Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2622

budesonide/formoterol (Symbicort® Turbohaler®) 200 micrograms/6 micrograms/inhalation, inhalation powder

AstraZeneca UK Ltd

05 April 2024

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and, following review by the SMC executive, advises NHS Boards and Area Drug and Therapeutics Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

budesonide/formoterol (Symbicort® Turbohaler®) is accepted for restricted use within NHSScotland.

Indication under review: As reliever therapy for adults and adolescents (12 years and older) with mild asthma.

SMC restriction: for use in patients who would otherwise receive low dose inhaled corticosteroid (ICS) maintenance therapy plus short-acting beta-2 adrenoceptor agonist (SABA) as needed.

Budesonide/formoterol used as needed was non-inferior to an ICS maintenance treatment plus a SABA used as needed for the annualised rate of severe asthma exacerbations, and it was superior to a SABA used as needed for the outcome of well-controlled asthma weeks.

Vice Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

This treatment combines budesonide and formoterol. Budesonide is a glucocorticosteroid that when inhaled reduces inflammation and symptoms in the lungs with fewer side effects compared to systemic steroids; its exact anti-inflammatory mechanism is unknown. Formoterol, a long-acting beta-2 adrenoceptor agonist (LABA), quickly relaxes airway muscles, offering rapid and long-lasting relief from airway obstruction, with a dose-dependent bronchodilating effect. This dual action medication can be used as both a preventive and a reliever for asthma. [1]

Budesonide plus formoterol is licensed in other asthma and chronic obstructive pulmonary disease indications; however, the indication under review is the first combination of an inhaled corticosteroid (ICS) plus a LABA for use only as reliever therapy for adults and adolescents with mild asthma.

When budesonide plus formoterol is used as a reliever, patients are recommended to take one inhalation as needed in response to symptoms, with the option for additional doses, if necessary, not exceeding six inhalations per occasion. A total daily dose of more than eight inhalations is not normally needed (up to 12 inhalations may be used temporarily). Patients should be assessed at regular intervals. [1]

1.2. Disease background

Asthma, a commonly occurring heterogeneous disease, is typically characterised by chronic inflammation of the airways. It is defined by a history of respiratory symptoms like shortness of breath and chest tightness, varying over time and in intensity, along with variable expiratory airflow limitation that may become persistent. Mild asthma is defined by Global Initiative for Asthma (GINA) as well-controlled asthma with low-intensity treatment (for example as needed low dose ICS-formoterol or low dose ICS plus as needed short-acting beta-2 adrenoceptor agonists [SABA]). Unfortunately, mild asthma is often wrongly interpreted as meaning low risk, leading to inadequate ICS-containing treatment, despite up to 30% of asthma exacerbations and deaths occurring in those with infrequent symptoms. [2]

1.3. Company proposed position

The submitting company has requested that budesonide plus formoterol is restricted for use in patients who would otherwise receive low dose ICS maintenance therapy (without an additional controller) plus SABA as needed.

1.4. Treatment pathway and relevant comparators

According to most recent UK guidelines, which are currently undergoing review, an inhaled SABA is prescribed as short-term reliever therapy for all patients with symptomatic asthma; and ICSs, generally administered twice daily, are recommended as the primary preventive medicine for both adults and children to achieve overall treatment goals. Based on symptom control, add-on therapy can be considered. [3]

The GINA 2023 report notes that relying solely on SABA for asthma treatment in adults and adolescents is not recommended for safety reasons. Instead, patients should receive ICS-

containing treatment to reduce the risk of serious exacerbations and control symptoms. These guidelines suggest ICS-containing treatment can be delivered either through regular daily treatment or, in adults and adolescents with mild asthma, with as needed low dose ICS-formoterol taken whenever needed for symptoms relief. [2] Summaries of product characteristics of SABA-only reliever medicines were recently updated to highlight that the over-use of SABA may mask the progression of the underlying disease and contribute to deteriorating asthma control, leading to an increased risk of severe asthma exacerbations and mortality.[4]

