Slides for the public– no ACIC information

Chair's presentation Benralizumab for treating inadequately controlled asthma

3rd Appraisal Committee meeting

Committee A

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ERG: Peninsula technology Assessment Group (PenTAG)

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Company: AstraZeneca

18th September 2018

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Key issues for consideration

- The committee decided that three comparators in the scope – mepolizumab, reslizumab and standard of care – were relevant depending on the patient characteristics and current eligibility for biologics. Would the committee like to reconsider the company base-case comparing benralizumab for the whole population to SOC alone with an ICER of £25,192 per QALY gained?
- Should existing biologics be ignored in the cost effectiveness on the basis of poor uptake?
- Is benralizumab cost effective compared with mepolizumab (when both confidential PAS's are considered)?
- If not should the use of benralizumab second-line to mepolizumab be considered?
- For patients currently ineligible for biologics what is the committee's view of the company's ICER vs SoC of £38,304 per QALY gained
- 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 to other anti-IL-5 antibody (mepolizumab, reslizumab), which result 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: updated PAS

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History of appraisal

- 1st committee meeting 17th April 2018
  - Benralizumab was not recommended
  - The cost effectiveness estimates of benralizumab compared with standard care and mepolizumab are above the range considered to be a cost-effective use of NHS resources
- 2nd committee meeting 19th June 2018
  - Benralizumab, as an add-on therapy, is recommended as an option for treating severe eosinophilic asthma that is inadequately controlled in adults despite maintenance therapy with high-dose inhaled corticosteroids and long-acting beta-agonists, only if: (ie only as an alternative to reslizumab, not for those eligible for mepolizumab, and not for a non- biologic eligible population)
    - the blood eosinophil count has been recorded as 400 cells per microlitre or more in the past 12 months and
    - the person has agreed to and followed the optimised standard treatment plan, and has had at least 3 asthma exacerbations in the past 12 months
    - mepolizumab is not a treatment option and
    - the company provides benralizumab according to the commercial arrangement

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What the ACD2 means:

- Benralizumab vs mepolizumab
  Benralizumab is not recommended in people who are eligible for mepolizumab (eosinophils 300 and 4 or more exacerbations, and / or on maintenance oral corticosteroids). This includes any people on maintenance corticosteroids – **benralizumab is not cost-effective compared with mepolizumab**
- Benralizumab vs reslizumab
  Beralizumab is recommended in people who are eligible for reslizumab (eosinophils 400 and 3 or more exacerbations, not on maintenance oral corticosteroids) – **benralizumab is cost-effective compared with reslizumab**
- Benralizumab vs SoC
  Benralizumab is not recommended in people who are not eligible for other biological treatments (eosinophils 300 and 3 exacerbations, not on maintenance oral corticosteroids) – **no ICER was presented for this 'new' subgroup vs standard of care**

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Benralizumab clinical studies and subgroup for recommendation sought

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

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

Estimate, 95% CI Primary efficacy endpoint: Marginal annual exacerbation rate	Placebo (N=136)	Benralizumab 30mg Q8W (N=123)
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

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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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Key ICER's in ACD2

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

Results for whole population 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
Mepolizumab	[redacted]		[redacted]		

ERG base case with 2 amendments maintenance oral corticosteroids (mOCS) use at baseline 41.7% for SOC comparison and assuming same administration time for mepolizumab and benralizumab: **£32,179**
ERG scenario analysis for comparison whole population with SoC with 0% of people on mOCS: **£40,379**

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Committee's considerations – clinical

- Benralizumab is clinically effective as an addition to SoC in people with a blood eosinophil count of at least 300 cells per microlitre, who have had 3 or more severe exacerbations or are taking mOCS, but the absolute benefit would be greater for patients who have had more exacerbations and higher eosinophil counts
- The mixed population proposed by the company included the same patient mix as in the trial, and compared benralizumab in the whole population with SoC. Committee concerns:
  - There is no evidence that the patient mix in the NHS would be the same as in the trial, and the patient mix would determine the cost effectiveness
  - Ignored the availability of biologics in the NHS
  - Therefore more appropriate to consider the clinical and cost effectiveness of benralizumab depending on what treatments are available to them in the NHS
- MAIC vs. NMA was not been adequately justified and uncertainty about the clinical effectiveness of benralizumab compared with mepolizumab (MAIC) and reslizumab (assumed equivalence) remains
- No evidence presented on the effectiveness of benralizumab in people for whom biologics are not an option (300 to 400 cells per microlitre, who have had 3 exacerbations and who are not taking oral corticosteroids).

