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Chair's presentation Benralizumab for treating inadequately controlled asthma

2nd Appraisal Committee meeting

Committee A

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Company: AstraZeneca

19th June 2018

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Key issues for consideration (1)

- Proposed population (compared with SoC) - blood eosinophil count of 300 or more per microliter, 3 or more exacerbations in the previous year **or** taking maintenance oral corticosteroids
  - blood eosinophil count of **300 cells** or more **and** have had **4 or more** exacerbations in past 12 months **or** are taking oral corticosteroids (eligible for mepolizumab)
  - blood eosinophil count of **400 cells** or more **and** have had **3 or more** exacerbations in past 12 months (eligible for reslizumab)
  - Blood eosinophil count of **300 cells** with **3** exacerbations not taking oral corticosteroids (not currently eligible for biologics). Is this a large sub-population?
    - Those with more exacerbations will have more absolute benefit than those with fewer, and those on mOCS will also have more predicted benefit. Does the blended comparator accurately predict the mixture of people who would receive benralizumab in practice?
    - Is SoC the most appropriate comparator for all 3 subpopulations in the blend?

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Key issues for consideration (2)

- The company has not provided the ICER for people with 3 exacerbations not on OCS.
  - It is appropriate to consider the ICER vs. SOC in the blended population?
  - How many in the model have 3 exacerbations no OCS? Generalisable?
  - New treatment pathway for less severe? Would they be offered benralizumab before OCS? How big is this 'new' population?
  - What value for mOCS use at baseline is most appropriate 41.7% (severe asthma registry) or 60-66% (clinical experts) or 80% (NHS England)
- Take-up of mepolizumab appears to be modest, why is this? Would the same be true for benralizumab?
- Take-up of reslizumab appears to be low, why is this?
- Is the MAIC a robust method for comparing benralizumab with mepolizumab
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- Should additional weight be given to an 8 weekly vs 4 weekly dosing schedule and prefilled syringes?

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Benralizumab

Marketing authorisation	Add-on maintenance for severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting β-agonists (LABA) European marketing authorisation granted in January 2018
Mechanism of action	Binds through interleukin (IL)-5Rα and inhibits IL-5 which reduces eosinophil numbers and activity. Different mode of action than other anti-IL-5 antibody (mepolizumab, reslizumab), which results in eosinophil reduction, but not depletion.
Administration	30 mg dose every 4 weeks for first 3 doses, then 8 weekly as subcutaneous injection (accessorised pre-filled syringe)
Acquisition cost	List price: £1955/vial (30 mg SC injection) PAS price: superseded by updated PAS

ACD: preliminary recommendations

Benralizumab is **not recommended** for treating severe eosinophilic asthma that is inadequately controlled in adults despite maintenance therapy with high-dose inhaled corticosteroids and long-acting beta-agonists.

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Benralizumab clinical studies

Study	Population (ITT)	Intervention	Comparator	Outcomes
SIROCCO (n=1205) **24/374 UK centres**	• **high dose** ICS + LABA, • **2+ exacerbations** prior year, • Blood eosinophil ≥300/μL	30 mg SC injection for 48 wks: • Benralizumab Q4W or • Benralizumab Q4W x 3 and Q8W x 4	Placebo Q4W	**Primary outcome:** Annual asthma exacerbation rate (AER)
CALIMA (n=1306) **No UK centres**	• **medium to high dose*** ICS + LABA • **2 or more asthma exacerbations** • blood eosinophil ≥300/μL	30 mg subcutaneous injection for 56 weeks of either: • Benralizumab Q4W or • Benralizumab Q4W x 3 and Q8W x 5		**Primary outcome:** Annual asthma exacerbation rate ratio versus placebo

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Clinical effectiveness results: pooled SIROCCO/CALIMA subgroup in which NICE recommendation is sought

