaler 200/6 was compared with placebo and the corresponding mono-products (budesonide Turbuhaler 200 μg and eformoterol Turbuhaler 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 Symbicort 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 Symbicort 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. Symbicort Rapihaler 200/6, fixed combination of 200 µg budesonide and 6 µg eformoterol per actuation, administered as 2 actuations twice daily;
2. Symbicort Rapihaler 100/6, fixed combination of 100 µg budesonide and 6 µg eformoterol per actuation, administered as 2 actuations twice daily;
3. Eformoterol Turbuhaler, 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 eformoterol 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 Symbicort Rapihaler 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 FEV₁ 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).

- Symbicort Turbuhaler significantly improved mean FEV₁ compared with placebo and budesonide by 15% (p<0.001) and 9% (p<0.001) respectively.
- Symbicort Turbuhaler significantly reduced the number of severe exacerbations compared with placebo and eformoterol 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 Symbicort Turbuhaler compared with eformoterol 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).

- Symbicort Turbuhaler significantly improved mean FEV_1 compared with placebo, budesonide and eformoterol by 14% ($p < 0.001$), 11% ($p < 0.001$), and 5% ($p = 0.002$) respectively.
- Symbicort 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 eformoterol was reduced by 29% ($p = 0.006$), 23% ($p = 0.033$), and 30% ($p = 0.003$) respectively.

Symbicort Turbuhaler also significantly reduced the number of severe COPD exacerbations compared to placebo and eformoterol by 24% ($p = 0.029$) and 26% ($p = 0.015$) respectively. The NNT to prevent one COPD exacerbation in a year compared to eformoterol 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:

- Symbicort 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 eformoterol 6 µg (LS mean = 0.02 L; $p = 0.161$).
- Symbicort Rapihaler 200/6 significantly improved 1-hour pre-dose FEV_1 compared with eformoterol and placebo by 0.04 L ($p = 0.008$) and 0.09 L ($p < 0.001$) respectively.
- Symbicort Rapihaler 200/6 significantly improved post-dose FEV_1 over the treatment period compared with eformoterol 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 Symbicort 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):

Symbicort 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: Symbicort Rapihaler 200/6, 30.8%; Symbicort Rapihaler 100/6, 32.6%; placebo 37.2%. The majority of exacerbations were treated with oral glucocorticosteroids: Symbicort Rapihaler 200/6, 96.5% of exacerbations; Symbicort Rapihaler 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. Symbicort 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 eformoterol respectively. Symbicort Rapihaler 100/6 reduced the exacerbation rate by 41% compared with placebo ($p < 0.001$).

Symbicort 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 number needed to treat (NNT) to prevent one severe COPD exacerbation in a year for Symbicort Rapihaler compared with eformoterol 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 FEV₁ over the treatment period.

- Symbicort Rapihaler 100/6: Post-dose FEV₁ increased significantly from baseline to the average of the treatment period (LS mean [95%CI] = 0.19 [0.17, 0.22]). Symbicort Rapihaler 100/6 caused a significantly greater change from baseline compared to budesonide (LS mean = 0.16; $p < 0.001$). Pre-dose FEV₁ 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 eformoterol, for pre-dose FEV₁ was not statistically significant, LS mean = 0.02 [-0.02, 0.05; $p = 0.335$].
- Symbicort Rapihaler 200/6 significantly improved pre-dose FEV₁ compared with eformoterol by 0.04 L ($p = 0.026$) and compared with placebo and budesonide by 0.08 L ($p < 0.001$) for both comparators.
- Symbicort Rapihaler 200/6 significantly improved 1-hour post-dose FEV₁ compared with eformoterol 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 FEV₁ measures over 12 hours were obtained in subsets of patients (n=618). The median time to onset of bronchodilation (>15% improvement in FEV₁) was seen within 5 minutes at the end of treatment in patients receiving Symbicort Rapihaler 200/6 (N=101). Maximal improvement in FEV₁ occurred at approximately 2 hours post-dose and post-dose bronchodilator effect was generally maintained over 12 hours.

INDICATIONS

Asthma

Symbicort Rapihaler is indicated for the treatment of asthma where use of a combination (inhaled corticosteroid and long-acting β_2 -agonist) is appropriate in adults and adolescents. This includes:

- patients who are symptomatic on inhaled corticosteroid therapy,
- patients who are established on regular long acting β_2 -agonist and inhaled corticosteroid therapy.

There are two alternative treatment regimens:

- *Symbicort maintenance and reliever therapy*
- Symbicort maintenance therapy

The 100/6** and 200/6 strengths should not be used for the *Symbicort maintenance and reliever therapy* regimen.