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Committee's considerations - costs

- Difficult to determine proportion taking mOCS in company's mixed population:
  - key area of uncertainty in the model had a substantial impact on the cost effectiveness
- ICERs for benralizumab compared with SoC in the mixed population provided by the company in response to consultation (£29,896 per QALY gained) and ERG (£32,179 per QALY gained) were not relevant to decision-making:
  - generalisability concerns about the mixed population
  - did not separate out those who are eligible for biologics in whom biologics are the appropriate comparator
  - ICER vs. SoC in people who were not eligible for biologics was not provided
- Therefore….
  - Benralizumab is not cost effective if:
    - mepolizumab is appropriate (eosinophil count of at least 300 cells per microlitre and 4 or more exacerbations or who are taking mOCS)
    - SoC is the only treatment option (eosinophil count between 300–400 cells per microlitre, who have had 3 exacerbations and who are not taking mOCS)
  - Benralizumab is only cost effective in people who are eligible for reslizumab (taking relevant patient access schemes into consideration)

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Understanding the recommendations

- Why wasn't benralizumab recommended in the mixed population?
  - It includes people with different severities of asthma for whom there are different comparators. It is more appropriate to consider the clinical and cost effectiveness of benralizumab depending on what treatments are available to people in the NHS
- Why was benralizumab recommended in people with a blood eosinophil count of 400 not 300 (inclusion criteria for the clinical trials)?
  - Benralizumab is only recommended when reslizumab is the comparator (eosinophil count of 400) - it is clinically and cost effective in this group
  - For those with a lower eosinophil count they are eligible for mepolizumab if they have 4 exacerbations or are on mOCS. Benralizumab is not cost effective compared with mepolizumab
- Why isn't it recommended in people on continuous oral steroids?
  - Individuals on mOCS are all eligible for mepolizumab and benralizumab is not cost effective vs mepolizumab
- Is benralizumab recommended 2nd line after mepolizumab?
  - No. There is no evidence of its effectiveness after mepolizumab

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ACD consultation responses

- Consultee comments from:
  - Company (AstraZeneca)
  - British Thoracic Society (BTS)
  - Association of Respiratory Nurse Specialists (ARNS)
  - NHS England
  - Royal College of Physicians (endorsing BTS statement)
- Commentator comments from:
  - Teva UK (reslizumab)
  - GSK (mepolizumab)
- Clinical expert web comment from:
  - Andrew Menzies-Gow (Consultant Respiratory Physician)
  - Brian Lipworth (Professor of allergy and pulmonology)
- Web comments from:
  - Asthma UK
  - Patient expert

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Consultation issues (1)
400 cells/microlitre eosinophil cut-off

Asthma UK, ARNS, BTS, NHS England, USAN and patient expert

- Unclear why a cut off of 400 cell/microlitre was used when 300 cell/microlitre was the entry criterion in the pivotal trials
- Patients who stand to benefit most from treatment with benralizumab have eosinophil counts suppressed by oral steroids
- People with an eosinophil count of 300-399 cell/uL and 3 exacerbations are currently not eligible for other monoclonal antibodies available, and their only treatment option is mOCS which causes significant adverse side effects

- The recommendations for benralizumab are not the same as the trial inclusion criteria because it is only recommended when reslizumab is a treatment option (recommended with a blood eosinophil count of 400)
- The date at which a high eosinophil count has to be recorded should not be specified
- No evidence was supplied that benralizumab is cost effective in people with eosinophil counts of 300-400 and 3 exacerbations who are not on mOCS;
- There has been no comparison of benralizumab with mOCS

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Consultation issues (2)
benralizumab second line to mepolizumab