Clinical experts consulted by SMC confirmed that, in the proposed positioning, the predominant treatment consists of low dose ICS maintenance plus SABA used as needed. Though some of the experts noted some patients solely rely on SABA as needed.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Key evidence to support the efficacy and safety of budesonide plus formoterol as reliever therapy for adults and adolescents with mild asthma comes from SYGMA 1 and 2. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant studies [5-9]

Criteria	SYGMA 1	SYGMA 2
Study design	Phase 3, randomised, placebo-controlled, double blind, international study.	
Eligible patients	• ≥12 years. • Diagnosis of asthma according to GINA criteria with a documented history of at least 6 months. • Uncontrolled on inhaled short-acting bronchodilator(s) as needed as judged by the investigator for the last 30 days before visit two, or controlled on mono-maintenance therapy - with low stable dose inhaled glucocorticoid or LTRA - in addition to as needed use of inhaled short-acting bronchodilator(s), as judged by the investigator for the last 30 days prior to visit two. • Based on lung function tests, patients pre-treated with: ○ an inhaled short-acting bronchodilator only had pre-bronchodilator FEV_1 ≥60% predicted and post-bronchodilator FEV_1 ≥80% predicted according to the ERS guidelines. ○ low dose inhaled glucocorticoid or LTRA medication in addition to inhaled short-acting bronchodilator(s) had pre-bronchodilator FEV1 ≥80% predicted according to the ERS guidelines. • Reversible airway obstruction according to a reversibility test. • For randomisation: use of terbutaline as needed due to asthma symptoms on at least 3 separate days during the last week of the run-in period.	
Treatments	• Twice daily placebo and budesonide plus formoterol 200/6 micrograms as needed (n=1,277) • Twice daily budesonide (200 micrograms) maintenance therapy plus the SABA terbutaline (0.5 mg) as needed (1,282) • Twice daily placebo plus terbutaline (0.5 mg) as needed (n=1,277)	• Twice daily placebo and budesonide plus formoterol 200/6 micrograms as needed (n=2,089) • Twice daily budesonide (200 micrograms) maintenance therapy plus terbutaline (0.5 mg) as needed (n=2,087)
Randomisation	Equal randomisation stratified by country and pre-study treatment.	Equal randomisation stratified by site.
Primary outcome	Well-controlled asthma weeks was used to test superiority between as needed budesonide plus formoterol versus as needed terbutaline.	Annual severe asthma exacerbation rate was used to first test non-inferiority then superiority between as needed budesonide plus formoterol

	A week was considered as a well-controlled asthma week if the conditions below were fulfilled:
	• no nighttime awakenings due to asthma,
	• no additional inhaled and/or systemic glucocorticosteroid treatment due to asthma,
	• and at least two of the following are fulfilled:
	  ○ no more than 2 days with a daily asthma symptom score >1,
	  ○ no more than 2 days of as needed medication use up to a maximum of 4 occasions per week (multiple occasions per day should be regarded as separate occasions),
	  ○ morning Peak Expiratory Flow ≥80% of Predicted Normal every day.
		versus budesonide twice daily plus as needed terbutaline.
		A severe exacerbation was defined as a deterioration of asthma requiring any of the following:
		• Use of systemic glucocorticosteroids for at least 3 days or of an injection of depot glucocorticosteroids due to asthma worsening.
		• Inpatient hospitalisation.
		• Emergency room visit, or other urgent unscheduled health care visit due to asthma that required systemic glucocorticosteroids.