Chronic obstructive pulmonary disease (COPD)

Symbicort 200/6 is indicated for the symptomatic treatment of moderate to severe COPD (FEV₁ \leq 50% predicted normal) in adults with frequent symptoms despite long-acting bronchodilator use, and/or a history of recurrent exacerbations. Symbicort is not indicated for the initiation of bronchodilator therapy in COPD.

CONTRAINDICATIONS

Hypersensitivity to budesonide, eformoterol or any other ingredients present in this formulation.

PRECAUTIONS

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

Patients with asthma should have a personal asthma action plan designed in association with their general practitioner. This plan should incorporate a stepwise treatment regime which can be instituted if the patient's asthma improves or deteriorates. It is recommended that the dose is tapered when long-term treatment is discontinued and should not be stopped abruptly.

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. Patients should be advised to seek medical attention if they find the treatment ineffective or they have exceeded the prescribed dose of Symbicort.

Patients should be advised to have their rescue inhaler available at all times, either Symbicort (for asthma patients on *Symbicort maintenance and reliever therapy*) or a separate rapid-acting bronchodilator (for other patients using Symbicort as maintenance therapy only)

Symbicort therapy should not be initiated to treat a severe exacerbation.

Oral corticosteroid usage

Symbicort should not be used to initiate treatment with inhaled steroids in patients being transferred from oral steroids. Care should be taken when commencing Symbicort treatment, particularly if there is any reason to suspect that adrenal function is impaired from previous systemic steroid therapy.

Potential systemic effects of inhaled corticosteroids

Inhaled steroids 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, inhaled steroids may have adverse effects; possible systemic effects of inhaled steroids include depression of the HPA axis, reduction of bone density, cataract and glaucoma, and retardation of growth rate in children and adolescents. In steroid-dependent patients, prior systemic steroid usage may be a contributing factor but such effects may occur amongst patients who use only inhaled steroids 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 switched from oral corticosteroids (see *PRECAUTIONS – Oral corticosteroid usage*) and patients administering concomitant medication metabolised by CYP3A4 (see *Interactions with other medicines*). 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.

Bone density

Whilst corticosteroids may have an effect on bone mass at high doses, long-term follow up (3 to 6 years) studies of budesonide treatment in adults at recommended doses, have not demonstrated a negative effect on bone mass compared to placebo, including a 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 3 large, medium-to-long-term (12 months to 6 years) studies in children (5 to 16 years), no effects on bone-mineral density were observed after treatment with budesonide (189 to 1322 µg/day) compared to nedocromil, placebo or age matched controls. However, in a randomised 18 month paediatric study (n=176; 5 to 10 years), bone-mineral density was significantly decreased by 0.11 g/cm² (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 of growth (approximately 1 cm) has been observed. This generally occurs within the first year of treatment. Physicians should closely follow the growth of children and adolescents taking long-term corticosteroids.

Rare individuals may be exceptionally sensitive to inhaled corticosteroids. 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 inhaled corticosteroids, each patient should be titrated to his/her lowest effective dose (see *DOSAGE & ADMINISTRATION*).

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), eformoterol 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 eformoterol 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 -adrenoceptor agonists. Caution is advised when eformoterol 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 *PRECAUTIONS - Interactions with other medicines*). 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 eformoterol.

Impaired renal and hepatic function

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

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 *Adverse effects* section.

Carcinogenicity

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

In eformoterol 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 2 years, and a mesovarian leiomyoma was observed in a female rat dosed by inhalation at 0.13 mg/kg/day for 2 years. The effects observed are expected findings with high-dose exposure to β_2 -agonists.

Eformoterol carcinogenicity studies performed by other companies used systemic exposure levels 800 to 4800-fold higher than those expected upon clinical use of eformoterol (based on an 18 μ g 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 eformoterol 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 eformoterol fumarate is no greater than for other β_2 -adrenoceptor agonists.

The carcinogenic potential of budesonide has been evaluated in the mouse and rat at oral doses up to 200 and 50 μ g/kg/day respectively. In male rats dosed with 10, 25, and 50 μ g budesonide/kg/day, those receiving 25 and 50 μ g/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.

Genotoxicity

Individually, budesonide and eformoterol 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 eformoterol), chromosomal damage and DNA repair. The combination of budesonide and eformoterol has not been tested in genotoxicity assays.

Effects on fertility

There are no animal studies on the effect of the budesonide/eformoterol combination on fertility.

Long-term treatment of female mice and rats with eformoterol 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 eformoterol 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 eformoterol fumarate at 15 mg/kg/day for two weeks.

