Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2155

benralizumab 30mg solution for injection in pre filled syringe (Fasenra®)

AstraZeneca UK Limited

10 May 2019

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

ADVICE: following a full submission

benralizumab (Fasenra®) is accepted for restricted use within NHSScotland.

Indication under review: As an add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting β-agonists.

SMC restriction: patients with blood eosinophils ≥150 cells/microlitre, and either ≥4 prior asthma exacerbations needing systemic corticosteroids in the previous 12 months or treatment with continuous oral corticosteroids over the previous 6 months.

Benralizumab, compared with placebo, reduced asthma exacerbation rates and was associated with greater reductions in continuous oral corticosteroid dose while maintaining stable asthma in patients with severe eosinophilic asthma.

This SMC advice takes account of the benefit of a Patient Access Scheme (PAS) that improves the cost effectiveness of benralizumab. This advice is contingent upon the continuing availability of the PAS in NHSScotland or a list price that is equivalent or lower.

Chairman
Scottish Medicines Consortium

Indication

As an add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids (ICS) plus long-acting β-agonists (LABA).[1]

Dosing Information

The recommended dose of benralizumab is 30mg by subcutaneous injection every 4 weeks for the first 3 doses, and then every 8 weeks thereafter. It is administered by a healthcare professional.

Benralizumab is intended for long-term treatment. A decision to continue the therapy should be made at least annually based on disease severity, level of exacerbation control and blood eosinophil counts. It should not be used to treat acute asthma exacerbations.

Benralizumab should be prescribed by physicians experienced in the diagnosis and treatment of severe asthma.[1]

Product availability date

25 January 2018

Summary of evidence on comparative efficacy

Benralizumab is a humanised monoclonal antibody which binds to the interleukin-5 receptor (IL-5Rα) expressed on the surface of eosinophils and basophils. Benralizumab signals through immune effectors cells which leads to apoptosis of eosinophils and basophils through enhanced antibody-dependent cell-mediated cytotoxicity, which reduces eosinophilic inflammation.[1] The submitting company has requested that SMC considers benralizumab when positioned for use in patients with severe eosinophilic asthma, inadequately controlled, despite high-dose ICS plus LABA, with blood eosinophils ≥150 cells/microlitre, and either (1) ≥4 prior asthma exacerbations needing systemic corticosteroids in the previous 12 months or (2) treatment with continuous oral corticosteroids (OCS) over the previous 6 months.

The evidence for benralizumab in patients with severe eosinophilic asthma comes from the SIROCCO, CALIMA and ZONDA studies. The SIROCCO and CALIMA studies were asthma exacerbations studies with replicate design and are presented together, the ZONDA study was an OCS reduction study and is presented separately.

SIROCCO and CALIMA studies

SIROCCO and CALIMA were randomised, double-blind, placebo-controlled phase III studies in patients with severe uncontrolled asthma.[2-4] The studies included patients aged 12 to 75 years with a diagnosis of asthma requiring treatment with medium to high dose ICS (>250 microgram/day [medium] or >500 microgram/day [high] fluticasone dry powder formulation equivalent) plus LABA for at least 1 year prior to enrolment; who had at least two documented asthma exacerbations requiring systemic corticosteroid treatment or a temporary increase in their

usual maintenance dose of oral corticosteroids (OCS) within 1 year prior to enrolment; and who had been treated with ICS plus LABA for ≥3 months prior to enrolment, with or without OCS and additional asthma controllers for ≥30 days. Additionally, adult patients were required to have a pre-bronchodilator forced expiratory volume in 1 second (FEV_1) of <80% predicted at screening; a documented post-bronchodilator reversibility of ≥12% and ≥200mL in FEV_1 within 12 months before enrolment; uncontrolled asthma with a score of 1.5 (on a scale of 0 to 6) on the Asthma Control Questionnaire (ACQ-6) to evaluate daytime and night-time symptoms, and rescue β-agonist use, measured during the 7 days prior to randomisation.[2-4]