Asthma UK, ARNS, NHS England, USAN and clinical expert

- Important to have different biologics within the same class (benralizumab works via a different receptor mediated mechanism of depleting eosinophil):
  - response rate to mepolizumab in clinical setting is around 30% in highly selected patients, only one default anti-IL5 will have adverse impact on patient care
- Benralizumab has been recommended 2nd line to mepolizumab – there is no logic to this, they are alternative drugs. Concern that mepolizumab should be tried before benralizumab is recommended:
  - People with inadequately controlled asthma on mepolizumab will have depleted eosinophils and it will take months of treatment on OCS for them to recover to 400 cell/uL to meet the criteria for benralizumab and reslizumab
  - In this time, the patient is at risk of deteriorating, experiencing serious exacerbations and will be experiencing concomitant side-effects from OCS

The use of benralizumab in people who had tried mepolizumab has not been considered in this appraisal – these patients were not included in the trials

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Consultation issue (3)
maintenance OCS as an eligibility criterion?

ARNS, Asthma UK, BTS, NHS England, USAN and patient expert

- The criteria should include patients who have had 3 or more exacerbations within the previous 12 months OR those also on continuous oral steroids.
  - ability to reduce/remove OCS use is frequently as, or more, important than preventing future attacks & illogical to have a clinically significant reduction in OCS as an outcome for adequate response in people not on OCS
- Recommendation does not consider potential benefits to patients who are on mOCS to manage symptoms but may not have asthma exacerbations. Benralizumab is potentially steroid sparing and should be considered as an option for these patients
- Patients on mOCS may appear ineligible for benralizumab because eosinophil levels and asthma exacerbations are reduced by OCS use

- Benralizumab is recommended only as an alternative to reslizumab, where it is cost-effective
  - People on mOCS OR 4 exacerbations are eligible for mepolizumab and benralizumab is not cost-effective compared with mepolizumab
- The time at which a high eosinophil count was recorded should not be stated

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Consultation issues (4)
self-administration / dosing of benralizumab

- Asthma UK and patient expert
- Insufficient weight on the benefit of 8 weekly administration of benralizumab (vs. 4 weekly mepolizumab) considered by committee. This and self-administration of benralizumab may reduce the burden of managing severe asthma:
  - people travelling long distances to visit specialist clinics (time off work)
  - people with chronic condition are constantly fearful of losing their jobs due to a poor sickness records and taking time off work for appointments etc.
  - impact of long term OCS use not considered as many people may have co-morbidities, thereby juggling lots of hospital appointments
  - therefore, self-administration would be huge step forward for patients and would free up a significant amount of time in specialist centres
  - patient choice and wellbeing is an important factor in deciding which monoclonal antibody should be prescribed by clinicians

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Consultation issue (5)
suitability of "mixed population"

Asthma UK and NHS England

- 'Mixed' population is suitable for comparing benralizumab with SoC:
  - mepolizumab and omalizumab HTA's not based on trial data and included the same mixed population (suggests this is appropriate)
  - incorrect assumption that mixed population includes people with different severities of asthma. Clinicians do not differentiate between in the way suggested by the committee
  - eosinophil level does not differentiate between asthma severity; people with mild asthma can have elevated blood eosinophil levels.
- Lower eosinophil count does not mean that a patient's asthma is less severe and such people should still be eligible for benralizumab

- Benralizumab is the 3rd to market product and needs to be compared against comparators specified in scope
- Benralizumab recommendations specified eospinophil count, number of exacerbations and OCS use (used in the mepolizumab and reslizumab guidance) to show where it is recommended in the current treatment pathway
- Eosinophil count was an inclusion criterion for the main trial

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Consultation issues (6)
recommendations not suitable for the NHS

ARGN, Asthma UK and BTS:

- Summaries of clinical effectiveness used to generate the patient group recommended in the second consultation document are not reasonable interpretations of the evidence
  - current provisional recommendations are not sound and are not a suitable basis for guidance to the NHS
  - recommendations should be reconsidered based on the evidence currently available
- Eligibility criteria for benralizumab are too restrictive and may mean people miss out on life changing treatments

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Consultation issues (7)
GSK (comparator)

