SYMBICORT® TURBUHALER® PRODUCT INFORMATION

NAME OF THE MEDICINE

Budesonide

Budesonide is a non-halogenated glucocorticoid structurally related to 16α-hydroxy prednisolone. The chemical name is 16α, 17α - 22 R, S-propylmethylene dioxygena -1, 4-diene-18, 21-diol-3, 20-dione.

CAS Number: 51333-22-3

Eformoterol fumarate dihydrate

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

\[
\begin{align*}
\text{HOOC} & \quad \text{HO} \\
\text{CH3} & \quad \text{NH} \\
\text{OCH3} & \quad \text{COOH} \\
\text{H} & \quad 2(\text{H2O}) \\
\end{align*}
\]

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 β₂-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 12, Presentation 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 0-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 100μg of budesonide and 6μg eformoterol and 200μg of budesonide and 12μg eformoterol respectively. Similarly, Symbicort 400/12 refers to the metered dose of the corresponding monoproducts ie 400μg of budesonide and 12μg eformoterol.

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 (IGGs) with a separate short acting or long acting β₂-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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hazard Ratio</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SMILE 734</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Symbicort maintenance and reliever therapy vs. Symbicort + eformoterol prn</td>
<td>0.73</td>
<td>0.59, 0.90</td>
</tr>
<tr>
<td>2. Symbicort maintenance and reliever therapy vs. Symbicort + terbutaline prn</td>
<td>0.55</td>
<td>0.45, 0.68</td>
</tr>
<tr>
<td>3. Symbicort + eformoterol prn vs. Symbicort + terbutaline prn</td>
<td>0.76</td>
<td>0.63, 0.92</td>
</tr>
<tr>
<td><strong>COMPASS 735</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Symbicort maintenance and reliever therapy vs. Symbicort + terbutaline prn</td>
<td>0.74</td>
<td>0.56, 0.96</td>
</tr>
<tr>
<td>2. Symbicort maintenance and reliever therapy vs. Seretide + terbutaline prn</td>
<td>0.67</td>
<td>0.52, 0.87</td>
</tr>
<tr>
<td>3. Symbicort + terbutaline prn vs. Seretide + terbutaline prn</td>
<td>0.91</td>
<td>0.72, 1.16</td>
</tr>
</tbody>
</table>
The majority of secondary variables supported the superiority of Symbicort maintenance and reliever therapy compared with both comparators.

### Table 3: Secondary efficacy variables for Study 734

<table>
<thead>
<tr>
<th>Variable†</th>
<th>Symb. maintenance + reliever</th>
<th>Symb. + eformoterol prn</th>
<th>Symb. + terbutaline prn</th>
<th>Symb. maintenance + reliever v Symb + eformoterol prn</th>
<th>Symb. maintenance + reliever v Symb + terbutaline prn</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPEF (L/min)</td>
<td>15.3</td>
<td>10.6</td>
<td>7.9</td>
<td>4.8 (1.5, 8.0)</td>
<td>7.5 (4.2, 10.7)</td>
</tr>
<tr>
<td>ePEF (L/min)</td>
<td>13.8</td>
<td>8.5</td>
<td>7.5</td>
<td>5.4 (2.1, 8.6)</td>
<td>6.3 (3.1, 9.5)</td>
</tr>
<tr>
<td>FEV₁ (% of predicted)</td>
<td>94.00 (0.024, 0.075)</td>
<td>0.049</td>
<td>0.076</td>
<td>0.076 (0.050, 0.101)</td>
<td>0.076 (0.050, 0.101)</td>
</tr>
<tr>
<td>Total asthma symptom score (0–6)</td>
<td>-0.69</td>
<td>-0.57</td>
<td>-0.58</td>
<td>-0.12 (-0.18, -0.06)</td>
<td>-0.11 (-0.17, -0.05)</td>
</tr>
<tr>
<td>Nocturnal awakenings due to asthma (% nights)</td>
<td>-16.0</td>
<td>-14.0</td>
<td>-13.5</td>
<td>-2.0 (-3.7, -0.4)</td>
<td>-2.6 (-4.3, -0.9)</td>
</tr>
<tr>
<td>Symptom free days% (days)</td>
<td>31.3</td>
<td>28.9</td>
<td>29.4</td>
<td>2.4 (-0.3, 5.0)</td>
<td>1.9 (-0.8, 4.6)</td>
</tr>
<tr>
<td>Rescue medication use (inhalations/24 hours)</td>
<td>-0.84</td>
<td>-0.67</td>
<td>-0.64</td>
<td>-0.17 (-0.25, -0.08)</td>
<td>-0.20 (-0.28, -0.11)</td>
</tr>
</tbody>
</table>