Selected secondary outcomes	• Well-controlled asthma weeks (for SYGMA 1: non-inferiority test between as needed budesonide plus formoterol versus budesonide twice daily plus as needed terbutaline). • Annual rate of severe exacerbations (for SYGMA 1). • Change in Pre-Bronchodilator FEV_1 from baseline. • ACQ-5 questionnaire contains five questions on patients' symptoms, which are assessed on a 7-point scale from 0 (representing good control) to 6 (representing poor control). • Number of inhalations of as needed medication (outcome used in the economic model).	
Statistical analysis	Efficacy analysis set: all randomised patients receiving any investigational product, irrespective of their protocol adherence and continued participation in the study.	
	Hierarchical testing procedure: testing first the comparison of budesonide plus formoterol used as needed versus terbutaline used as needed (superiority test), and then testing budesonide plus formoterol used as needed versus twice daily budesonide plus as needed terbutaline (non-inferiority test)	Hierarchical testing procedure: testing first the primary outcome for non-inferiority, then for superiority.

Abbreviations: ACQ-5: Asthma Control Questionnaire 5-item version; ERS: European Respiratory Society; FEV_1: forced expiratory volume in 1 second; GINA: Global Initiative for Asthma; LTRA: leukotriene receptor antagonist; SABA: short acting beta-2 adrenoceptor agonist.

SYGMA 1 showed that for the outcome of well-controlled asthma weeks budesonide plus formoterol used as needed was superior to terbutaline (a SABA) used as needed, meeting its primary outcome; but it was inferior to budesonide maintenance treatment plus SABA as needed.[5] SYGMA 2 showed budesonide plus formoterol used as needed was non-inferior to budesonide maintenance therapy plus as needed SABA for the annualised rate of severe asthma exacerbations, meeting its primary outcome. Budesonide plus formoterol used as needed was not shown to be superior to budesonide maintenance therapy plus SABA as needed in reducing the annual severe asthma exacerbation rate (rate ratio 0.97; 95% confidence interval [CI] 0.78 to 1.20; p=0.75). [8] Primary and selected secondary outcomes results are summarised in the table 2.2.

Table 2.2. Primary and selected secondary outcomes' results. [5-10]

	SYGMA 1			SYGMA 2	
	budesonide plus formoterol as needed	**budesonide maintenance therapy plus terbutaline as needed**	**terbutaline as needed**	**budesonide plus formoterol used as needed**	**budesonide maintenance therapy plus terbutaline as needed**
Well-controlled asthma week (SYGMA 1 primary outcome – comparison with terbutaline as needed)					
n	1,269	1,279	1,272		
WCAW per patient, mean percentage	34%	44%	31%	-	
budesonide plus formoterol odds ratio[a]	-	0.64	1.14		
95% CI		0.57 to 0.73[b]	1.00 to 1.30, p-value = 0.046		
Annual rate of severe exacerbations (SYGMA 2 primary outcome)					
n	1,277	1,282	1,277	2,084	2,083
Annual rate of severe exacerbations	0.07	0.09	0.20	0.11	0.12
Rate ratio between as needed budesonide plus formoterol and other regimen[c]	-	0.83	0.36	0.97	
95% CI	-	0.59 to 1.16	0.27 to 0.49	NA to 1.16[d]	
ACQ-5 [e]					
n	1,241	1,237	1,225	1,963	1,947
Mean change from baseline	-0.33	-0.48	-0.17	−0.35	−0.46
Estimate for difference	-	0.149	-0.154	0.11	
95% CI	-	0.101 to 0.198	-0.203 to -0.105	0.07 to 0.15	
Pre-bronchodilator FEV_1[f]					
n	1,261	1,261	1,243	2,079	2,075
Mean change from baseline, mL	65.0	119.3	11.2	104.0	136.6
Estimate for difference, mL	-	-54.3	53.8	−32.6	
95% CI	-	-78.8 to -29.8	29.1 to 78.5	−53.7 to −11.4	
Number of inhalations of as needed medication					
n	1,276	1,281	NR	2,089	2,084
Mean number of inhalations of as needed medication per day, SD	0.47 (0.51)	0.39 (0.56)[g]	NR	0.52 (0.55)	0.49 (0.70)

