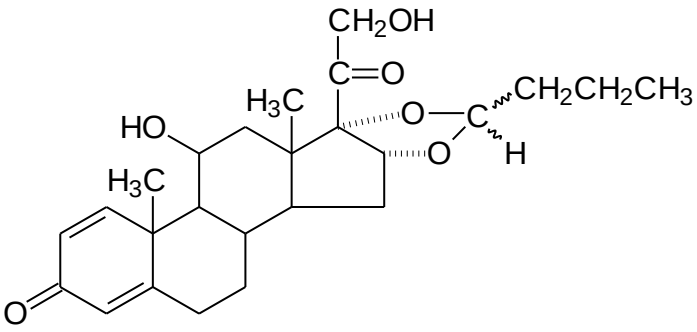
# SYMBICORT® TURBUHALER®

## PRODUCT INFORMATION

## NAME OF THE MEDICINE

### Budesonide

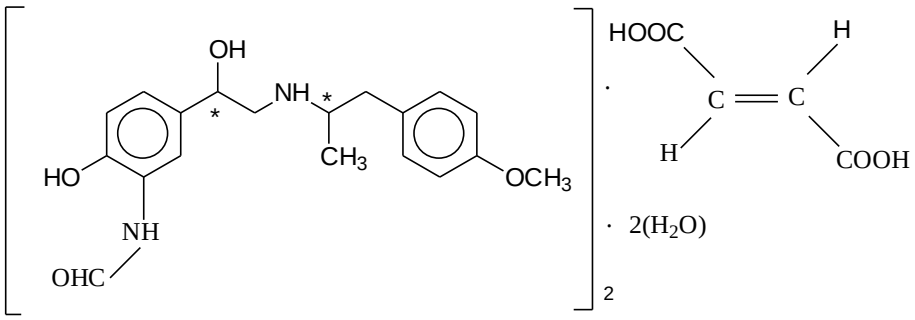
Budesonide is a non halogenated glucocorticoid structurally related to 16α hydroxyprednisolone. The chemical name is 16α, 17α - 22 R, S-propylmethylenedioxypregna-1,4-diene-ß, 21-diol-3, 20-dione.




CAS number: 51333-22-3

### Eformoterol fumarate dihydrate

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




CAS Number: 43229-80-7

## DESCRIPTION

Symbicort Turbuhaler contains budesonide and eformoterol fumarate dihydrate (hereafter referred to as eformoterol) as the active ingredients. Symbicort Turbuhaler also contains the inactive ingredient lactose.

## 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 both as maintenance and reliever therapy for asthma or as maintenance treatment for asthma and for symptomatic treatment of patients with moderate to severe COPD.

### Budesonide

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

### Eformoterol

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

### Pharmacokinetics

Symbicort Turbuhaler and the corresponding monoproducts (budesonide Turbuhaler and eformoterol Turbuhaler as per Table 13, *Presentation and storage conditions* section) have been shown to be bioequivalent with regard to systemic exposure of budesonide and eformoterol, respectively.

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

Pharmacokinetic parameters for the respective substances were comparable after the administration of budesonide and eformoterol as monoproducts or as Symbicort Turbuhaler.

#### *Budesonide*

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

Budesonide undergoes an extensive degree (approx. 90%) of biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity. Elimination is via metabolism mainly catalysed by the enzyme CYP3A4. The metabolites are excreted in urine as such or in conjugated form with only negligible amounts of unchanged budesonide being detected in the urine. Budesonide has a high systemic clearance (approx. 1.2 L/min) and the plasma elimination half life after i.v. dosing averages 4 hours.

### *Eformoterol*

In studies the mean lung deposition of eformoterol after inhalation via Turbuhaler ranged from 21-37% of the metered dose. The total systemic bioavailability for the higher lung deposition is approximately 46%. Plasma protein binding is approximately 50% with a volume of distribution of approximately 4 L/kg.

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

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

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

## CLINICAL TRIALS

Symbicort 100/6 and 200/6 refers to the metered dose of the corresponding monoproducts (budesonide/eformoterol) ie 100 µg of budesonide and 6 µg eformoterol and 200 µg of budesonide and 6 µg eformoterol respectively. Similarly, Symbicort 400/12 refers to the metered dose of the corresponding monoproducts ie 400 µg of budesonide and 12 µg eformoterol. See also Table 13 in *Presentation and storage conditions* section.