† Mean change from mean of run-in to mean of the treatment period; mPEF – morning peak expiratory flow; ePEF – evening peak expiratory flow; FEV₁ – forced expired volume in 1 second; ‡ 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 bd plus additional inhalation as needed
2. **Sere tide Inhaler 125/25, 2 inhalations bd with terbutaline Turbuhaler as needed**
3. **Symbicort Turbuhaler 400/12, 1 inhalation bd 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 Sere tide 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 Sere tide 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 737 (STAY), Study 668 (STEP) and Study 667 (STEAM)

In Studies 673, 668 and 677, 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

<table>
<thead>
<tr>
<th>Variable†</th>
<th>Symb. maintenance + reliever</th>
<th>Symb. + terb prn</th>
<th>Bud. + terb prn</th>
<th>Symb maintenance + reliever v Symb + terb prn</th>
<th>Bud + terb prn</th>
<th>Symb maintenance + reliever v Bud + terb prn</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPEF (L/min)</td>
<td>29.9</td>
<td>22.0</td>
<td>13.0</td>
<td>7.9 (4.2, 11.7)</td>
<td>16.9 (13.2, 20.7)</td>
<td></td>
</tr>
<tr>
<td>ePEF (L/min)</td>
<td>26.5</td>
<td>18.3</td>
<td>9.2</td>
<td>8.3 (4.5, 12.0)</td>
<td>17.4 (13.7, 21.1)</td>
<td></td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>0.22</td>
<td>0.15</td>
<td>0.12</td>
<td>0.075 (0.044, 0.106)</td>
<td>0.102 (0.071, 0.132)</td>
<td></td>
</tr>
<tr>
<td>Total asthma symptom score (0-6)</td>
<td>-0.88</td>
<td>-0.59</td>
<td>-0.46</td>
<td>-0.09 (-0.16, -0.02)</td>
<td>-0.21 (-0.28, -0.15)</td>
<td></td>
</tr>
<tr>
<td>Nocturnal awakenings due to asthma (% nights)</td>
<td>-12.7</td>
<td>-8.8</td>
<td>-8.4</td>
<td>-3.9 (-5.4, -2.3)</td>
<td>-4.3 (-5.9, -2.7)</td>
<td></td>
</tr>
<tr>
<td>Symptom free days† (% days)</td>
<td>29.1</td>
<td>28.2</td>
<td>21.6</td>
<td>0.9 (-1.9, 3.5)</td>
<td>7.5 (4.6, 10.3)</td>
<td></td>
</tr>
<tr>
<td>Rescue medication use (inhalations/24 hours)</td>
<td>-1.40</td>
<td>-1.18</td>
<td>-0.93</td>
<td>-0.22 (-0.33, -0.11)</td>
<td>-0.46 (-0.57, -0.35)</td>
<td></td>
</tr>
</tbody>
</table>

† Mean change from mean of run-in to mean of the treatment period; mPEF – morning peak expiratory flow; ePEF – evening peak expiratory flow; FEV₁ – forced expiratory volume in 1 second; ∆ day and night with no symptoms and a night with no awakenings.