Patients were randomised equally in both studies to treatment with benralizumab 30mg subcutaneous (SC) every 4 weeks (n=399 in SIROCCO, n=425 in CALIMA), or every 8 weeks (first three doses every 4 weeks, n=398 in SIROCCO, n=441 in CALIMA), or matching placebo every 4 weeks (n=407 in SIROCCO, n=440 in CALIMA), for 48 weeks in SIROCCO and 56 weeks in CALIMA, in addition to their standard treatment. Randomisation was stratified by the following factors: age group (adult or adolescent), country (in adults) or region (within or outside the EU for adolescents), and 2:1 according to blood eosinophil counts (≥300 cells/microlitre or <300 cells/microlitre).[2, 4] Patients randomised in CALIMA were additionally stratified by inhaled corticosteroids dosage at enrolment (high or medium).[4] Patients continued with pre-existing treatment (ICS and LABA) with or without other asthma-controller medicines including: leukotriene modifiers, long-acting muscarinic antagonists, oral corticosteroids and theophylline. Rescue therapy with short-acting β_2-agonists was permitted to control worsening asthma symptoms.[2, 4] The benralizumab 30mg every 4 week regimen has not been licensed and will not be discussed further.

The primary outcome was the annualised asthma exacerbation rate versus placebo for patients receiving high-dose inhaled corticosteroids plus LABA with baseline blood eosinophils ≥300 cells/microlitre.[2-4] The criteria for an exacerbation included a worsening of asthma that resulted in one of the following: use of systemic corticosteroids; temporary increase in a previously stable oral corticosteroid dose for ≥3 days or a single injectable dose of corticosteroids; emergency department or urgent care centre visit lasting <1 day because of asthma that needed systemic corticosteroids; or hospitalisation for ≥1 day because of asthma.[2-4] All efficacy analyses were performed on the full analysis set, which included all randomised patients who received any study treatment.[2, 4]

Treatment with benralizumab significantly improved the annualised exacerbation rate (primary outcome), pre-bronchodilator FEV_1 and total asthma symptom score (key secondary outcomes) compared with placebo.[2, 3] Total asthma symptom score is a composite of daytime symptoms, night-time symptoms, rescue medication use and an evening assessment of activity impairment, scored on a scale of 0 to 6; a decrease in score suggests improvement.[2] The primary outcome and key secondary outcomes are shown in Table 1.

Table 1. Results of the primary efficacy analyses of the SIROCCO and CALIMA studies for patients with baseline blood eosinophil counts ≥300 cells/microlitre and receiving high dose ICS plus LABA.[3]

	SIROCCO[3]		CALIMA[3]	
	Benralizumab	**Placebo**	**Benralizumab**	**Placebo**
Annualised rate of asthma exacerbations				
	n=267	n=267	n=239	n=248
Rate/year	0.74	1.52	0.73	1.01
Rate ratio (95% CI)	0.49 (0.37 to 0.64)		0.72 (0.54 to 0.95)	
p-value	<0.001		0.019	
Change from baseline in pre-bronchodilator FEV_1 at end of study* (L)				
	n=264	n=261	n=238	n=244
LS mean	0.398	0.239	0.330	0.215
Difference (95% CI)	0.159 (0.068 to 0.249)		0.116 (0.028 to 0.204)	
p-value	0.001		0.010	
Change from baseline in total asthma symptom score at the end of the study*				
	n=263	n=267	n=237	n=247
LS mean	-1.30	-1.04	-1.40	-1.16
Difference (95% CI)	-0.25 (-0.45 to -0.06)		-0.23 (-0.43 to -0.04)	
p-value	0.012		0.019	

CI = confidence interval; FEV_1 = forced expiratory volume in one second; LS = least squares; *end of study was at week 48 in the SIROCCO study and at week 56 in the CALIMA study.