Estimate, 95% CI	Placebo (N=136)	Benralizumab 30mg Q8W (N=123)
Primary efficacy endpoint: Marginal annual exacerbation rate		
Rate estimate	1.83 (1.45, 2.30)	0.85 (0.63, 1.15)
Marginal absolute difference vs placebo	-	-0.98 (-1.46, -0.50)
Rate ratio	-	0.47 (0.32, 0.67)
P value	-	<0.001
Key secondary endpoints **ACQ-6 score (decrease in score represents improvement)**		
Change from baseline	-1.16	-1.59
Estimate for difference vs placebo	-	-0.43 (-0.69, -0.16)
P value	-	0.002
Mean EQ-5D-5L score		
Change from baseline	0.06 (0.04, 0.09)	0.10 (0.08, 0.13)
Estimate for difference vs placebo	-	0.04 (0.01, 0.08)
P value	-	0.019

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Comparison with mepolizumab and reslizumab

Mepolizumab

- Network meta-analysis (NMA) ruled out by company. Anchored matched adjusted indirect comparison (MAIC) chosen to adjust for the cross-trial differences in patient characteristics
- MAIC was conducted in the ITT population and applied to the severe subgroup
- 3 benralizumab (SIROCCO, CALIMA, ZONDA) and 3 mepolizumab (MENSA, DREAM,SIRIUS) trials
- MUSCA trial not included in base case (primary objective was HRQoL / not powered to detect differences in efficacy outcomes) but was included in a SA

Reslizumab

- MAIC analysis was considered unfeasible (heterogeneity of the trials) and equivalent clinical efficacy was assumed for benralizumab and reslizumab based on this.
- ERG- there is no evidence to support this strong assumption

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Original cost effectiveness results

Company model base case: add-on benralizumab vs. SoC	Inc Costs	Inc QALYs	ICER per QALY
	[redacted]	[redacted]	£34,284

ERG base case: item changed in company model	ICER for pairwise comparison of benralizumab vs SoC
1.Asthma-related mortality	£36,398
2.mOCS use at baseline	£36,531
3.Administration costs of biologics	£34,646
4.Acquisition cost for reslizumab	NA
5.Treatment discontinuation rate	£34,346
ERG base case (1+2+3+4+5)	£39,135

Benralizumab is dominant in all cases when compared to reslizumab and mepolizumab using list prices. See confidential part 2 appendix for comparisons with PAS prices

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ERG base-case: key scenario analyses
(using list prices)

Scenario analyses showed that the results are most sensitive to including risk of asthma death from an exacerbation, equal utility /disutility across treatment arms, costs and utilities associated with mOCS

Assumptions	ICER for benralizumab compared with SoC
ERG Base Case	£39,135
Set asthma-related mortality to zero	£73,560
mOCS use at baseline (17% in Kerkhof et al.)	£44,425

mOCS use at baseline	Technology	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER
ERG'S base-case vs. SoC (0% on mOCS)	BEN	[redacted]	[redacted]	[redacted]	[redacted]	£48,883
	SoC	[redacted]	[redacted]	-	-	-
ERG'S base-case vs. SoC (100% on mOCS)	BEN	[redacted]	[redacted]	[redacted]	[redacted]	£30,278
	SoC	[redacted]	[redacted]	-	-	-

Committee's considerations – clinical

- People with severe eosinophilic asthma that is uncontrolled on standard care (SoC) would welcome a new treatment option that reduces / avoids the use of oral corticosteroids.
- Benralizumab easier/ less frequent administration vs. with existing biologics
- Mepolizumab is the most relevant comparator for people who have had at least 4 exacerbations or are taking maintenance oral corticosteroids (mOCS)
- SoC is the relevant comparator for people who have had 3 exacerbations and are not taking mOCS (not eligible for mepolizumab). Reslizumab is not often used in UK clinical practice in people with at least 400 cells per microlitre
- Benralizumab is clinically effective as an addition to standard care in people with a blood eosinophil count of at least 300 cells per microlitre, who have had 3 or more exacerbations or are taking mOCS
- The clinical effectiveness of benralizumab compared with reslizumab and mepolizumab is highly uncertain
  - simple assumption of equivalence for reslizumab,
  - MAIC used for the comparison with mepolizumab was not considered robust