Table 5: Secondary efficacy variables for Study 668

<table>
<thead>
<tr>
<th>Variable†</th>
<th>Symb. maintenance + reliever</th>
<th>Bud. + terb prn</th>
<th>Symb maintenance + reliever v Bud + terb prn</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPEF (L/min)</td>
<td>34.2</td>
<td>13.9</td>
<td>20.3 (16.5, 24.1)</td>
</tr>
<tr>
<td>ePEF (L/min)</td>
<td>21.8</td>
<td>7.9</td>
<td>14.0 (10.4, 17.5)</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>0.19</td>
<td>0.09</td>
<td>0.100 (0.071, 0.130)</td>
</tr>
<tr>
<td>Total asthma symptom score (0-6)</td>
<td>-0.81</td>
<td>-0.61</td>
<td>-0.21 (-0.28, -0.13)</td>
</tr>
<tr>
<td>Nocturnal awakenings due to asthma (% nights)</td>
<td>-13.8</td>
<td>-10.6</td>
<td>-3.3 (-4.8, -1.7)</td>
</tr>
<tr>
<td>Symptom free days† (% days)</td>
<td>33.1</td>
<td>25.7</td>
<td>7.5 (4.5, 10.4)</td>
</tr>
<tr>
<td>Rescue medication use (inhalations/24 hours)</td>
<td>-0.99</td>
<td>-0.55</td>
<td>-0.44 (-0.54, -0.34)</td>
</tr>
</tbody>
</table>

† Mean change from mean of run-in to mean of the treatment period; mPEF – morning peak expiratory flow; ePEF – evening peak expiratory flow; FEV₁ – forced expiratory volume in 1 second; ∆ day and night with no symptoms and a night with no awakenings.

Table 6: Secondary efficacy variables for Study 667

<table>
<thead>
<tr>
<th>Variable†</th>
<th>Symb. maintenance + reliever</th>
<th>Bud. + terb prn</th>
<th>Symb maintenance + reliever v Bud + terb prn</th>
</tr>
</thead>
<tbody>
<tr>
<td>ePEF (L/min)</td>
<td>25.4</td>
<td>6.6</td>
<td>18.8 (13.3, 24.3)</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>0.21</td>
<td>0.06</td>
<td>0.148 (0.103, 0.193)</td>
</tr>
<tr>
<td>Total asthma symptom score (0-6)</td>
<td>-0.55</td>
<td>-0.38</td>
<td>-0.17 (-0.26, -0.07)</td>
</tr>
</tbody>
</table>

† More correct way of expressing dose
In a study in predominantly adult patients (<3% of patients were adolescents) with moderate to severe asthma (mean FEV1 66% predicted normal and reversibility 22.2%), Symbicort 100/6 (1 inhalation twice daily) was compared with Symbicort 400/12 than with a doubled dose of budesonide.

In conclusion, there was a greater improvement in lung function and asthma control with moderate to severe asthma (mean FEV1 66% predicted normal and reversibility 22.2%) Symbicort 100/6 than with a doubled dose of budesonide.

Symptom free days\( ^{4,5} \) (% 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

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

<table>
<thead>
<tr>
<th>Variable(^1)</th>
<th>Symb.</th>
<th>Bud.</th>
<th>Free comb.</th>
<th>Comparison p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPEF(^3) (L/min)</td>
<td>37.4</td>
<td>4.5</td>
<td>36.2</td>
<td>&lt;0.001 ns</td>
</tr>
<tr>
<td>ePEF (L/min)</td>
<td>30.7</td>
<td>-0.1</td>
<td>31.3</td>
<td>&lt;0.001 ns</td>
</tr>
<tr>
<td>FEV(_1) (^3) (L)</td>
<td>0.303</td>
<td>0.143</td>
<td>0.280</td>
<td>&lt;0.001 ns</td>
</tr>
<tr>
<td>Total asthma symptom score (0-6)</td>
<td>-0.62</td>
<td>-0.36</td>
<td>-0.66</td>
<td>0.0051 ns</td>
</tr>
<tr>
<td>Daytime symptom score (0-3)</td>
<td>-0.39</td>
<td>-0.19</td>
<td>-0.43</td>
<td>&lt;0.001 ns</td>
</tr>
<tr>
<td>Night-time symptom score (0-3)</td>
<td>-0.23</td>
<td>-0.18</td>
<td>-0.23</td>
<td>ns</td>
</tr>
<tr>
<td>Nocturnal awakenings due to asthma (% patients)</td>
<td>-14.4</td>
<td>-11.8</td>
<td>-13.1</td>
<td>ns</td>
</tr>
<tr>
<td>Symptom free days( ^{4,5} ) (% patients)</td>
<td>31.2</td>
<td>15.6</td>
<td>32.2</td>
<td>&lt;0.001 ns</td>
</tr>
<tr>
<td>Rescue medication use (inhalations/24 hours)</td>
<td>-1.08</td>
<td>-0.50</td>
<td>-1.20</td>
<td>&lt;0.001 ns</td>
</tr>
</tbody>
</table>