Abbreviations: ACQ-5: Asthma Control Questionnaire 5-item version; CI: confidence interval; FEV_1: Forced Expiratory Volume in 1 Second; n: number of participants; NA: not applicable; NR: not reported; SD: standard deviation; WCAW: well controlled asthma weeks.
Notes: a) Odds ratio >1 indicates the odds of having a week with well-controlled asthma during the 52-week trial period were higher in the budesonide plus formoterol group.
b) Concluding non-inferiority of budesonide plus formoterol as needed versus budesonide maintenance therapy plus SABA as needed was possible only if the lower limit of the 95% CI was ≥0.8.
c) A risk ratio <1 indicates a decreased risk for the budesonide plus formoterol group.
d) Non-inferiority test results. Concluding non-inferiority of budesonide plus formoterol used as needed versus budesonide maintenance therapy plus as needed SABA was possible only if the upper 1-sided 95% confidence limit of the rate-ratio was < 1.2.
e) The minimal clinically important difference in ACQ-5 score is 0.5 units. An increased ACQ-5 score (≥ 0.5) shows a worsened asthma control.
f) Authors noted the approximate minimal clinically important difference is not well established but is likely to be 100 to 200 mL.
g) Inhalation number reflects only the SABA (terbutaline) as needed therapy.

2.2. Evidence to support the positioning proposed by the submitting company

The key studies' populations represent the proposed positioning population.

2.3. Health-related quality of life outcomes

In both SYGMA studies, Health Related Quality of Life (HRQoL) was assessed using the Asthma Quality of Life Questionnaire (AQLQ, Standardised Version), which includes 32 questions, all assessed on a 7-point Likert scale from 1 to 7, with higher values indicating better HRQoL. There were four domains: activity limitation, symptoms, emotional function, and exposure to environmental stimuli. A difference of 0.5 in the overall AQLQ score is defined as minimally clinically important difference.

Results suggest a trend for better QoL improvement in the budesonide maintenance group compared with as needed budesonide plus formoterol; however, differences were not clinically meaningful. [5, 8]

2.4. Supportive studies

Novel START and PRACTICAL were two open-label, randomised, active-controlled, 52-week studies. [11, 12] The submitting company reported the trial was conducted to reflect real-world treatment practices, with all patients randomised in an open-label manner to an active treatment.

In the international Novel START study, patients were aged 18 to 75 years with asthma solely treated with a SABA in the past 3 months, and they reported use of the SABA on at least two occasions, but on an average of two or fewer occasions per day in the previous 4 weeks. There was no minimum requirement for SABA use among patients who had had a severe exacerbation in the previous 12 months. Patients (n=675) with asthma were randomly assigned to; as needed salbutamol 200 micrograms (n = 226), budesonide 200 micrograms one inhalation twice daily plus as needed salbutamol 200 micrograms (n= 227), or as needed budesonide plus formoterol 200 micrograms/6 micrograms (n = 222). The annualised rate of asthma exacerbations (primary outcome) with budesonide plus formoterol was not statistically significantly different versus budesonide plus as needed salbutamol (absolute rate 0.195 versus 0.175 respectively; relative rate 1.12 [95% CI 0.70 to 1.79]; p= 0.65). The number of severe exacerbations was lower with budesonide plus formoterol versus budesonide plus as needed salbutamol (9 versus 21; relative

risk 0.44 [95% CI 0.20 to 0.96]). Across all study visits, ACQ-5 score was higher (representing poorer asthma control) in the budesonide–formoterol group than in the budesonide maintenance group, though differences were not clinically meaningful (mean difference 0.14 [95% CI 0.05 to 0.23]). The FEV_1 in the budesonide plus formoterol group did not seem to differ significantly from the FEV_1 from the budesonide maintenance group (mean difference across all study visits 0.004 L [95% CI −0.03 to 0.04]). [11] The mean number of reliever inhalations as required per day appeared similar in the budesonide plus formoterol as needed group compared with the low dose budesonide maintenance therapy plus SABA group (0.53 [SD 0.54] vs 0.52 [SD 1.03]).[10]