A pooled analysis of the SIROCCO and CALIMA studies was conducted and reported an annual asthma exacerbation rate of 0.66 for benralizumab 30mg every 8 weeks versus 1.14 for placebo, an absolute difference estimate of -0.48, rate ratio 0.58 (95% confidence interval [CI]: 0.48 to 0.70).[3]

In SIROCCO, treatment with benralizumab was associated with reduced asthma exacerbations leading to emergency department visits or hospital admissions compared with placebo in patients with baseline blood eosinophil counts ≥300 cells/microlitre.[2] In the CALIMA study there was no evidence of a difference for this outcome.[4] For the subgroup of patients with baseline blood eosinophil counts <300 cells/microlitre, results from the SIROCCO study for the primary and key secondary outcomes favoured treatment with benralizumab. Results from the CALIMA study were inconsistent and marginally favoured placebo for the two key secondary outcomes.

A pooled study subgroup analysis in adult patients with blood eosinophil level ≥150 cells/microlitre and ≥4 severe exacerbations in the previous year, who had inadequate response on high-dose ICS plus LABA therapy was performed. Results shown in Table 2 indicate treatment with benralizumab was associated with a reduction in annual asthma exacerbation rate and improvements in FEV_1

pre-bronchodilator from baseline compared with placebo. There was no evidence of a difference between benralizumab and placebo for annual exacerbation rate associated with emergency department visit or hospitalisation and ACQ-6 score change from baseline.[5]

Table 2. Key efficacy outcome results for the pooled subgroup of patients from the SIROCCO and CALIMA studies with blood eosinophils ≥150 cells/microlitre, and ≥4 asthma exacerbations in the previous 12 months.[5]

	Benralizumab (N=66)	**Placebo (N=83)**
Annualised rate of asthma exacerbations		
Rate/year	1.29	2.12
Rate ratio (95% CI)	0.61 (0.39 to 0.93)	
Annual exacerbation rate associated with ER or hospitalisation		
Rate/year	0.30	0.39
Rate ratio(95%CI)	0.77 (0.28 to 2.10)	
FEV_1 pre-bronchodilator change from baseline (L)	n=56	n=73
LS mean	0.401	0.172
Estimate for difference	0.229 (0.053 to 0.405)	

CI = confidence interval; FEV_1 = forced expiratory volume in one second; LS = least squares

For the patient reported outcome instruments ACQ-6 and Asthma Quality of Life Questionnaire for 12 Years and Older (AQLQ[S]+12), benralizumab was associated with statistically significant improvements compared with placebo.[2-4] A responder analysis of AQLQ(S)+12, which required an improvement of ≥0.5 points to be considered clinically meaningful, indicated no significant differences between benralizumab and placebo groups in SIROCCO (55 to 57% versus 49%) and CALIMA (60 to 61% versus 59%) studies.[3]

Patients who completed SIROCCO, CALIMA, or ZONDA were eligible to continue therapy for a second year of treatment in BORA, a randomised, double-blind, phase III safety extension study of benralizumab which did not include a control group. ZONDA patients were not included in a published integrated analysis which reported results supportive of the findings of the SIROCCO and CALIMA studies and provide some evidence of longer-term efficacy of benralizumab in this patient group.[6]

ZONDA study

ZONDA was a randomised, double-blind, placebo-controlled phase III study which included adults with a diagnosis of asthma and blood eosinophil counts ≥150 cells/microlitre, who had been treated with medium to high-dose ICS and LABA therapy for ≥1 year prior to enrolment and were treated with high-dose ICS and LABA therapy ≥6 months, and OCS therapy (equivalent to a prednisolone or prednisone dose of 7.5 to 40mg/day) for ≥6 continuous months prior to enrolment. Patients were required to have been on a stable dose of OCS for ≥2 weeks prior to randomisation, to have a pre-bronchodilator FEV_1 of less than 80% predicted, and to have ≥1 asthma exacerbations in the prior year.[3, 7]

The study comprised a run-in phase to stabilise patients on the minimum OCS dose that could maintain asthma control; a randomised intervention period which included an induction phase (weeks 0 to 4), during which patients continued receiving their established OCS dose from the run-in phase; a dose-reduction phase (weeks 4 to 24) during which OCS dose was reduced by 2.5 to 5mg every 4 weeks; a dose-maintenance phase (weeks 24 to 28), during which the reduced OCS dose was maintained; and a follow-up visit.[7] Patients were randomised equally to treatment with benralizumab 30mg SC either every 4 weeks (n=72) or every 8 weeks (first three doses every 4 weeks) (n=73) or matching placebo every 4 weeks (n=75), for 28 weeks, in addition to standard treatment. Randomisation was stratified by country and according to blood eosinophil counts (≥300 cells/microlitre or <300 cells/microlitre).[7] Patients continued pre-existing treatment including other asthma-controller medicines and rescue therapy with short-acting β_2-agonists was permitted to control worsening asthma symptoms.[7] The benralizumab 30mg every 4 week regimen has not been licensed and will not be discussed further.