### Asthma

### *Symbicort maintenance and reliever therapy*

The safety and efficacy of Symbicort in the *Symbicort maintenance and reliever therapy* regimen have been investigated in six clinical trials using two dose strengths (100/6 and 200/6) of Symbicort 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 Symbicort maintenance and reliever therapy. Of the overall patient population 7% were smokers. In comparison with the usual patient proportions seen in practice, smokers and the elderly were under-represented in the trials. However, the results for these subgroups were generally consistent with the results for the whole study population. Patients with chronic obstructive pulmonary disease were excluded.

The studies showed that *Symbicort maintenance and reliever therapy* was significantly superior compared with fixed dose combination products or higher doses of inhaled glucocorticosteroids (GCSs) with a separate short acting or long acting β-agonist used as reliever (see Tables 1 and 2). In the 5 double blind long term studies, patients receiving *Symbicort maintenance and reliever therapy* used no reliever inhalations on 57% of treatment days and 0-2 reliever inhalations on 87% of treatment days.

**Table 1 Summary of primary efficacy variable**

| Treatment | Hazard Ratio | 95% confidence interval |
|---|---|---|
| **Time to first severe asthma exacerbation** | | |
| *SMILE 734* | | |
| 1. Symbicort maintenance & reliever therapy vs Symbicort + eformoterol prn | 0.73 | 0.59, 0.90 |
| 2. Symbicort maintenance & reliever therapy vs Symbicort + terbutaline prn | 0.55 | 0.45, 0.68 |
| 3. Symbicort + eformoterol prn vs Symbicort + terbutaline prn | 0.76 | 0.63, 0.92 |
| *COMPASS 735* | | |
| 1. Symbicort maintenance & reliever therapy vs Symbicort + terbutaline prn | 0.74 | 0.56, 0.96 |
| 2. Symbicort maintenance & reliever therapy vs Seretide + terbutaline prn | 0.67 | 0.52, 0.87 |
| 3. Symbicort + terbutaline prn vs Seretide + terbutaline prn | 0.91 | 0.72, 1.16 |
| *STAY 673* | | |
| 1. Symbicort maintenance & reliever therapy vs Symbicort + terbutaline prn | 0.55 | 0.44, 0.67 |
| 2. Symbicort maintenance & reliever therapy vs budesonide + terbutaline prn | 0.53 | 0.43, 0.65 |
| 3. Symbicort + terbutaline prn vs budesonide + terbutaline prn | 0.97 | 0.82, 1.16 |
| *STEP 668* | | |
| Symbicort maintenance & reliever therapy vs budesonide + terbutaline prn | 0.61 | 0.50, 0.74 |
| *COSMOS 691* | | |
| Symbicort maintenance & reliever therapy vs Seretide + Ventolin prn | 0.75 | 0.61, 0.93 |
| **Morning peak flow (L/min)** | | |
| *STEAM 667* | | |
| Symbicort maintenance & reliever therapy vs budesonide + terbutaline prn | Mean diff 25 L/min | 19, 31 |

**Table 2 Summary of the number of severe asthma exacerbations**

| Treatment | No. of exacerbations | No. of patients with exacerbations / total patients (%) |
|---|---|---|
| *SMILE 734 (12 months)* | | |
| 1. Symbicort maintenance & reliever therapy | 194 | 143/1107 (13%) |
| 2. Symbicort + eformoterol prn | 296 | 195/1137 (17%) |
| 3. Symbicort + terbutaline prn | 377 | 245/1138 (22%) |

| Treatment | No. of exacerbations | No. of patients with exacerbations / total patients (%) |
|---|---|---|
| *COMPASS 735 (6 months)* | | |
| 1. Symbicort maintenance & reliever therapy | 125 | 94/1103 (9%) |
| 2. Symbicort + terbutaline prn | 173 | 126/1099 (11%) |
| 3. Seretide + terbutaline prn | 208 | 138/1119 (12%) |
| *STAY 673 (12 months)* | | |
| 1. Symbicort maintenance & reliever therapy | 303 | 148/922 (16%) |
| 2. Symbicort + terbutaline prn | 553 | 248/906 (27%) |
| 3. Budesonide + terbutaline prn | 564 | 256/925 (28%) |
| *STEP 668 (12 months)* | | |
| 1. Symbicort maintenance & reliever therapy | 331 | 170/947 (18%) |
| 2. Budesonide + terbutaline prn | 546 | 259/943 (27%) |
| *STEAM 667 (6 months)* | | |
| 1. Symbicort maintenance & reliever therapy | 43 | 27/354 (8%) |
| 2. Budesonide + terbutaline prn | 94 | 54/342 (16%) |
| *COSMOS 691 (12 months)* | | |
| 1. Symbicort maintenance & reliever therapy | 255 | 159/1064 (15%) |
| 2. Seretide + Ventolin prn | 329 | 204/1071 (19%) |

