





ATC codes: **R03AK07**

Indication	Asthma ICD11 code: CA23
INN	Budesonide + formoterol
Medicine type	Chemical agent
List type	Core
Formulations	Respiratory > Inhalation > dry powder: 100 µg + 6 µg per dose ; 200 µg + 6 µg per dose
EML status history	First added in 2017 (TRS 1006)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	Medicines within the same pharmacological class can be used
Therapeutic alternatives limitations	A square box applies to each component of the combination
Patent information	Patents have expired in most jurisdictions Read more about patents . 
Wikipedia	Budesonide + formoterol 
DrugBank	Budesonide  , Formoterol 

Expert Committee recommendation

The Expert Committee noted the evidence of greater benefit and the acceptable safety profile of the budesonide + formoterol combination inhaler. The Expert Committee recommended the addition of budesonide + formoterol combination inhaler to the core list of EML (with a square box indication) as “single-inhaler therapy” for the management of asthma, in which a single inhaler can be used as regular therapy (“maintenance therapy”) to control the disease in patients who have failed first-line therapy. The Expert Committee did not recommend the addition of budesonide + formoterol combination inhaler to the core list of the EMLc. The Committee noted concerns in relation to safety concerns with high doses of inhaled steroids in children. The Committee noted the risks and safety concerns of the use of long-acting beta-2 agonist bronchodilators in rescue therapy and therefore did not recommend the use of budesonide + formoterol combination inhaler as rescue therapy, especially in children.

Background

The application requested addition of budesonide + formoterol combination inhaler to the core list of EML and EMLc as single-inhaler therapy for the management of asthma, in which a single inhaler can be used both as regular therapy to control the disease and as rescue therapy to relieve acute asthma symptoms – “maintenance and reliever therapy”. Listing was requested with a square box symbol, representing alternative combination formulations containing an inhaled corticosteroid and a beta-2 agonist bronchodilator. Single-ingredient inhalers containing budesonide are currently included on the EML and EMLc. The EML also includes the ICS beclometasone as a single-ingredient inhaler. Salbutamol, a short-acting beta-2 agonist (SABA), is the only beta-2 agonist currently listed on the EML and EMLc. Formoterol is a long-acting beta-2 agonist (LABA). Both salbutamol and formoterol are full (as opposed to partial) beta-2 agonists, with the rapid onset of action essential for rescue/reliever therapy of acute

asthmatic episodes (1).

Public health relevance

The Global Asthma Network's Global asthma report 2014 estimates that asthma affects approximately 334 million people globally and is the 14th most important disorder in terms of global years lived with disability. Although effective therapy exists for treating asthma, it is not currently available to most individuals with asthma living in low-income countries (2).

Benefits

The application presented the results of two systematic reviews of the comparative effectiveness of single-inhaler therapy with budesonide + formoterol as maintenance and reliever therapy versus current best practice (3) and versus combination inhaler maintenance therapy (4). The combination of budesonide + formoterol as single-inhaler therapy was assessed against treatment of a control group with inhaled steroids and a separate reliever inhaler in 13 trials involving 13 152 adults; one of these trials also involved 224 children under 12 years of age (3). Among adults not well controlled on ICS, there was no significant advantage for single-inhaler therapy over current best practice in terms of a reduction in exacerbations needing hospital admission (odds ratio (OR) 0.81; 95% confidence interval (CI) 0.45–1.44; low-quality evidence due to risk of bias and imprecision). Single-inhaler therapy significantly reduced the risk of exacerbations requiring treatment with oral corticosteroids (OR 0.83; 95% CI 0.70–0.98; moderate-quality evidence due to risk of bias). Most trials found a reduction of total ICS dose when single-inhaler therapy was used. The study that included children compared single-inhaler therapy with higher-dose budesonide. Among patients using single inhaler therapy, there was a significant reduction in the number experiencing exacerbations that required increased ICS or other treatment (OR 0.33; 95% CI 0.1–0.77). Single-inhaler therapy with budesonide + formoterol as maintenance and reliever therapy was compared with higher-dose ICS/LABA combination inhaler maintenance therapy plus SABA reliever in four studies involving 9130 adolescent and adult patients with asthma (4). The number of people who had at least one severe exacerbation requiring hospitalization or an emergency outpatient visit was significantly lower in the single-inhaler therapy group (OR 0.72; 95% CI 0.57–0.90; high-quality evidence). The number of people who had an exacerbation requiring a course of oral steroids was also significantly lower in the single-inhaler therapy group (OR 0.75; 95% CI 0.65–0.87; high-quality evidence). Nocturnal awakenings were significantly reduced in the single-inhaler therapy group.