In the multicentre PRACTICAL study, conducted in New Zealand, patients (n = 890) were aged 18 to ≤75 years with asthma who received SABA with or without low to moderate dose ICS in the past 3 months. Patients were randomly assigned to as needed budesonide plus formoterol 200 micrograms/6 micrograms (n=440) or maintenance budesonide 200 micrograms twice daily plus as needed terbutaline 0.5mg (n=448). The number of severe exacerbations per patient, per year (primary outcome) were statistically significantly lower with as needed budesonide plus formoterol versus budesonide plus as needed terbutaline (absolute rate per patient per year: 0·12 versus 0·17; relative rate 0·69 [95% CI 0·48 to 1·00]; p=0·049). Across all study visits, ACQ-5 score and FEV_1 with budesonide plus formoterol did not seem to differ from budesonide maintenance plus terbutaline (mean ACQ-5 difference 0·06 [95% CI –0·005 to 0·12], and mean FEV_1 difference 0·006 L [95% CI –0·026 to 0·04]). The mean number of reliever inhalations as required per day was higher in the budesonide plus formoterol reliever therapy group compared with the low dose ICS (budesonide) maintenance therapy plus SABA as needed treatment group (0.9 [standard deviation 0.7] vs 0.5 [standard deviation 0.6]). [12]

There are no direct data comparing budesonide plus formoterol with other ICSs maintenance therapy, which may be used in practice such as beclomethasone, plus a SABA as needed. The submitting company conducted a systematic literature review (SLR) of SLRs and meta-analyses to assess whether medicines used to treat mild asthma have equivalent efficacy (that is whether all ICSs are clinically equivalent and whether the different SABAs are clinically equivalent). Ten studies were identified (three systematic reviews with a meta-analysis, two meta-analysis, and five systematic reviews). All assessed the relative efficacy and safety of ICSs. Efficacy outcomes considered were different indicators of asthma exacerbations and asthma symptom control. Actual measures varied between studies. Across the wide range of ICS comparisons made, few demonstrated differences in efficacy and there was no consistently superior treatment across each outcome. Additionally, differences that were observed appeared small and may not be clinically meaningful. Therefore, the submitting company concluded all ICSs for the management of mild asthma appeared to be clinically equivalent. There was insufficient evidence to draw conclusions on the equivalence of as needed SABAs. Clinical experts consulted by the submitting company reported that terbutaline and salbutamol can be considered clinically equivalent. [13] In summary, the submitting company suggested that budesonide plus formoterol reliever therapy and regular low dose ICS (including beclomethasone) plus as needed SABA are clinically equivalent.

3. Summary of Safety Evidence

In the pooled analysis of SYGMA 1 and 2, any treatment-emergent adverse event (AE) was reported by 41% (1,372/3,366) of patients in the as needed budesonide plus formoterol group and 42% (1,431/3,369) in the budesonide twice daily as maintenance plus as needed terbutaline group. Patients with a reported serious AE were 3.1% versus 3.3% and patients an AE leading to discontinuation was 0.7% versus 1.1%. [14]

The most frequently reported emergent AEs of any grade with an incidence >2% in the as needed budesonide plus formoterol group versus the budesonide twice daily as maintenance plus as needed terbutaline group were: viral upper respiratory tract infection (URTI; 6.8% versus 7.5%), any URTI (4.5% versus 5.4%), asthma (when symptoms met serious AE or discontinuation due to AE criteria or the event was new to the patient or inconsistent with the pre-existing asthma history, as judged by the investigator; 4.0% versus 4.6%), pharyngitis (2.5% versus 3.3%), bronchitis (2.9% versus 3.4%), headache (2.2% versus 2.4%), rhinitis allergic (2.3% versus 1.9%). [14]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- A large clinical trial programme suggests budesonide plus formoterol is an effective reliever therapy in patients with mild asthma.
- This is the first inhaler containing both an ICS and a beta-2 adrenoceptor agonist with rapid and long-lasting effects with a marketing authorisation for use as reliever therapy for mild asthma.