*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. *Symbicort maintenance and reliever therapy* - Symbicort Turbuhaler 200/6, 1 inhalation twice daily plus additional inhalations as needed

2. Symbicort 200/6, 1 inhalation twice daily with eformoterol Turbuhaler as needed

3. Symbicort 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 *Symbicort maintenance and reliever therapy* compared with Symbicort plus eformoterol and Symbicort plus terbutaline (see Table 1).

Use of oral steroids due to exacerbations was lower in the Symbicort maintenance and reliever therapy group (1204 days total vs 2063 and 2755 days in the Symbicort plus eformoterol and Symbicort plus terbutaline groups, respectively).

The majority of secondary variables supported the superiority of *Symbicort maintenance and reliever therapy* over both comparators (see Table 3). The average daily as-needed use in the *Symbicort maintenance and reliever therapy* group was 1.02 inhalations/day and the frequency of high as-needed use was

lower for Symbicort maintenance and reliever therapy compared to both comparators.

**Table 3 Secondary efficacy variables for Study 734**

| Variable† | Symb maintenance & reliever | Symb + eform prn | Symb + terb prn | Comparison (mean difference & 95% confidence interval) | |
|---|---|---|---|---|---|
| | | | | Symb maintenance & reliever v Symb & eform prn | Symb maintenance & reliever v Symb + 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; $^{\Delta}$ day and night with no symptoms and a night with no awakenings.

The study specifically demonstrates that both the budesonide and the eformoterol components of Symbicort contribute to improved asthma control achieved through the as-needed dosing of Symbicort within the *Symbicort maintenance and reliever 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. *Symbicort maintenance and reliever therapy* - Symbicort Turbuhaler 200/6, 1 inhalation twice daily plus additional inhalation as needed

2. Seretide Inhaler 125/25, 2 inhalations twice daily with terbutaline Turbuhaler as needed

3. Symbicort 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 *Symbicort maintenance and reliever therapy* compared with both Seretide plus terbutaline and Symbicort at a higher maintenance dose plus terbutaline (see Table 1).

Use of oral steroids due to exacerbations was lower in the *Symbicort maintenance and reliever therapy* group compared to Seretide plus terbutaline and Symbicort 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 *Symbicort maintenance and reliever therapy* and the other two groups. The average daily as-needed use in the *Symbicort maintenance and reliever therapy* group was 1.02 inhalations/day.

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

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

In Studies 673, 668 and 667, *Symbicort maintenance and reliever therapy* prolonged the time to the first exacerbation compared to Symbicort 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 1). Symptoms and reliever use were reduced and lung function improved compared with all other treatments (see Tables 4, 5 and 6).

**Table 4 Secondary efficacy variables for Study 673**

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

**Table 5 Secondary efficacy variables for Study 668**

| Variable† | Symb maintenance + reliever | Bud. + terb prn | Comparison (mean difference & 95% confidence interval) Symb maintenance & reliever v Bud + terb prn |
|---|---|---|---|
| mPEF (L/min) | 34.2 | 13.9 | 20.3 (16.5, 24.1) |
| ePEF (L/min) | 21.8 | 7.9 | 14.0 (10.4, 17.5) |
| $FEV_1$ (L) | 0.19 | 0.09 | 0.100 (0.071, 0.130) |
| Total asthma symptom score (0-6) | -0.81 | -0.61 | -0.21 (-0.28, -0.13) |
| Nocturnal awakenings due to asthma (% nights) | -13.8 | -10.6 | -3.3 (-4.8, -1.7) |
| Symptom free days$^{\Delta}$ (% 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; $^{\Delta}$ day and night with no symptoms and a night with no awakenings.

**Table 6 Secondary efficacy variables for Study 667**

| Variable† | Symb maintenance + reliever | Bud. + terb prn | Comparison (mean difference & 95% confidence interval) Symb maintenance & reliever v Bud + terb prn |
|---|---|---|---|
| ePEF (L/min) | 25.4 | 6.6 | 18.8 (13.3, 24.3) |
| $FEV_1$ (L) | 0.21 | 0.06 | 0.148 (0.103, 0.193) |
| Total asthma symptom score (0-6) | -0.55 | -0.38 | –0.17 (-0.26, -0.07) |
| Nocturnal awakenings due to asthma (% nights) | -8.3 | -6.1 | –2.2 (-4.5, 0.01) |
| Symptom free days$^{\Delta}$ (% 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; $^{\Delta}$ day and night with no symptoms and a night with no awakenings.