Testicular atrophy was observed in mice given eformoterol fumarate in the diet at 0.2 to 50 mg/kg/day for 2 years, but no effect on male fertility was observed in rats dosed orally at 60 mg/kg/day for 9 weeks, in studies undertaken by another company.

Use in pregnancy – Category (Category B3)

For the concomitant treatment with budesonide and eformoterol, no clinical data on exposed pregnancies are available. Fetal malformations (umbilical hernia and cleft palate), typical of glucocorticoid toxicity in animals, occurred in rats dosed with the Symbicort Rapihaler formulation at the inhaled dose of 12 µg/kg/day budesonide and 0.66 µg/kg/day eformoterol, with plasma AUC values for both drugs below that expected in patients at the maximum recommended clinical dose. No teratogenic effect was detected at 2.5 µg/kg/day of budesonide and 0.14 µg/kg/day of eformoterol.

Symbicort Rapihaler should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Only after special consideration should Symbicort Rapihaler be used during the first 3 months and shortly before delivery.

Because β-agonists, including eformoterol, may potentially interfere with uterine contractility due to a relaxant effect on uterine smooth muscle, Symbicort Rapihaler should be used during labour only if the potential benefit justifies the potential risk.

Budesonide

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

If treatment with glucocorticosteroids during pregnancy is unavoidable, inhaled corticosteroids 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.

Eformoterol

No teratogenic effects were observed in rats receiving eformoterol fumarate at doses up to 60 mg/kg/day orally or 1.2 mg/kg/day by inhalation. Foetal 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 foetuses from rabbits dosed orally at 60 mg/kg/day. Decreased birth weight and increased perinatal/postnatal mortality were observed when eformoterol 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 eformoterol passes into human breast milk. In rats, eformoterol was excreted into breast milk. There are no studies in lactating animals using the budesonide/eformoterol combination. Increased postnatal mortality at maternal eformoterol doses of 0.2 mg/kg/day PO or greater, and retardation of pup growth at 15 mg/kg/day PO were observed in a rat study. There are no well-controlled human studies using Symbicort Rapihaler in nursing mothers. Because many drugs are excreted in human breast milk, administration of Symbicort Rapihaler 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.

Use in children

Symbicort Rapihaler is not recommended for children under the age of 12 years because of lack of data on efficacy and safety.

Effect on driving or operating machinery

Driving or using machinery should be undertaken with caution until the effect of Symbicort Rapihaler on the individual is established. Symbicort Rapihaler does not generally affect the ability to drive or use machinery.

INTERACTIONS WITH OTHER MEDICINES

Pharmacokinetic interactions

The metabolism of budesonide is primarily mediated by the enzyme CYP3A4. Inhibitors of this enzyme, eg ketoconazole, may therefore increase systemic exposure to budesonide. This is of limited clinical importance for short-term (1 to 2 weeks) treatment with ketoconazole, but should be taken into consideration during long-term treatment with ketoconazole or other potent CYP 3A4 inhibitors.

Pharmacodynamic interactions

Neither budesonide nor eformoterol 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 β₂-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 eformoterol, since the effects will be

cumulative. Patients who have already received large doses of sympathomimetic amines should not be given eformoterol.

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 *PRECAUTIONS - Hypokalaemia*).

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

The adverse cardiovascular effects of eformoterol 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 eformoterol 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).

ADVERSE EFFECTS

Since Symbicort Rapihaler contains both budesonide and eformoterol, 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.

In the clinical program comparing Symbicort Rapihaler with Symbicort Turbuhaler, 679 adults and adolescents (Study 681 and Study 715) were exposed to Symbicort Rapihaler 800/24 μg daily with a median duration of 359 days and a range of 1 to 427 days.

There were no apparent differences in the overall pattern of AE's between the Symbicort Rapihaler and Symbicort Turbuhaler groups in the clinical program. The AEs were generally mild to moderate in intensity and the pattern was that usually seen in a population with persistent asthma and dominated by symptoms of upper respiratory events.

Overall, the AE profile was similar for patients receiving Symbicort Rapihaler and Symbicort Turbuhaler with regard to total daily dose, age, sex and ethnic group and no new safety concerns were identified with Symbicort Rapihaler.

If oropharyngeal *candidiasis* develops, it may be treated with appropriate anti-fungal therapy whilst still continuing with Symbicort 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, eformoterol, and Symbicort, are given below.