The primary outcome was the comparison of benralizumab with placebo for the percentage reduction in the OCS dose from baseline to week 28 while maintaining asthma control.[3, 7] Worsening of asthma was defined as new or increased asthma symptoms or clinical signs that were troubling to the patient or were related to an electronic Asthma Daily Diary alert.[7] The primary analysis, conducted in all randomised patients, reported the median reduction in OCS dose from baseline to week 28 as 75% for patients treated with benralizumab and 25% for patients treated with placebo, median difference in reduction 38% (95% CI: 21 to 50%), p<0.001.[3,7]

In the benralizumab and placebo groups respectively the following proportions were reported for patients with a ≥90% reduction from baseline in OCS dose: 37% versus 12%, ≥50% reduction: 66% versus 37%, any reduction: 79% versus 53%, ≤5mg/day dose of OCS at week 28: 59% versus 33%.[3,7] There was no evidence of a difference between benralizumab and placebo in total asthma symptoms score change from baseline to the end of the study.[7] Treatment with benralizumab was associated with an advantage, albeit slight, over placebo for the secondary outcomes annualised rate of asthma exacerbation and annual asthma exacerbation rate associated with an emergency department visit or hospitalisation.[3, 7] Benralizumab was associated with greater improvements in ACQ-6 and AQLQ[S]+12 compared with placebo.[7]

Subgroup analyses indicate treatment with benralizumab is associated with a greater reduction in OCS dose compared with placebo for patients with blood eosinophil counts ≥300 cells/microlitre but not for patients with blood eosinophil counts <300 cells/microlitre: patient numbers in this subgroup were small (n=12 and n=11 respectively).[7]

An interim analysis of the BORA extension study in patients who had participated in ZONDA, was conducted following ≥12 additional weeks of treatment. It reported that 39% of patients treated with benralizumab every 8 weeks had discontinued treatment with OCS, and 16% had no change/increase in dose. The median OCS dose was 5mg/day and the number of asthma exacerbations seemed stable.[3]

Summary of evidence on comparative safety

Benralizumab was generally well tolerated with a broadly consistent safety profile across the SIROCCO, CALIMA and ZONDA studies as well as interim data from extension studies.[3] In a pooled analysis of the SIROCCO and CALIMA studies the following were reported for patients treated with benralizumab 30mg every 8 weeks (n=822) and placebo (n=847) respectively: proportions of patients with any adverse event (AE) 74% versus 78%, any serious AE 12% versus 14% and any AE leading to study medicine discontinuation 2.2% versus 0.9%.[3] For the ZONDA study the following were reported for patients treated with benralizumab 30mg every 8 week regimen (n=73) and placebo (n=75) respectively: proportions of patients with any adverse event (AE) 75% versus 83%, any serious AE 9.6% versus 19% and any AE leading to study medicine discontinuation 4.1% versus 2.7%.[7]

From the pooled analysis of the SIROCCO and CALIMA studies (n=2,510) the most common treatment emergent AEs were nasopharyngitis (16%), asthma (14%), upper respiratory tract infection (8.7%), and bronchitis (8.3%). These AEs were similar across treatment groups. For the ZONDA study the following were reported for patients treated with benralizumab 30mg every 8 week regimen (n=73) and placebo (n=75) respectively: nasopharyngitis (15% versus 20%), asthma (3% versus 24%), upper respiratory tract infection (6.8% versus 6.7%), and bronchitis (9.6% versus 16%), headache (8.2% versus 5.3%), sinusitis (5.5% versus 11%) and rhinitis (8.2% versus 2.7%).[7]