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Committee's considerations - costs

- The model structure is appropriate for decision making
- Different proportions of mOCS use at baseline were used in the company model depending on the comparator (54.1% for SoC and 78.6% for mepolizumab) and ERG model (41.7% for both from a UK registry of patients with severe asthma)
  - clinical experts noted 60% of people starting on mepolizumab are on mOCS
- Asthma-related mortality estimates in the company model are too high and if lowered, the ICER's would increase
- The company's ICER of £34,284 per QALY gained compared with SoC was in a mixed population of 3 or more exacerbations, including people who were and were not taking mOCS
  - People with 3 exacerbations not taking mOCS have less severe disease. The absolute treatment effect of benralizumab is therefore likely to be lower and the ICER could therefore be considerably higher than the company £34,285
- ERG exploratory analyses:
  - mixed population **not taking mOCS** – ICER £48,883 per QALY
  - mixed population **taking mOCS** – ICER £30,278 per QALY gained
- **ICER's are above the range normally considered a cost-effective use of NHS resources for both populations (**when SoC or mepolizumab are comparators)

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ACD consultation responses

- Consultee comments from:
  - Company (AstraZeneca)
  - NHS England Specialised Respiratory Clinical Reference Group
  - Asthma UK
  - Royal College of Physicians (no comments, in agreement with ACD)
- Commentator comments from:
  - GSK UK (mepolizumab)
  - Teva UK (reslizumab)
- Clinical expert comment from:
  - Professor Tim Harrison
- Web comments from:
  - Professor of allergy and pulmonology working in the NHS

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Consultation issues – unmet need

- **NHS England** support the development of products which can be self-administered (reduced burden on patients currently having to attend hospital services) BUT it needs to be cost-effective price for the NHS
- **Asthma UK** note that there are only limited treatment options available to people with severe eosinophilic asthma. Despite adherence to current recommended asthma treatments, symptoms can persist and patients' asthma can remain uncontrolled, putting them at risk of potentially life-threatening attacks as well as significantly disrupting their quality of life
  - Benralizumab could provide an (additional) alternative option for people with severe eosinophilic asthma who respond poorly to oral steroids and result in cost-savings for the NHS

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Consultation issues – reslizumab as a comparator

Reslizumab: (recommended for adults with a blood eosinophil count of **400 cells** per microlitre or more and have had 3 or more exacerbations in past 12 months)

NHS England. Reslizumab is SoC for 10-20% people who have had 3 or more exacerbations and are not taking mOCS.

Teva UK. Reslizumab is used at tertiary asthma centres and an appropriate comparator for people who have had 3 or more exacerbations not taking mOCS

- Usage of reslizumab is currently lower than mepolizumab because it received a positive recommendation NICE only 9 months ago
- Recommended anti-IL5 biologics are administered monthly within a hospital setting - patients have to travel each month irrespective of the treatment
- Reslizumab is not inconvenient for patients

Teva UK. A recent subgroup analysis in patients with 3 or more exacerbations showed a reslizumab to be more effective than benralizumab:

- Reslizumab: 67% (RR 0.33, 95% [0.22, 0.49]) published at the ERS 2017 (Chauhan et al). compared to benralizumab 53% (RR 0.47, 95% [0.32 to 0.67])

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Consultation issues – mepolizumab as a comparator

Mepolizumab: recommended in adults with a blood eosinophil count of **300 cells** per microlitre or more and have had 4 or more exacerbations in previous 12 months or taking continuous oral corticosteroids over previous 6 months

- **Clinical expert** – although mepolizumab is recommended some people choose to remain on SoC (prefer not to travel for many hours to receive a 4-weekly injection). **SoC is also an appropriate comparator**
- Web comment from an NHS professional- only 5-10% of eligible patients receive mepolizumab. Mepolizumab is therefore not the main comparator for this population

mOCS use at baseline:

- NHS England – 80% not 60% of people starting mepolizumab are on mOCS:
  - Suggest using data from UK severe asthma registry. Value from registry is 41.7% (preferred by the ERG and used in their base-case)…
- A **clinical expert** noted that the value of 47% is based on data from the BTS severe asthma registry which includes **all patients** with severe asthma, many of whom are **less severe** than the population being considered in this appraisal
  - 66% of patients being considered for mepolizumab are on maintenance prednisolone and discussions with other severe asthma centres suggests this to be a better estimate

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Consultation comments – GSK UK

- Do not agree with the methodology of the MAIC of benralizumab vs. mepolizumab.
- Relevant evidence has been excluded :
  - DREAM should not be included in MAIC as not all patients in DREAM met criteria for severe eosinophilic asthma and used a unlicensed dose for mepolizumab of 100mg 4-weekly sub-cutaneous injection. Bias towards benralizumab
  - abstract reporting a post-hoc analysis of MENSA in people with ≥300 eosinophils /µL and 3 exacerbations in prior year excluded but could have been included in a sensitivity analysis to the MAIC
  - Published meta-analysis of MENSA and DREAM included an analysis of the reduction in exacerbation rate stratified by baseline blood eosinophil count - indirect comparison through other methods was possible
- MUSCA (a health related quality of life study) should have been included. Numerical advantage for benralizumab is improved by exclusion of MUSCA
- Other methods of matching may have produced different results:
  - Matching using the ACQ-6
  - Matching using more eosinophil cell bands
- Eosinophil dose response for mepolizumab but not for benralizumab – ITT results therefore not appropriate to apply to the higher eosinophil subgroup

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AstraZeneca response – comparators

- Most relevant comparators for appraisal are ***both*** mepolizumab and SoC
  - SoC is still established NHS practice for significant majority of people eligible for mepolizumab. Analysis of prescription data shows that mepolizumab is only being used in, at most, 15.5% of eligible people
- Cost-effectiveness results presented for:
  - Benralizumab vs. SoC in the base case population (300+ EOS; AND either 3+ exacerbations in prior year OR receiving mOCS, and
  - Benralizumab vs mepolizumab in the mepolizumab NICE-recommended population
- Results for benralizumab vs. SoC in patients with (exactly) 3 exacerbations in the prior year, not taking mOCS were not presented:
  - Appropriate to combine mepolizumab NICE-recommended population and population with 3 exacerbations not taking mOCS for the purpose of cost effectiveness analysis vs. SoC as SoC appropriate comparator for both. Combining populations yields company 'base case' population
  - Consistent with approach in mepolizumab and reslizumab NICE appraisals, where the committee's decision-making was based on a single ICER for the whole of the population of interest (i.e. cost-effectiveness analysis was not stratified by number of exacerbations in prior year or presence/absence of maintenance OCS, in either case)

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Company: estimated population of people with 3 exacerbations, not taking OCS

- Estimates for the likely size of population with 3 exacerbations, not taking OCS with an eosinophil count of 400 or more [who are eligible for reslizumab] and people with 3 exacerbations and not taking OCS with an eosinophil count of less than 400) provided by the company:

Population	Estimated Size (eligible patients)	Size as percentage of 'base case' population
People with 3 exacerbations, not taking OCS with an eosinophil count of 400 or more	[redacted]	[redacted]
people with 3 exacerbations, not taking OCS with an eosinophil count of less than 400 (but greater than 300)	[redacted]	[redacted]

- ERG note that these estimates could not be verified since results for these subpopulations not reported in the CSRs for SIROCCO and CALIMA.
  - CSRs report the proportion of patients with ***exactly 3 exacerbations***: [redacted] in Q8W and placebo arms of SIROCCO trial; and [redacted] in Q8W arm and [redacted] in placebo arm of CALIMA. Estimates based on people ***with and without mOCS use at baseline***.
  - Proportion of people with ***exactly 3 exacerbations, not taking mOCS*** provided by the company in their response to ACD (31%) is not consistent with the CSRs. Number of eligible patients is substantially overestimated.