- Draft recommendation is balanced reflection of the evidence presented
- Implementation of 'and mepolizumab is not a treatment option' may be open to interpretation and may be given to larger than anticipated population with increased budget impact.
  - Consider changing to 'and where an individual is ineligible for mepolizumab based on clinical criteria or has previously not adequately responded to mepolizumab'.
- Update draft guidance to include the word "severe": *"has had at least 3* ***severe*** *asthma exacerbations in the past 12 months"*
- Update draft guidance to avoid ambiguity regarding people ineligible for mepolizumab.
  - Consider adding "*has had 3 asthma exacerbations needing systemic corticosteroids in the past 12 months or*
  - *at least 4 asthma exacerbations needing systemic corticosteroids and is ineligible for mepolizumab based on clinical criteria (or has previously not adequately responded to mepolizumab)"*
- Reiterate disagreement with company assumption that relative efficacy between benralizumab and mepolizumab in the ITT population can be applied to more severe sub-groups
- The innovation benefit offered by benralizumab is short-lived

[redacted]

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Consultation issues (8)
Teva (comparator)

- Concern raised regarding statement in appraisal consultation document that 'the simple assumption of clinical equivalence between the 2 treatments (reslizumab and mepolizumab) is questionable, however it is reasonable to assume that they are not very different.'
  - No clinical data directly comparing benralizumab and resilzumab; assumption is unfounded
- Indirect evidence indicates a efficacy difference between the 2 treatments. Subgroup analysis from phase III trials report efficacy results for reslizumab of 67% (RR 0.33, 95% [0.22, 0.49]) published at the ERS 2017 Chauhan et al. compared to 53% (RR 0.47, 95% [0.32 to 0.67]) as reported in the appraisal document

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Company response
Appropriateness of the mixed population

- Company seeking recommendation in the **same mixed population**: people with a blood eosinophil count of 300 cells per microlitre or more AND either 3 or more asthma exacerbations in the prior year or treatment with continuous oral corticosteroids over the previous 6 months **(company base case population)**
  - SoC is still used in majority of people (84.5%) who meet eligibility criteria for mepolizumab NICE recommended population and is not the only relevant comparator for the non-biologic eligible population
  - SOC is a relevant comparator in the mepolizumab and reslizumab eligible populations
  - NICE methods guide section 6.2.2 and 6.2.3 SOC therefore represents established practice for the base case population *"The Committee will normally be guided by established practice in the NHS when identifying the appropriate comparator(s)"*
- There is strong clinical support for recommending benralizumab in a wider population (the mixed base case population, no pre-defined sequencing)

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Company response
Generalisability of mixed population

- Observational evidence provided in response to ACD1 showed that the proportion of people with exactly 3 exacerbations (and not on mOCS) was 31.2%:
  - This is a percentage of the entire base case population (300+ eosinophil count AND either 3+ exacerbations in prior year OR receiving mOCS)
  - The ERG reported percentages from CSRs of benralizumab trials of people with exactly 3 exacerbations (and not on mOCS) of the entire trial primary end point populations (300+ eosinophil count; AND 2+ exacerbations in prior year) and not as a percentage of base case population. **Populations not equivalent therefore percentages are different**

	Observational UK RWE	SIROCCO/CALIMA
	As % of base case population	
People with 3 exacerbations, not taking mOCS & eosinophil count of 300 or more	[redacted]	[redacted]
People with 3 exacerbations, not taking mOCS & eosinophil count of 300-399 (non-biologic-eligible population	[redacted]	[redacted]

  - 31.2% vs. 24.6% expected to have minimal impact on the ICER
  - 41.7% people on mOCS at baseline used in the ERG's SOC and the mepolizumab population based on all asthmatics is too low. 54.1% (300+ eosinophil and 3+ exacerbations would be more appropriate

Note: The ERG base-case included 60% of people on mOCS at baseline instead of 41.7%

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Company response
Precedent in previous appraisals

- The mepolizumab and reslizumab appraisals accepted the mixed population for decision making despite different severities of disease in mixed populations
- Mepolizumab was recommended in this mixed population with a final ICER of £29,163
- Reslizumab was more cost effective and was recommended in population of people with 400+ eosinophil count, AND 4+ exacerbations in prior year (ICER: £29,870) than in the full mixed population of patients with 400+ eosinophils, AND 3+ exacerbations in prior year. Unlikely that reslizumab would have been cost effective in a population of patients with exactly 3 exacerbations
- Given that NICE has on both of occasions accepted a mixed population to be appropriate for decision making, the company requests a similar approach for benralizumab