4.2. Key uncertainties

- The submitting company concluded the clinical trial program (SYGMA 1, SYGMA 2, Novel START and PRACTICAL) results demonstrated clinical equivalence of budesonide plus formoterol reliever therapy and low dose ICS (budesonide) maintenance therapy plus SABA as needed in patients with mild asthma. However, the studies showed mixed results across different clinical outcome measures. This heterogeneity in the results may be partially explained by clinical and methodological differences, such as the study designs, severity of asthma and outcome measure. It suggests that while budesonide plus formoterol as a reliever therapy may be an effective alternative option, its effectiveness can differ depending on the outcome measure considered.
- Of note, some of the clinical experts consulted by SMC noted that there is variability in adherence to ICS maintenance treatment in clinical practice. Compliance with ICS treatment also varied across clinical studies, and potentially exceeded typical adherence outside of a clinical study setting. This raises some generalisability concerns.
- Based on an SLR and clinical expert opinion, the submitting company suggested that budesonide plus formoterol reliever therapy has equivalent efficacy and safety versus regular low dose beclomethasone plus as needed SABA. There were limitations with the SLR, such as the methodological heterogeneity across studies; however, the company's conclusions seem

reasonable. Clinical experts consulted by SMC considered the assumption of clinical equivalence to be reasonable.

- The long-term effects of as needed budesonide plus formoterol regimens on airways inflammation and lung function are not determined from the presented data.
- The marketing authorisation has been granted in adults and adolescents with mild asthma. The GINA 2023 report defined mild asthma as asthma that is well controlled with low-intensity treatment, that is as needed low dose ICS plus formoterol, or low dose ICS plus as needed SABA.[2] In the key studies, patients had asthma for at least 6 months and were uncontrolled on as needed short-acting bronchodilator or controlled on mono-maintenance therapy with low stable dose ICS (or leukotriene receptor antagonist [LTRA]) in addition to as needed bronchodilator. This patient population seemed to adequately represent the proposed positioning population. Though, it is uncertain if this definition of mild asthma would be generalisable to Scottish practice.
- No data were presented for budesonide plus formoterol use as initial therapy in patients with mild asthma naive to treatment.

4.3. Clinical expert input

Clinical experts consulted by SMC generally considered that this medicine fills an unmet need and that it is a therapeutic advancement as the first inhaler with marketing authorisation as reliever therapy for mild asthma combining an ICS and a beta-2 adrenoceptor agonist with rapid and long-lasting bronchodilating effects. One expert noted the standard treatment in patients with mild asthma with fixed dose ICS and SABA as reliever therapy used as needed is associated with a high incidence of ICS under-dosing and SABA over-use due to tendency to stop ICS when patients are well and failure to recognise the need to re-start when they are needing to use more SABA.

4.4. Service implications

Clinical experts consulted by SMC considered that the introduction of this medicine would not have negative impact on the patient and/or service delivery.

5. Summary of Patient and Carer Involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from Asthma + Lung UK Scotland, which is a registered charity.
- Asthma + Lung UK Scotland has received 3.1% pharmaceutical company funding in the past two years, including from the submitting company.
- Asthma is one of the most common and debilitating long-term health conditions, affecting people of all ages, from children to the elderly. Many people with asthma struggle to live a normal life because of the debilitating symptoms they experience, placing significant limitations on their ability to work, live a fulfilling life and contribute to society.
- Asthma is a variable condition. Conventional treatment regimens for mild asthma include a low dose ICS every day and as-required SABA to treat symptoms. Many patients fail to see

a direct link between daily ICS to prevent symptoms that are variable and can be unpredictable, so adherence is poor. People with undertreated inflammation because of under use of ICS, or over-use of SABA are more likely to have symptoms; exacerbations/asthma attacks and admission to hospital.