*Study 691 (COSMOS)*

A 12-month, randomised, open, parallel group trial that compared the effectiveness of *Symbicort maintenance and reliever therapy* with Seretide plus Ventolin 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 7).

**Table 7 Treatments in the COSMOS (691) study**

| | Symbicort maintenance & reliever therapy | Seretide plus Ventolin |
|---|---|---|
| Fixed dose period (4 weeks) | Symbicort 200/6, 2 inhalations twice daily with additional inhalations as needed | Seretide 250/50, 1 inhalation twice daily + Ventolin as needed |
| Dose adjustment period (11 months) | Symbicort 200/6 either<br>- 2 inhalations twice daily + as needed, or<br>- 1 inhalation twice daily + as needed, or<br>- 2 inhalations once daily + as needed | Either<br>- Seretide 500/50, 1 inhalation twice daily + Ventolin as needed<br>- Seretide 250/50, 1 inhalation twice daily + Ventolin as needed, or<br>- Seretide 100/50, 1 inhalation twice daily + Ventolin as needed |

This study showed that *Symbicort maintenance and reliever therapy* treatment is more effective than adjustable therapy with Seretide plus Ventolin in controlling asthma in adults and adolescents. *Symbicort maintenance and reliever therapy* increased the time to first severe asthma exacerbations, reduced the total number of severe asthma exacerbations (see Tables 1 and 2), reduced use of oral steroids for severe asthma exacerbations, and reduced use of as needed medications as compared with Seretide at a similar daily inhaled GCS dose.

*Safety in the combined studies*

*Symbicort maintenance and reliever therapy* treatment has a safety profile that is similar to budesonide and Symbicort maintenance therapy with a decrease in asthma-related adverse events.

### *Symbicort maintenance therapy*

The efficacy and safety of Symbicort 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 short-acting $\beta_2$-agonist for rescue use. 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 Symbicort.

*Symbicort 100/6 and 200/6*

In one study the maximum recommended maintenance dose of Symbicort 200/6 (2 inhalations twice daily) was compared to corresponding doses of the free combination (budesonide Turbuhaler 200 μg + eformoterol Turbuhaler 6μg, 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 8 details the efficacy results after 12 weeks treatment.

**Table 8 Estimated treatment means and treatment contrasts: effects of 12 weeks treatment with twice daily Symbicort 200/6, budesonide 200 μg alone and the free combination of the monoproducts**

| Variable | Symb | Bud | Free comb | Comparison p values | |
|---|---|---|---|---|---|
| | | | | Symb v Bud | Symb 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; $^{\Delta}$ day and night with no symptoms and a night with no awakenings.

When administered twice daily, Symbicort 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%) Symbicort 100/6 (1 inhalation twice daily) was compared with budesonide Turbuhaler 200 μg (1 inhalation twice daily). Table 9 details the efficacy results after 12 weeks treatment.

**Table 9 Estimated treatment means and treatment contrasts: effects of 12 weeks treatment with twice daily Symbicort 100/6 and budesonide 200 μg alone**

| Variable | Symbicort | 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 Symbicort 100/6 than with a doubled dose of budesonide.

*Symbicort 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%) Symbicort 400/12 (2 inhalations twice daily) was compared to corresponding doses of the free combination (eformoterol Turbuhaler 12 µg+budesonide Turbuhaler 400 µg, two inhalations twice daily) and budesonide Turbuhaler 400 µg (2 inhalations twice daily) only. Table 10 details the efficacy results after 12 weeks treatment.

**Table 10 Mean change from baseline in efficacy variables: effects of 12 weeks treatment with twice daily Symbicort 400/12, budesonide 400 µg alone and the free combination of the monoproducts**

| Variable† | Symb | Bud | Free comb | Comparison p values | |
|---|---|---|---|---|---|
| | | | | Symb v Bud | Symb 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; $^{\Delta}$ day and night with no symptoms and a night with no awakenings.