Injection site reactions were reported by a slightly higher proportion of patients treated with benralizumab compared with placebo but the majority of reactions were mild in intensity. An interim analysis of the ongoing extension studies, with treatment duration beyond one year, did not suggest an increase in the reporting of serious AEs or any new safety signal.[3] One death, which was classed as being a result of pneumonia and pulmonary insufficiency, was considered by the study investigator to be related to treatment with benralizumab 30mg every 8 weeks in the ZONDA study.[3]

Summary of clinical effectiveness issues

Patients with asthma can be categorised into phenotypic subtypes of eosinophilic or non-eosinophilic based on the cell profile of induced sputum or blood samples. Severe asthma may be debilitating, requiring hospital admission, and even life-threatening. Treatment requires medium to high dose inhaled corticosteroids with or without systemic corticosteroids; in order to maintain control of their asthma patients may become steroid dependent, which is associated with increased morbidity.[3, 8] Mepolizumab, another anti-IL-5 monoclonal antibody, is accepted for restricted use within NHSScotland as an add-on treatment for severe refractory eosinophilic asthma in adult patients who have eosinophils of ≥150 cells/microlitre at initiation of treatment and have had at least four asthma exacerbations in the preceding year or are receiving maintenance treatment with OCS. Omalizumab, which interrupts IgE mediated pathways, may also

be a treatment option for the subgroup of patients with eosinophilic asthma who also have allergic asthma, as this medicine is licensed for use in allergic asthma.

The submitting company has requested that SMC considers benralizumab when positioned for use in patients with severe eosinophilic asthma, inadequately controlled despite high-dose ICS plus LABA, with blood eosinophils ≥150 cells/microlitre, and either (1) ≥4 prior asthma exacerbations needing systemic corticosteroids in the previous 12 months or (2) treatment with continuous OCS over the previous 6 months.

Asthma is a multidimensional disease with many features considered to be clinically relevant.[9] Both the SIROCCO and CALIMA studies met their primary outcome; in the pooled analysis, benralizumab significantly reduced the annual asthma exacerbation rate by approximately 40%, with an absolute difference of about 0.5 asthma exacerbations/year, compared with placebo. Key secondary outcomes of the SIROCCO and CALIMA studies demonstrated that benralizumab was associated with greater improvements in lung function and total asthma symptoms compared with placebo. The ZONDA study showed that benralizumab was associated with a significant reduction of the median OCS dose in patients requiring OCS to maintain asthma control, compared with placebo.[2-4, 7]

This difference between benralizumab and placebo in annual asthma exacerbation rate from the SIROCCO and CALIMA studies, of about 0.5 asthma exacerbations/year, was considered to be 'modest' by the European Medicines Agency (EMA).[3] The annualised rate of asthma exacerbations reported for the placebo groups (1.52 and 1.01) does not reflect the target population of the studies: uncontrolled asthma with ≥2 exacerbations/year. The number of severe asthma exacerbations may have been overestimated at study enrolment. Patients in SIROCCO had slightly more severe disease than those in CALIMA which may explain the differences in exacerbation rates reported between the placebo groups.[3] The clinical relevance of the small advantage demonstrated by benralizumab over placebo in terms of asthma symptoms, asthma control, emergency department visits or hospitalisation, and quality of life is uncertain.[3]

Neither of the SIROCCO and CALIMA studies were powered to evaluate differences between the subgroups of patients with baseline blood eosinophil counts <300 cells/microlitre or the relevant subgroup for the company's positioning: adult patients with blood eosinophil level ≥150 cells/microlitre and ≥4 severe exacerbations, for which patient numbers were small (n=149 for combined treatment groups). The results for the efficacy outcomes for these subgroups are inconsistent.

The ZONDA study was small (benralizumab 8 weekly group n=73, placebo group n=75) and the results are only generalisable to a proportion of the population in the proposed positioning. The effect of benralizumab on OCS use in patients with blood eosinophils ≥150 cells/microlitre and ≥4 prior asthma exacerbations in the previous 12 months is not clear. Over half (53%) of patients treated with placebo had any dose reduction of OCS therapy compared with 79% treated with benralizumab. The 28-week duration of the ZONDA study period was likely to be too short to account for seasonal variation in allergens.[9 3] Differences in baseline disease features (including

baseline eosinophil count) between the benralizumab and placebo groups may have confounded the study results.