\(^1\) Adjusted mean change from mean of baseline to mean of the 12 week treatment period; \(^2\) Primary efficacy variable; mPEF – morning peak expiratory flow; ePEF – evening peak expiratory flow; FEV\(_1\) – forced expiratory volume in 1 second; \(^3\) mean of the last value during treatment; \(^4\) mean of the treatment average value; \(^5\) 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:
- budesonide pMDI 200 µg per actuation, administered as 2 actuations twice daily;
- 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.
Serial FEV1 measures over 12 hours were obtained in subsets of patients (N=491). In Study 001, efficacy was evaluated over 12 months using the co-primary efficacy endpoints of post dose FEV1 and number of severe COPD exacerbations compared to placebo and eformoterol by 24% (p=0.029) and 26% (p=0.009). 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 FEV1, 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 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 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 FEV1, over the treatment period.

Primary endpoints:
• Symbicort Rapihaler 100/6 produced a significantly greater change in postdose FEV1 compared to placebo (LS mean = 0.16 L; p=0.001); however the change in pre-dose FEV1, 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 FEV1 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 FEV1 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 FEV1 measures over 12 hours were obtained in a subset of patients (N=491). The median time to onset of bronchodilation (>15% improvement in FEV1) was seen within 5 minutes at the end of treatment time point in patients receiving Symbicort Rapihaler 200/6 (N=121). Maximum improvement in FEV1 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: Postdose 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). Predose 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 predose 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=0.039) 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 (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 Turbuhaler is indicated for the treatment of asthma where use of a combination (inhaled corticosteroid and long acting β2-agonist) is appropriate. This includes:
• patients who are symptomatic on inhaled corticosteroid therapy
• patients who are established on regular long acting β2-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 (FEV1 ≤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 and international 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 maintenance therapy).*

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

Clinically important disturbances of the HPA axis and/or adrenal insufficiency induced by severe stress (eg trauma, surgery, infection in particular gastroenteritis or other conditions associated with severe electrolyte loss) may be related to inhaled budesonide in specific patient populations. These are patients with prolonged treatment at the highest recommended dose of 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 glucocorticoid 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/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 400µg b.i.d for 1 month, 200µg bd for 5 months and 100µg b.i.d for 12 months and the dose of disodium cromoglycate 10mg t.i.d. The clinical significance of this result remains uncertain.

**Growth:**

Long term studies show that children treated with inhaled budesonide ultimately achieve adult target height. However, an initial reduction of growth velocity (approximately 1cm) has been observed and is generally 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 (e.g. inadequately controlled hyperthyroidism), eformoterol should be used with caution.

**Cardiovascular disorders**

β₂-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 β₂-adrenoceptor agonists.

Patients with pre-existing cardiovascular conditions may be at greater risk of developing adverse cardiovascular effects following administration of β₂-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 β₂-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 β₂-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.

**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 in a female rat dosed orally at 0.13 mg/kg/day for two years. The effects observed are expected findings with high dose exposure to β₂-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 18μg daily dose).

Some carcinogenic 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 a β₂-agonist (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. In a 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-interleukin 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.

Teratological study 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 beta-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, e.g. 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. 

**β1-receptor blocking agents:**

β1-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:**

Hyponatremia may result from β2-agonist therapy and may be potentiated by concomitant treatment with xanthine derivatives, mineralocorticosteroids, and diuretics (see “Precautions - Hyponatremia” 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 (e.g. terfenadine, astemizole).