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

## COPD

The efficacy and safety of Symbicort in the treatment of patients with moderate to severe COPD (pre-bronchodilator $FEV_1$ ≤50% predicted normal) has been evaluated in four randomised, double-blind, placebo and active controlled, parallel-group, multi-centre clinical studies. Two 12-month studies were performed with the dry powder inhaler 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 $FEV_1$ 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).

- Symbicort Turbuhaler significantly improved mean $FEV_1$ 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 postdose $FEV_1$ compared to placebo (LS mean = 0.16 L; p<0.001); however the change in predose $FEV_1$ was not significantly different to 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 $FEV_1$ over the treatment period.

- Symbicort 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)). Symbicort Rapihaler 100/6 caused a significantly greater change from baseline compared to budesonide (LS mean = 0.16; $p<0.001$). Predose $FEV_1$ increased significantly from baseline to the average of the treatment period, LS mean = 0.06 (0.03, 0.08). However, the change from baseline, compared to eformoterol, for predose $FEV_1$ was not statistically significant, LS mean = 0.02 (-0.02, 0.05; $p=0.335$).

- Symbicort Rapihaler 200/6 significantly improved pre-dose $FEV_1$ 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 $FEV_1$ 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 $FEV_1$ 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 Symbicort 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.

## INDICATIONS

### Asthma

Symbicort Turbuhaler is indicated for the treatment of asthma where use of a combination (inhaled corticosteroid and long acting $\beta_2$-agonist) is appropriate. This includes:

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

There are two alternative treatment regimens:

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

Symbicort 400/12 should only be used in patients aged 18 years and over.

The 400/12 strength should not be used for the *Symbicort maintenance and reliever therapy* regimen.

### Chronic obstructive pulmonary disease (COPD)

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

## CONTRAINDICATIONS

Hypersensitivity to budesonide, eformoterol or lactose.

## 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 patients asthma improves or deteriorates.

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 asthma patients using Symbicort as maintenance therapy only and for COPD patients).

Sudden and progressive deterioration in control of asthma or COPD is potentially life threatening and the patient should undergo urgent medical assessment. In this situation, consideration should be given to the need for increased therapy with corticosteroids (e.g. a course of oral corticosteroids), or antibiotic treatment if a bacterial infection is present. Patients should be advised to seek medical attention if they find the treatment ineffective or they have exceeded the prescribed dose of Symbicort.

It is recommended that the dose is tapered when long-term treatment is discontinued and should not be stopped abruptly.

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 with prolonged treatment at the highest recommended dose of Symbicort and patients administered concomitant CYP3A4-inhibitors (see *Interactions with other drugs*). 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 (3-6 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 bid for 1 month, 200 µg bid for 5 months and 100 µg bid for 12 months and the dose of disodium cromoglycate 10mg tad. The clinical significance of this result remains uncertain.

### *Growth*

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

Rare individuals may be exceptionally sensitive to 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* section).

### 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

$\beta_2$-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 $\beta_2$-adrenoceptor agonists.

Patients with pre-existing cardiovascular conditions may be at greater risk of developing adverse cardiovascular effects following administration of $\beta_2$-adrenoreceptor agonists. Caution is advised when eformoterol is administered to patients with severe cardiovascular disorders such as ischaemic heart disease, tachyarrythmias or severe heart failure.

### Hypokalaemia

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

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

### Diabetes

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

### Other

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

### 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 two years, and a mesovarian leiomyoma was observed in a female rat dosed by inhalation at 0.13 mg/kg/day for two years. The effects observed are expected findings with high dose exposure to ß$_2$-agonists.

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 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 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 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.

### 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 fumarate), 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 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 Symbicort Turbuhaler or the concomitant treatment with budesonide and eformoterol, no clinical data on exposed pregnancies are available. Animal studies with respect to the reproductive toxicity of the combination have not been performed.

Symbicort Turbuhaler should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Only after special consideration should Symbicort Turbuhaler 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 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 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. 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 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 is excreted in human milk. In reproductive studies in rats eformoterol was excreted into breast milk. There are no well-controlled human studies of the use of Symbicort Turbuhaler in nursing mothers. Administration of Symbicort 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 is not recommended for children below 12 years of age.

## Effect on ability to drive and use or operate machines

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

## INTERACTIONS WITH OTHER DRUGS

### 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 (1-2 weeks) treatment with ketoconazole, but should be taken into consideration during long-term treatment with ketoconazole or other potent CYP3A4 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 $\beta_2$-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 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 $\beta_2$-agonist therapy and may be potentiated by concomitant treatment with xanthine derivatives, mineralocorticosteroids, and diuretics (see *Precautions - Hypokalaemia* section).