Common 1 to 10%	Cardiac disorders Infections & infestations Nervous system disorders Respiratory, thoracic & mediastinal disorders	Palpitations Candida infections in the oropharynx Headache, tremor Mild irritation in the throat, coughing, hoarseness
Uncommon 0.1 to 1%	Cardiac disorders Gastrointestinal disorders Metabolism & nutrition disorders Musculoskeletal & connective tissue disorders Nervous system disorders Psychiatric disorders	Tachycardia Nausea, diarrhoea Weight gain Muscle cramps Dizziness, bad taste, thirst, tiredness Agitation, restlessness, nervousness, sleep disturbances
Rare 0.01 to 0.1%	Immune system disorders Cardiac disorders Respiratory, thoracic & mediastinal disorders Skin & subcutaneous tissue disorders Metabolism & nutrition disorders	Immediate and delayed hypersensitivity reactions including dermatitis, exanthema, urticaria, pruritis, angioedema and anaphylactic reaction Cardiac arrhythmias eg atrial fibrillation, supraventricular tachycardia, extrasystoles Bronchospasm Skin bruising Hypokalaemia
Very rare (<0.01%)	Cardiac disorders Endocrine disorders Metabolism & nutrition disorders Psychiatric disorders Vascular disorders	Angina pectoris Signs or symptoms of systemic glucocorticosteroid effects eg hypofunction of the adrenal gland Hyperglycaemia Depression, behavioural disturbances 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 *Clinical trials/COPD* section) for the Symbicort (as Turbuhaler or Rapihaler 200/6) and comparative placebo arms.

Table 2 Pneumonia incidence (%) - Symbicort Turbuhaler and Symbicort Rapihaler pivotal Phase III COPD studies (6 months or 12 months duration)

<i>Symbicort Turbuhaler</i>				<i>Symbicort Rapihaler</i>			
<i>Study 629^a</i>		<i>Study 670^a</i>		<i>Study 001^a</i>		<i>Study 002^a</i>	
Symbicort 200/6	Placebo	Symbicort 200/6	Placebo	Symbicort 200/6	Placebo	Symbicort 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 Symbicort 200/6 and placebo arms are presented in this table, not all treatment arms within the clinical studies

^b Includes Symbicort 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 Symbicort-treated patients compared to patients on placebo.

DOSAGE AND ADMINISTRATION

Asthma

There are two alternative dosage regimens for the treatment of asthma with Symbicort:

- *Symbicort maintenance and reliever therapy*
- Symbicort maintenance therapy

Symbicort maintenance and reliever therapy

Symbicort Rapihaler taken as both regular maintenance treatment and as-needed in response to symptoms. The as-needed inhalations provide both rapid relief and improved asthma control. Patients should be advised to have Symbicort Rapihaler available for rescue use at all times. A separate inhaler for rescue use is not necessary.

Adults and adolescents (12 years and older):

The recommended maintenance dose is Symbicort Rapihaler 50/3 or 100/3 four inhalations per day, given as either two inhalations in the morning and evening or as four inhalations in either the morning or evening. For some patients, a maintenance dose of Symbicort Rapihaler 100/3 four inhalations twice daily may be appropriate. The maintenance dose should be titrated to the lowest dose at which effective control of asthma is maintained.

Patients may take 2 additional inhalations as needed in response to symptoms. If symptoms persist after a few minutes, 2 additional inhalations should be taken. No more than 12 inhalations should be taken on any single occasion.

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. A total daily dose of more than 16 inhalations is normally not needed, however a total daily dose of up to 24 inhalations can be used temporarily.

Symbicort maintenance therapy

Symbicort Rapihaler taken as regular maintenance treatment, with a separate rapid-acting bronchodilator as rescue. Patients should be advised to have their separate rapid-acting bronchodilator available for rescue use at all times.

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

Adults and adolescents (12 years and older)

Symbicort Rapihaler 50/3

2 or 4 inhalations of Symbicort Rapihaler 50/3 twice daily. The maximum recommended daily maintenance dose is 8 inhalations (4 inhalations twice daily corresponding to 400 µg budesonide/24 µg eformoterol).

Symbicort Rapihaler 100/3

2 or 4 inhalations of Symbicort Rapihaler 100/3 twice daily. The maximum recommended daily maintenance dose is 8 inhalations (4 inhalations twice daily corresponding to 800 µg budesonide/24 µg eformoterol).

*Symbicort Rapihaler 100/6***

2 inhalations of Symbicort Rapihaler 100/6 twice daily. The maximum recommended daily maintenance dose is 4 inhalations (2 inhalations twice daily corresponding to 400 µg budesonide/24 µg eformoterol).

Symbicort Rapihaler 200/6

2 inhalations of Symbicort Rapihaler 200/6 twice daily. The maximum recommended daily maintenance dose is 4 inhalations (2 inhalations twice daily corresponding to 800 µg budesonide/24 µg eformoterol).