- The patient group supports the introduction of the budesonide plus formoterol anti-inflammatory reliever therapy as it can relieve asthma symptoms and treat the underlying inflammation. As it is a single combination inhaler it may mean fewer inhalers are prescribed which may reduce the environmental impact of treatment.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-minimisation analysis
Time horizon	10-year time horizon. Savings were projected as consistent across time, but the company used a longer time horizon to facilitate scenario analysis over future prescribing.
Population	Adults and adolescents (12 years and older) with mild asthma who would otherwise receive low dose ICS maintenance therapy plus SABA as needed.
Comparators	Low dose ICS plus SABA as needed was the comparator in the base case. Very low dose ICS plus SABA as needed is used in the sensitivity analysis for children aged 12 for one year before receiving low dose ICS plus SABA as needed thereafter.
Model description	A cost-minimisation model has been developed due to the assumed equivalence between budesonide plus formoterol and low dose ICS plus SABA as needed.
Clinical data	Direct evidence was sourced from a clinical trial program that included two pivotal studies (SYGMA 1[5] and SYGMA 2[8]) and two pragmatic studies (Novel START[10] and PRACTICAL[11]) to highlight clinical equivalence between budesonide plus formoterol and lose dose ICS (budesonide) plus SABA as needed. Further evidence to support assumptions of clinical equivalence between budesonide plus formoterol and low dose ICS plus SABA as needed was sourced through a SLR of SLRs, meta-analysis and validation from clinical experts.
Extrapolation	Not applicable as clinical equivalence assumed between budesonide plus formoterol and comparators.
Quality of life	As comparable efficacy was assumed, it was not necessary to include health benefits.
Costs and resource use	Outcomes included total acquisition costs for both budesonide plus formoterol therapy and the comparator. An average weighted cost of low dose ICS maintenance therapy, SABA and spacers were calculated separately based on open prescribing data for Scotland. Number of inhalations per day for budesonide plus formoterol and SABA were taken from SYGMA 2, and BTS/SIGN guidelines[3] informed the number of inhalations per day for low dose ICS. Costs were determined by multiplying the cost per inhalation by the number of daily inhalations, then projecting this annually per patient. Adverse events and disease management costs not included in the model due to assumed clinical equivalence.
PAS	There was no Patient Access Scheme (PAS) included in this submission.

Abbreviations: BTS/SIGN = British Thoracic Society and the Scottish Intercollegiate Guidelines Network; CMA = cost-minimisation analysis; ICS = inhaled corticosteroid; SABA = short-acting β_2-agonist; SLR = systematic literature review; PAS = patient access scheme

6.2. Results

Over 10 years, budesonide plus formoterol therapy was associated with a cost saving of £157.87 (or 29% reduction in costs) per patient versus low dose ICS maintenance therapy plus SABA as needed.

Table 6.2. Base case results

	Total cost (£) 10 years discounted	Incremental cost (£)
Budesonide plus formoterol therapy	381.21	-157.87
Low dose ICS maintenance therapy plus SABA as needed	539.07	

Abbreviations: ICS = inhaled corticosteroid; LD= low dose; SABA= short-acting β_2-agonist.

6.3. Sensitivity analyses

One-way deterministic scenario analysis was provided in the submission:

Table 6.3 – scenario analysis

	Parameter	Base case	Scenarios	Incremental costs (£)	Incremental cost (% change)
-	Base case	-	-	-157.87	-
1	Inhalations per day - budesonide plus formoterol and SABA	SYGMA 2 Frequency: Budesonide plus formoterol =0.52, SABA = 0.49	SYGMA 1 frequency: budesonide plus formoterol =0.47, SABA =0.39	-£191.16	-36%
2			Novel START frequency: Budesonide plus formoterol =0.53, SABA = 0.52	-£151.54	-28%
3			PRACTICAL frequency: Budesonide plus formoterol =0.9, SABA =0.5	£120.37	22%
4	ICS dose in comparator	Low dose ICS maintenance therapy plus SABA as needed	Very low dose ICS maintenance therapy plus SABA as needed prescribed to 12-year-olds for 1 year, then low dose ICS plus SABA as needed thereafter	-£130.35	-25%
5	Future inhaler use	Future inhaler use matched to	Future inhaler use adjusted to match NHSScotland	-£211.77	-36%