### 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 Turbuhaler 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 $\beta_2$-agonist therapy, such as tremor and palpitations. These tend to be mild and usually disappear within a few days of commencing treatment.

If oropharyngeal candidiasis develops, it may be treated with appropriate anti-fungal therapy whilst still continuing with 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 in Table 11 below.

**Table 11 Tabulation of adverse reactions**

| | | |
|---|---|---|
| Common<br>1 to 10% | Cardiac disorders | Palpitations |
| | Infections and infestations | Candida infections in the oropharynx |
| | Nervous system disorders | Headache, tremor |
| | Respiratory:, thoracic & mediastinal disorders | Mild irritation in the throat, coughing, hoarseness |
| Uncommon<br>0.1 to 1% | Cardiac disorders | Tachycardia |
| | 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<br>0.01 to 0.1% | Immune system disorders | Immediate and 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<br>< 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 *Clinical trials/COPD* section) for the Symbicort (as Turbuhaler or Rapihaler 200/6) and comparative placebo arms.

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

| ***Symbicort Turbuhaler*** | | | | ***Symbicort Rapihaler*** | | | |
|---|---|---|---|---|---|---|---|
| ***Study 629*** [a] | | ***Study 670*** [a] | | ***Study 001*** [a] | | ***Study 002*** [a] | |
| **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 for asthma*

Symbicort 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 available for rescue use at all times. A separate inhaler for rescue use is not necessary.

**The 400/12 strength should not be used for Symbicort maintenance and reliever therapy regimen.**

*Adults and adolescents (12 years and older)*

The recommended maintenance dose is Symbicort 100/6 or Symbicort 200/6 two inhalations per day, given as either one inhalation in the morning and evening or as two inhalations in either the morning or evening. For some patients, a maintenance dose of Symbicort 200/6 two inhalations twice daily may be appropriate. The maintenance dose should be titrated to the lowest dose at which effective control of asthma is maintained.

Patients may take an additional inhalation as needed in response to symptoms. If symptoms persist after a few minutes, another inhalation should be taken. No more than 6 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 8 inhalations is normally not needed, however a total daily dose of up to 12 inhalations can be used temporarily.

***Symbicort maintenance therapy for asthma***

Symbicort 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 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)*

<u>Symbicort 100/6</u>

1-2 inhalations of Symbicort 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).

<u>Symbicort 200/6</u>

1-2 inhalations of Symbicort 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).

<u>Symbicort 400/12</u>

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

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

## COPD

### *Adults*

*Symbicort 200/6*

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

*Symbicort 400/12*

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

### General Information

For optimal benefit the patient should be instructed to take the maintenance dose of Symbicort Turbuhaler even when asymptomatic.

### Elderly

There are no special dosing requirements for elderly patients.

### Hepatic/renal impairment

There are no data available for use of Symbicort Turbuhaler 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 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:*

- Carefully read the instructions for use in the patient information leaflet that are provided with each pack of Symbicort
- 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 Symbicort 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 Turbuhaler due to the small amount of drug delivered.

## OVERDOSAGE

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

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

Withdrawing Symbicort 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 is available in a multidose inspiratory flow driven, metered dose dry powder inhaler (Turbuhaler). To avoid confusion Symbicort Turbuhaler is labelled as the metered dose of the corresponding monoproducts (Pulmicort (budesonide)/Oxis (eformoterol)). Pulmicort and Oxis Turbuhaler are also labelled as metered doses. The following table gives the corresponding dose delivered to the patient.

**Table 13**

| Symbicort | Metered dose* (µg) | | Corresponding dose delivered to patient (µg)** | |
|---|---|---|---|---|
| | Pulmicort (budesonide) | Oxis (eformoterol) | Budesonide | Eformoterol |
| 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 Symbicort; ** doses referred to in Symbicort publications

The following pack sizes are registered^ for Symbicort Turbuhaler:

- 100/6: 60 (sample pack) or 120 inhalations
- 200/6: 30 (sample pack), 60 or 120 inhalations
- 400/12: 60 inhalations single Turbuhaler (sample pack) or double Turbuhaler pack.

^ not all pack sizes may be supplied in Australia

### Storage conditions

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

## 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 DRUG

Prescription only medicine (Schedule 4).

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

27 May 2002 (Symbicort Turbuhaler 100/6 and 200/6)

## DATE OF MOST RECENT AMENDMENT

6 July 2017