All three studies excluded patients with unstable comorbidities, liver dysfunction, a smoking history of ≥10 pack-years and current smokers. This may limit the generalisability of the study results to these patients.

In the absence of direct data against mepolizumab, the relevant comparator for NHSScotland, the submitting company presented matching adjusted indirect comparisons (MAICs) that matched the pooled benralizumab study populations (SIROCCO and CALIMA) with the pooled mepolizumab study populations (MENSA and DREAM) to compare the outcomes of annual exacerbation rates, annual rate of exacerbations leading to emergency room visits or hospitalisation and lung function (using the pre-bronchodilator FEV_1). This MAIC has been published.[10] A separate MAIC matched the benralizumab study population (ZONDA) with the mepolizumab study population (SIRIUS) to compare the outcome of OCS dose reduction. Several variables were used to match the individual patient level data from the benralizumab studies with aggregate data from the mepolizumab studies. After matching, the treatment effect for benralizumab versus placebo was indirectly compared with the treatment effect for mepolizumab versus placebo for each outcome. The submitting company concluded that the MAICs found no statistically significant differences between benralizumab and mepolizumab in terms of exacerbation rates and lung function.

However, there are a number of limitations which affect the validity of these results including uncertainty over appropriate selection of co-variates and remaining confounding. Differences between results in the common placebo groups of studies suggest that differences between the study populations remained. Despite these limitations, it is reasonable to conclude that benralizumab and mepolizumab are not significantly different for the exacerbation rate and lung function outcomes. After matching, the effective sample size of the ZONDA population was greatly reduced and the results for OCS dose reduction should be interpreted with caution. Both comparisons were performed using the total study populations and not in the subgroup of patients supporting the company's proposed positioning and the results may not be generalisable to this narrower population. There was no formal comparison of patient reported outcomes or safety between benralizumab and mepolizumab.

Clinical experts consulted by SMC considered that the place in therapy of benralizumab is as an alternative treatment option to mepolizumab. Benralizumab is likely to be more convenient for patients as it requires less frequent administration of maintenance doses compared with mepolizumab (8-weekly versus 4-weekly dosing), and is administered in a subcutaneous pre-filled syringe whereas mepolizumab requires reconstitution before administration.

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

Summary of comparative health economic evidence

The company submitted a cost-minimisation analysis comparing benralizumab to mepolizumab for the treatment of adult patients with severe eosinophilic asthma inadequately controlled despite high-dose ICS plus LABA. The time horizon used in the analysis was 5 years. Based on SMC expert responses mepolizumab appears to be the comparator most likely to be displaced in Scotland.

The clinical data used to underpin the assumption of comparable efficacy between treatments were taken from the MAICs described above. The submitting company concluded that the MAICs found no statistically significant differences between benralizumab and mepolizumab in terms of exacerbation rates, lung function and OCS dose reduction.

Medicine, administration and monitoring costs were included in the analysis. Benralizumab is a subcutaneous treatment which does not require reconstitution prior to administration, whereas mepolizumab does. Benralizumab also requires less frequent administration. The analysis assumes benralizumab requires 5 minutes of specialist nurse time to administer, whilst mepolizumab was assumed to take 10 minutes of specialist nurse time to administer. The company assumed that both treatments would be associated with the same monitoring requirements. Based on clinical opinion, the analysis incorporates 2 hours of monitoring after the first administration, 1 hour for the subsequent 3 administrations and 30 minutes for every administration thereafter. No adverse event costs were included.

A patient access scheme (PAS) was submitted by the company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. A PAS discount is in place for mepolizumab and this was included in the results used for decision-making by using estimates of the comparator PAS price.