For adults 18 years and over who require a higher daily maintenance dose, the maximum recommended maintenance dose may be increased to 4 inhalations of Symbicort Rapihaler 200/6 twice daily (corresponding to 1600 µg budesonide/48 µg eformoterol).

COPD – Adults

2 inhalations of Symbicort Rapihaler 200/6 twice daily. The maximum recommended daily dose is 4 inhalations (corresponding to 800 µg budesonide / 24 µg eformoterol).

General information

For optimal benefit the patient should be instructed to take Symbicort Rapihaler even when asymptomatic.

Elderly

There is no need to adjust the dose in elderly patients.

Hepatic/renal impairment

There are no data available for use of Symbicort Rapihaler in patients with hepatic or renal impairment. As budesonide and eformoterol are primarily eliminated via hepatic metabolism, an increased systemic availability can be expected in patients with severe liver disease.

Instruction for correct use of Rapihaler

On actuation of the Symbicort Rapihaler, a volume of the suspension is expelled from the canister at high velocity. When the patient inhales through the mouthpiece at the same time as actuating the inhaler, the substance will follow the inspired air into the airways.

NOTE: It is important to instruct the patient to:

- Carefully read the instructions for use in the patient information leaflet that are provided with each pack of Symbicort Rapihaler.
- Shake the inhaler well prior to each use to mix its contents properly.
- Prime the inhaler by actuating it twice for Symbicort Rapihaler 100/6** and 200/6, or three times for Symbicort Rapihaler 50/3 and 100/3, into the air when the inhaler is new, if it has not been used for more than one week or if it has been dropped.
- Place the mouthpiece into the mouth. While breathing in slowly and deeply, press the inhaler firmly to release the medication. Continue to breathe in and hold the breath for approximately 10 seconds or as long as is comfortable. Shake the inhaler again and repeat this step for the second inhalation.
- Rinse the mouth with water after inhaling the maintenance dose to minimise the risk of oropharyngeal thrush.
- Clean the mouthpiece of the inhaler regularly, at least once a week with a clean dry cloth. Do not put the inhaler into water.

OVERDOSAGE

An overdose of eformoterol 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 μ g administered during 3 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 Symbicort Rapihaler or decreasing the dose of budesonide will abolish these effects, although the normalisation of the HPA-axis may be a slow process.

PRESENTATION AND STORAGE CONDITIONS

Symbicort Rapihaler is a pressurised metered dose inhaler with an actuation counter. The inhaler is comprised of a pressurised aluminium canister with an attached actuation counter, a red plastic actuation body with a white mouthpiece and attached grey mouthpiece cover. Each inhaler is individually wrapped in a foil laminate pouch with desiccant sachet.

Symbicort Rapihaler is registered as packs of one or two** inhalers. Each inhaler contains 120 inhalations and is registered in the following strengths:

- *Symbicort Rapihaler 50/3*
Each delivered dose (the dose that leaves the mouthpiece) contains as active constituents: budesonide 40 µg/inhalation and eformoterol 2.25 µg/inhalation.
- *Symbicort Rapihaler 100/3*
Each delivered dose (the dose that leaves the mouthpiece) contains as active constituents: budesonide 80 µg/inhalation and eformoterol 2.25 µg/inhalation.
- *Symbicort Rapihaler 100/6***
Each delivered dose (the dose that leaves the mouthpiece) contains as active constituents: budesonide 80 µg/inhalation and eformoterol 4.5 µg/inhalation.
- *Symbicort Rapihaler 200/6*
Each delivered dose (the dose that leaves the mouthpiece) contains as active constituents: budesonide 160 µg/inhalation and eformoterol 4.5 µg/inhalation.

To avoid confusion, Symbicort Rapihaler is labelled as metered dose like Symbicort Turbuhaler. The following table gives the corresponding dose delivered to the patient.

Symbicort	Metered dose (µg)		Corresponding dose delivered to patient (µg)*	
	Budesonide	Eformoterol	Budesonide	Eformoterol
50/3	50	3	40	2.25

100/3	100	3	80	2.25
100/6**	100	6	80	4.5
200/6	200	6	160	4.5

* doses referred to in Symbicort publications

Storage conditions

Store below 30°C.

The inhaler should be discarded within 3 months after removal from the foil pouch.

NAME AND ADDRESS OF THE SPONSOR

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

Telephone: 1800 805 342

POISON SCHEDULE OF THE MEDICINE

Prescription only medicine (Schedule 4)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

22 February 2006 (Symbicort Rapihaler 100/6** and 200/6)

DATE OF MOST RECENT AMENDMENT

28 March 2017

*** Not marketed in Australia*

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