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Company: MAIC vs NMA

- MAIC adjusts for the differences between the benralizumab and mepolizumab trials, to give a more accurate estimate of relative efficacy
  - Limitations such as the potential for the occurrence of extreme weights are considerably outweighed by the advantage of adjusting for cross-trial differences
- High level of heterogeneity would be ignored if an NMA was used instead (principle of exchangeability does not hold due to substantial differences between the benralizumab and mepolizumab trials)
  - robust estimates of relative effectiveness would not be produced
- Relative treatment effect for benralizumab versus mepolizumab (MAIC ITT population) assumed to be generalisable to the mepolizumab NICE-recommended population. No evidence/reason that relative effect would differ

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Company: changes to model inputs

Input	Value	Justification
Price of benralizumab	[redacted] per vial	Revised PAS
Mortality associated to Asthma exacerbations	Scaled by 0.4	As per ERG base case
% patients on mOCS	54.1% in the base case population 60% in the mepolizumab NICE recommended population	As per UK RWE As per committee meeting clinical expert opinion and ACD document
Administration time	5 minutes for benralizumab 20 minutes for mepolizumab	As per committee meeting clinical expert opinion
Clinical effectiveness of benralizumab vs mepolizumab	As per MAIC results	MAIC is the most appropriate way of assessing relative clinical effectiveness between these two medications (see section 2)
Treatment discontinuation	Set at 0.0041 per cycle	As per ERG base case
All other model inputs remain as in manufacturer submission base case		

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Company: revised cost effectiveness estimates

- Results based on the revised PAS price of benralizumab and the list price of mepolizumab :

Results vs SoC in base case population					
	Total cost	Δ cost	Total QALYs	ΔQALYs	ICER
Benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	£29,896
SoC	[redacted]		[redacted]		

Results vs mepolizumab in mepolizumab NICE recommended population					
	Total cost	Δ cost	Total QALYs	ΔQALYs	ICER
Benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
SoC	[redacted]		[redacted]		

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ERG critique – ERG base-case for comparison with SoC

	Item	PenTAG's base case	Company's revised base case (post-ACD)	BEN vs SoC
1	Asthma-related mortality	assumed ~2.5 times lower than in the company's initial model for some patients (BTS asthma audit 2016)	assumed ~2.5 times lower than in the company's initial model for some patients (BTS asthma audit 2016)	£29,807
2	mOCS use at baseline	41.7% (Heaney et al., 2010-asthma registry) for SOC comparison, 60% for the MEPO comparison	54.1% for SoC comparison, 60% for the MEPO comparison	£29,996
3	Administration costs of biologics	Costed supervision after the admin of biologics; assumed the same admin time for MEPO and BEN.	Monitoring time not costed; administration of MEPO takes 15 mins longer than for BEN	£28,479
4	Treatment discontinuation rate	0.0041/cycle (average across the pivotal trials)	0.0041/cycle (average across the pivotal trials)	£28,173
	ERG's base case: 1+2+3+4			**£32,179**
	Company's revised base case (post-ACD with revised PAS):			**£29,896**

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ERG critique-ERG scenario analysis for comparison with SoC

Scenario	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER
Patient's age at the start of treatment set to 44.9	[redacted]	[redacted]	[redacted]	[redacted]	£31,525
	[redacted]	[redacted]	-	-	-
Proportion of patients responding to all treatments after 52 weeks set to 50% for both OCS and non-OCS users	[redacted]	[redacted]	[redacted]	[redacted]	£31,429
	[redacted]	[redacted]	-	-	-
Use EQ-5D-5L utilities directly, rather than mapped values onto EQ-5D-3L	[redacted]	[redacted]	[redacted]	[redacted]	£32,944
	[redacted]	[redacted]	-	-	-
Set asthma-related mortality to zero	[redacted]	[redacted]	[redacted]	[redacted]	£59,961
	[redacted]	[redacted]	-	-	-
0% of people on mOCS	[redacted]	[redacted]	[redacted]	[redacted]	£40,379
	[redacted]	[redacted]	-	-	-

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