Harms

Evidence for the safety of budesonide was evaluated at the time of listing and was not discussed further. Formoterol shares the known side-effects of beta-2 adrenergic receptor agonists, including increased heart rate and palpitations, transient decrease in arterial partial pressure of oxygen (PaO₂) in patients with airway obstruction, increased glycogenolysis and hyperglycaemia, hypokalaemia, and dose-related tremor (5). The application presented the results of a systematic review of 20 trials involving 10 578 adolescents and adults and seven studies of 2788 children and adolescents to assess the risk of fatal and non-fatal serious adverse events in individuals with chronic asthma given regular formoterol with ICS over 12 weeks versus the same dose of ICS alone (6). Among adults, six deaths occurred in the ICS + formoterol group versus one in the ICS alone group; the difference was not statistically significant (OR 3.56; 95% CI 0.79–16.03, low-quality evidence). In adults and adolescents, there was no difference in the proportions of non-fatal serious adverse events between treatment groups (OR 0.98; 95% CI 0.76–1.27; moderate-quality evidence). Among children, there was weak, moderate-quality evidence of an increase in non-fatal serious adverse events in the formoterol + ICS group (OR 1.62; 95% CI 0.80–3.28). Asthma-related serious events were lower in the formoterol + ICS arm among adults (OR 0.49; 95% CI 0.28–0.88, moderate-quality evidence), but a greater number were reported in children. However, this finding was not statistically significant (OR 1.49; 95% CI 0.48–4.61; low-quality evidence). Both systematic reviews found there to be no significant differences in fatal or non-fatal serious adverse events between treatment groups (3, 4).

Cost / cost effectiveness

The application estimates the annual treatment costs for low-dose budesonide + formoterol in the United Kingdom to be £181–230 and of high-dose budesonide + formoterol to be £363–461. Two studies assessed the cost-effectiveness of budesonide + formoterol versus ICS alone (9, 10). In both studies patients receiving budesonide + formoterol therapy had more symptom-free days and fewer exacerbation events than patients given budesonide or fluticasone alone. In one study, the budesonide + formoterol therapy cost slightly more than ICS alone. The incremental cost-effectiveness ratio (ICER) was €2.32 (US\$ 2.62) per symptom-

free day gained (9). In the second study, the budesonide + formoterol therapy was dominant (more effective, and less expensive at €80 or US\$ 90 less per patient over 12 weeks) (10). Cost-effectiveness of the single-inhaler therapy was also assessed in other several studies versus a higher-dose ICS plus SABA reliever therapy, or a similar ICS/LABA therapy plus SABA or LABA reliever therapy, or a higher-dose ICS/LABA therapy plus SABA reliever therapy. In most comparisons, the budesonide + formoterol single-inhaler therapy was more effective at lower total cost and was thus dominant (11).

WHO guidelines

There are no current WHO guidelines for the treatment of asthma. Recommendations of the Global Initiative for Asthma (GINA) in Global strategy for asthma management and prevention are for low-dose ICS + formoterol as both maintenance and reliever therapy for moderate and severe asthma in adults and adolescents (7). The British guidelines on the management of asthma state that it is generally considered that combination ICS + LABA inhalers will aid adherence and have the advantage of ensuring LABA is not administered without ICS. The guidelines also state that efficacy studies have revealed no difference in efficacy between giving ICS and LABA in combination and giving them separately in circumstances where there is good adherence. The guidelines recommend that patients taking budesonide + formoterol as rescue/reliever therapy at least daily on a regular basis should be reviewed (8).

Availability

Budesonide + formoterol is available as Symbicort Turbuhaler® (AstraZeneca) and DuoResp Spiromax® (TEVA Pharma B.V)

Other considerations

Current British guidelines recommend the single-inhaler therapy at steps 2-3 of treatment and higher but do not address the question of asthma management in resource-limited settings. The role of single-inhaler therapy should be investigated for all levels of asthma severity in resource-limited settings (12).

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