**ADVERSE REACTIONS**

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 β2-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**

<table>
<thead>
<tr>
<th>Common 1 to 10%</th>
<th>Cardiac disorders</th>
<th>Palpitations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Infections and infestations</td>
<td>Candida infections in the oropharynx</td>
</tr>
<tr>
<td></td>
<td>Nervous system disorders</td>
<td>Headache, tremor</td>
</tr>
<tr>
<td></td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>*Mild irritation in the throat, coughing, hoarseness</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Uncommon 0.1 to 1%</th>
<th>Cardiac disorders</th>
<th>Tachycardia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gastrointestinal disorders</td>
<td>Nausea, diarrhoea</td>
</tr>
<tr>
<td></td>
<td>Metabolism and nutrition disorders</td>
<td>Weight gain</td>
</tr>
<tr>
<td></td>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Muscle cramps</td>
</tr>
<tr>
<td></td>
<td>Nervous system disorders</td>
<td>Dizziness, bad taste, thirst, tiredness</td>
</tr>
<tr>
<td></td>
<td>Psychiatric disorders</td>
<td>Agitation, restlessness, nervousness, sleep disturbances</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rare 0.01 to 0.1%</th>
<th>Immune system disorders</th>
<th>Immediate and delayed hypersensitivity reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cardiac disorders</td>
<td>Cardiac arrhythmias e.g. atrial fibrillation, supraventricular tachycardia, extrasystoles</td>
</tr>
<tr>
<td></td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Bronchospasm</td>
</tr>
<tr>
<td></td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Skin bruising</td>
</tr>
<tr>
<td></td>
<td>Metabolism and nutrition disorders</td>
<td>Hypokalaemia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Very Rare &lt; 0.01%</th>
<th>Cardiac disorders</th>
<th>Angina pectoris</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Endocrine disorders</td>
<td>Signs or symptoms of systemic glucocorticosteroid effects, e.g. hypofunction of the adrenal gland</td>
</tr>
<tr>
<td></td>
<td>Metabolism and nutrition disorders</td>
<td>Hyperglycaemia</td>
</tr>
<tr>
<td></td>
<td>Psychiatric disorders</td>
<td>Depression, behavioural disturbances</td>
</tr>
<tr>
<td></td>
<td>Vascular disorders</td>
<td>Variations in blood pressure</td>
</tr>
</tbody>
</table>

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

Treatment with β1-sympathomimetics may result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies.

**DOSE 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 not normally 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):

**Symbicort 100/6**
1 - 2 inhalations of Symbicort 100/6 twice daily. The maximum recommended daily maintenance dose is 4 inhalations (2 inhalations twice daily corresponding to 400µg budesonide / 24µg eformoterol).

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

**Symbicort 400/12**
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 1600µg budesonide / 48µg 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 800µg budesonide / 24µg eformoterol).

Symbicort 400/12
1 inhalation of Symbicort 400/12 twice daily. The maximum recommended daily dose is 2 inhalations (corresponding to 800µg budesonide / 24µg 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 β2-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 120µg 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**

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>
<thead>
<tr>
<th>Symbicort</th>
<th>Metered dose (µg)</th>
<th>Corresponding dose delivered to patient (µg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmicort (budesonide)</td>
<td>Oxis (eformoterol)</td>
<td>Budesonide</td>
</tr>
<tr>
<td>100 / 6</td>
<td>100</td>
<td>6</td>
</tr>
<tr>
<td>200 / 6</td>
<td>200</td>
<td>6</td>
</tr>
<tr>
<td>400/12</td>
<td>400</td>
<td>12</td>
</tr>
</tbody>
</table>

*not possible to measure metered dose for Symbicort

**doses referred to in Symbicort publications**

Symbicort 100/6 and 200/6 are available as a 60 or 120 dose Turbuhaler. Symbicort 400/12 is available as a 120 dose double Turbuhaler pack.

**Storage conditions**

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

**POISON SCHEDULE OF THE DRUG**

Prescription only medicine (Schedule 4).

**NAME AND ADDRESS OF THE SPONSOR**

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Rd, North Ryde
NSW 2113 Australia

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Date of TGA approval letter: 13 August 2010
AZAE0212.SYM000184.WL180131 0211

*Please note changes in Product Information