		current proportions	emissions reduction plan - MDI use reduced by 70% over 5 and replaced by DPIs.		
6	Comparator	Basket comparator based on Scotland's open prescribing data	Most common regimen in Scotland – Beclomethasone dipropionate (Clenil Modulite Inhaler 100 µg) and salbutamol	-£146.10	-28%
7	Threshold analysis	Inhalations per day for budesonide plus formoterol =0.52	The number of budesonide plus formoterol therapy inhalations per day increased to breakeven point = 0.74.	£0	0%

Abbreviations: ICS = inhaled corticosteroid; SABA = short-acting β_2-agonist; MDI = metered dose inhaler; DPI = dry powder inhalers

6.4. Key strengths

- Direct evidence from four studies, comparing budesonide plus formoterol with low dose ICS, specifically budesonide, plus a SABA as needed, was used to support the cost-minimisation analysis.
- All costing data were obtained from reputable sources, and the inhalation data for both budesonide plus formoterol and SABAs were taken from the SYGMA 2 study.
- The analysis demonstrates cost savings in the base case and in most of the scenarios presented.

6.5. Key uncertainties

- The economic case relies on the assumption of clinical equivalence between budesonide plus formoterol and low dose ICS plus a SABA as needed. As described in the clinical section, this is a source of uncertainty. However, the assumption of clinical equivalence was supported by SMC clinical experts.
- In scenario 3 of table 6.3 above, the intervention shifts from being cost-saving to potentially more costly when using the PRACTICAL study as a source of as needed inhalations for budesonide plus formoterol and SABAs. The submitting company attributed this variance to a more severe patient population in the PRACTICAL study and to potential differences in data collection across studies, leading to an increase in as-needed inhalation rates for budesonide plus formoterol. While the threshold analysis (scenario 7) offered reassurance by identifying the inhalation frequency at which the intervention would cease to be cost-effective, the discrepancy in inhalation rates across the studies highlighted an area of uncertainty.
- The economic analysis utilised BTS/SIGN guidelines to estimate the number of ICS inhalations patients in Scotland currently take. These values represented the prescribed dosing. There is a

known adherence issue within patients with mild asthma, and so these values may overestimate the amount of ICS that patients receive. This could potentially artificially increase the costs in the comparator arm if patients use their inhaler longer as a result of reduced use. However, greater adherence in study settings may have biased treatment efficacy in favour of low dose ICS plus SABA as needed in the clinical data. Overall, the impact of this in the economics is uncertain although likely small.

7. Conclusion

After considering all the available evidence, the Committee accepted budesonide plus formoterol for restricted use in NHSScotland.

8. Guidelines and Protocols

The British Thoracic Society and the Scottish Intercollegiate Guidelines Network (BTS/SIGN) published in 2019 the British guideline on the management of asthma, SIGN 158. [3]

The National Institute for Health and Care Excellence published in 2008: Inhaled corticosteroids for the treatment of chronic asthma in adults and in children aged 12 years and over. Technology appraisal guidance [TA138]. [15]

The Global Initiative for Asthma published in 2023 its updated report on: Global strategy for asthma management and prevention (2023 update). [2]

9. Additional Information

9.1. Product availability date

21 March 2023

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
budesonide plus formoterol (Symbicort® Turbohaler®) 200 micrograms/6 micrograms/inhalation, inhalation powder	**Inhalation as needed in response to symptoms**	**56**

Costs from BNF online on 01 February 2024. Costs calculated assuming an average of 0.5 inhalations per day based on observed use in SYGMA studies, assuming wastage. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

SMC is unable to publish the budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

References

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This assessment is based on data submitted by the applicant company up to and including 15 March 2024.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.