Table 3. Base case results using the list prices for benralizumab and mepolizumab. Incremental results are presented per patient over 5 years

Treatment	Total cost	Incremental results
mepolizumab	£55,815	-
benralizumab	£63,681	£7,866

Table 4. Scenario analyses results using the list prices for benralizumab and mepolizumab (administration based on band 5 nurse time)

Treatment	Total cost	Incremental results
mepolizumab	54,945	-
benralizumab	£63,255	£8,310

The results presented do not take account of the PAS for mepolizumab or the PAS for benralizumab but these were considered in the results used for decision-making at SMC. SMC is unable to present the results provided by the company which used an estimate of the PAS price for mepolizumab due to commercial confidentiality and competition law issues.

There were a number of limitations with the analysis which include the following;

- The MAICs used to underpin the assumption of comparable efficacy were subject to a number of limitations as outlined in clinical effectiveness section of the DAD. However, overall benralizumab was considered to demonstrate comparable efficacy in terms of exacerbation rates and lung function compared with mepolizumab.
- There may be some uncertainty surrounding the appropriate pay band used to estimate administration costs. However the company's base case approach of estimating administration costs based on specialist nurse time is consistent with previous SMC submissions for this disease area, and therefore seems reasonable. For completeness the company did provide a scenario analysis which assessed the impact of using band 5 nurse time to estimate administration costs.

Despite the uncertainties outlined above the economic case has been demonstrated.

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

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 UK, which is a registered charity.

- Asthma UK has received 2.5% pharmaceutical company funding in the past two years, including from the submitting company.

- Symptoms of severe asthma include difficulty breathing and limited mobility, leaving many people housebound. Persistent symptoms may also lead to sleep deprivation, feelings of despair and depression, low activity levels, weight gain and increased dependence on family and carers. Additionally, repeated hospital admissions may lead to further social isolation and economic disadvantage.

- People with severe asthma require intensive therapies to control symptoms and prevent attacks, hospitalisations and death. The side effects of these medicines, especially long-term oral corticosteroids, may be significant, potentially causing concern and distress to patients. There is a need for more effective therapies, particularly steroid sparing medicines for severe asthma.

- Even when taking oral steroids, some patients' severe asthma remains poorly controlled. Benralizumab would provide an alternative treatment option for people with severe eosinophilic asthma who do not respond well to existing options. It may be more convenient for patients and carers than mepolizumab as it requires less frequent dosing.

Additional information: guidelines and protocols

In September 2016 the Scottish Intercollegiate Guidelines Network (SIGN) issued national clinical guideline number 153, British guideline on the management of asthma. This guideline recommends subcutaneous omalizumab may be considered in patients with a high steroid burden as a potential steroid-sparing treatment and does not recommend the use of subcutaneous immunotherapy for the treatment of asthma in adults or children. There is a brief discussion on the evidence to support the use of mepolizumab in patients with severe eosinophilic asthma, however no recommendation are made. [11] This guidance predates the marketing authorisation of benralizumab.

In November 2018, the Global Initiative for Asthma (GINA) issued international guidance, titled "Difficult-to-treat & severe asthma in adolescent and adult patients. Diagnosis and management". This guideline recommends that benralizumab be considered for patients with severe asthma with exacerbations and allergic/eosinophilic biomarkers on high dose ICS plus LABA, with or without daily OCS. Predictors of response such as higher blood eosinophils and number of exacerbations in the last year should be considered before commencement of treatment, as well as cost and patient preference. The same advice applies to mepolizumab, and omalizumab can be considered at the same stage of the treatment algorithm provided that the patient is eligible.

Additional information: comparators

Mepolizumab.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
Benralizumab	**30mg 8 weekly subcutaneous (every 4 weeks for the first 3 doses)**	**First year 15,640** **Subsequent years (mean) 12,707**
Mepolizumab	100mg every 4 weeks subcutaneous	10,920

Doses are for general comparison and do not imply therapeutic equivalence. Costs from BNF online on 01 March 2019. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The company estimated the number of patients eligible for treatment to be 5,497 in year 1 rising to 5,867 in year 5 to which confidential estimates of treatment uptake were applied

SMC is unable to publish the with PAS 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.**

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This assessment is based on data submitted by the applicant company up to and including 11 April 2019.

**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: http://www.scottishmedicines.org.uk/About_SMC/Policy*

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.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

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.