- In both the reslizumab and mepolizumab appraisals, recommendations were made in optimised mixed base case population vs. the benralizumab proposed population (which is a trial subgroup chosen by the company)
- In both the reslizumab and mepolizumab appraisals the comparators in the scope were SoC (+ omalizumab for the subgroup with persistent allergic IgE-mediated eosinophilic asthma). They were not compared with each other
- Benralizumab scope includes mepolizumab and reslizumab as relevant comparators according to NICE guidance

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Company response
Revised model inputs to company model

Input	Value	Justification
Price of benralizumab	[redacted] per vial	Revised PAS
% patients on mOCS	54.1% in the base case population 60% in the mepolizumab NICE recommended population	As per UK real world evidence* As per base case at ACD1
Administration time	5 minutes for benralizumab 20 minutes for mepolizumab (15 mins extra administration time vs benralizumab)	As per first committee meeting clinical expert opinion
All other model inputs are aligned with ERG's base case		

*source: sub analysis of a UK AstraZeneca sponsored study not available in the public domain. Raw data provided

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Company response
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]	£25,192
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
Mepolizumab	[redacted]		[redacted]		

Results vs SoC in the non-biologic eligible population					
	Total cost	Δ cost	Total QALYs	ΔQALYs	ICER
Benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	£38,304
SoC	[redacted]		[redacted]		

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Company response
Further points

- Advantage of benefits of administration method (pre-filled syringe) and less frequent dosing of benralizumab reiterated
  - [redacted]
- [redacted]
  - [redacted]

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ERG critique – SOC only population

- Cost effectiveness results for population with 300-399 eosinophil count, (exactly) 3 exacerbations, and no mOCS use at baseline (non-biologic-eligible population) is highly uncertain for the following reasons:
  - small sample size: 16 and 14 people in each arm of trial used to obtain updated transition probabilities and utility values
  - proportions of patients responding to benralizumab in the 300-399 eosinophil count, no mOCS use and ≥300 eosinophil count or receiving mOCS populations are the same
  - distribution of exacerbations in 300-399 eosinophil count population and ≥300 eosinophil count also the same. Hospitalisation rate is likely to be lower in 300-399 SOC only group
    - same hospitalisation rate assumption improves cost-effectiveness of benralizumab in the non-biologic eligible population
  - inconsistency between the updated exacerbation rate ratio (0.39) which improves the cost-effectiveness of benralizumab compared with SOC and the results of the pooled SIROCCO and CALIMA analysis reported by FitzGerald et al. (2017)
    - rate ratio (RR) likely to be between 0.45-0.73 and is higher for lower eosinophil at baseline
    - RR of 0.47 (used in company base case analysis) could be considered the lower bound for the RR in the sub-population of interest (ERG used transition probabilities from company base-case incorporating this RR in their updated analyses)

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ERG critique – mixed population

Cost-effectiveness results for non-biologic eligible population

- Using the same transition probabilities as the base-case population, updated utility values from company response to ACD2 and all other assumptions as in the ERG's base case, the ICER for 300-399 eosinophil count, 3 exacerbations and no mOCS subpopulation is £45,406 per QALY gained.
  - This estimate represents *the lower bound* for the ICER in the benralizumab vs. SoC comparison in this particular population

Cost-effectiveness results for benralizumab vs. SOC for the base-case population

- Assuming 54.1% in the base-case population are taking mOCS at baseline and updated PAS price (with all other assumptions as in the ERG's base case), the ICER for the comparison of benralizumab vs. SoC is £25,587 per QALY gained.

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Key issues for consideration

- The committee decided that three comparators in the scope – mepolizumab, reslizumab and standard of care – were relevant, depending on the patient characteristics and current eligibility for biologics. Would the committee like to reconsider the company base-case comparing benralizumab for the whole population to SOC alone with an ICER of £25,192 per QALY gained?
- Should existing biologics be ignored in the cost effectiveness on the basis of poor uptake?
- Is benralizumab cost effective compared with mepolizumab (when both confidential PAS's are considered)?
- If not should the use of benralizumab second-line to mepolizumab be considered?
- For patients currently ineligible for biologics what is the committee's view of the company's ICER vs SoC of £38,304 per QALY gained
- Should additional weight be given to an 8 weekly vs 4 weekly dosing schedule and prefilled syringes?

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