Benralizumab for treating severe asthma

Errata

Location in report	Original text	Corrected text
Section 1.3, p. 20	The ERG noted that the treatment effect of benralizumab appeared to consistently favour benralizumab in both pooled trials only for the Asian population. While benralizumab has been shown in the CS to effectively reduce annual asthma exacerbations, the ERG noted a small clinically negligible 6% reduction in nocturnal awakenings (reported in SIROCCO CSR only).	The ERG noted that the treatment effect of benralizumab appeared to consistently favour benralizumab in both SIROCCO and CALIMA trials only for the Asian population.
Section 1.5.2, p. 24	Mortality due to asthma is also a key parameter in this appraisal.	It is also an important parameter in this appraisal.
Section 1.5.2, p. 25	In the ERG's analysis, all probabilities related to asthma-induced death were reduced except those in patients of 45-100 years old (for OCS burst and ER visit) and 65-100 years old (for hospitalisation) as it was not possible to conduct extensive searches for relevant sources due to time constraints (Table 60)	In the NRAD report which was used by AstraZeneca to parameterise asthma mortality risk in hospital settings, it is stated that the majority of people (57%) who died from asthma between February 2012 and January 2013, "*were not recorded as being under specialist supervision during 12 months prior to death*". However, the patient population considered in this appraisal are patients with severe asthma *who have been on asthma treatment during the previous 12 months*. In this analysis, only the probabilities of asthma-related death in hospitalised patients from 45-54 and 55-64 age categories were reduced by factor of 2.5 (see Table 60). The probabilities of asthma death in patients 45 years of age and older requiring OCS burst or ER visit, and hospitalised patients ≥65 years of age were kept unchanged as it was not possible to conduct extensive searches for relevant evidence sources due to time constraints.

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Section 1.5.3, p. 26		However, under a PAS price for mepolisumab, this assumption had a moderate effect on the cost-effectiveness of BEN vs. MEPO.
Section 1.5.4, p. 26		The ERG noted (p. 164, company's submission): "In order to calculate the percentage of patients in each population who would be dependent on mOCS at baseline in UK clinical practice, an analysis of the Kerkhof 2017 paper, a UK observational research study, was undertaken. For a full description of the baseline characteristics refer to Table 22". However, the proportions reported by Kerkhof - 16.5% in patients 18-64 y.o. and 17.1% in patients >=65 y.o. - were substantially lower than those in the company's base case. Also, as shown in Table 22 (company's submission) which the company referred to, *only about 23% of patients in pooled SIROCCO/CALIMA* dataset were on mOCS at baseline.
Section 1.5.7, p. 28		Of note, in the MEPO appraisal, the annual attrition rate was 10%.
Section 1.5.8.1, p. 29		In the appraisal of mepolizumab, committee considered that utilities should be age-adjusted, and this adjustment was incorporated in the updated base case (p. 73, committee papers dated 1 December, 2016).
Section 1.5.8.2, p. 29		In the revised base case, the respective assumptions were *20.3, 19.2 and 24.4 days*, which were based on the midpoint values between MENSA and Lloyd et al. (2007) [16]. In the updated base-case analysis for reslizumab appraisal, the length of severe exacerbations was confidential but definitely *less than the model cycle of 4 weeks*.
Section 1.3, p. 31	While benralizumab has been shown in the CS to effectively reduce annual asthma exacerbations, [redacted]. This may have implications for HRQoL.	While benralizumab has been shown in the CS to effectively reduce annual asthma exacerbations, [redacted]
Section 1.6.2.2, p. 32	The company assumed that the same percentage of patients	

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	taking mOCS respond to benralizumab and reslizumab. The ERG noted, however, that these drugs have different mechanisms of action, and therefore, this assumption would need further clarification (Section 5.2.2.1).	
Section 4.1.5, p. 58	[redacted]	
	In summary, reporting bias is a concern in the ZONDA trial due to incomplete reporting of data in the trial publication and appendices, particularly with regard to nocturnal awakening and rescue medication [redacted]	
Section 4.2.1, p. 75	However, the difference in total asthma score reduction (-0.25), though statistically significantly, did not reach MCID.	However, the difference in total asthma score reduction (-0.25), though statistically significantly, did not reach Minimum Clinically Important Difference (MCID) defined as score changes of 0.5 point or more for ACQ-6 and AQLQ(S)+12 [13].
Section 4.2.1, p. 78	Data in this main analysis included patients with two exacerbations in the year preceding trial enrolment.	Data in this main analysis included also patients with two baseline exacerbations in addition to patients who qualified for inclusion per NICE scope (i.e. ≥ 3 baseline exacerbations).
Section 4.2.1, p. 80	The ERG believed that a meta-analysis of the summary estimates derived from the analysis of each trial's individual patient data would provide a more precise estimate without losing trial identity.	The ERG believed that a fixed-effects meta-analysis of the summary estimates derived from the analysis of each trial's individual patient data would give the same result as the pooled analysis but a random effects meta-analysis would provide a wider confidence interval. However, the ERG noted that the relationships were not statistically significant as there were overlaps in all 95% CI.
Section 4.2.1.1,		The reduction in AER in the subgroup population is similar to result from the ITT

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p. 86		analysis of benralizumab Q8W from the SIROCCO (51%) trial but higher than AER reduction reported for the ITT analysis of benralizumab Q8W from the CALIMA trial (28%).
Section 4.2.1.1, p. 87	[redacted]	[redacted]
Section 4.6, p. 137	While benralizumab has been shown in the CS to effectively reduce annual asthma exacerbations, the [redacted]	The reduction in AER for the pooled subgroup analysis was similar to that from the ITT analysis of the SIROCCO trial (51%) but higher than the AER reduction from the ITT analysis of the CALIMA trial (28%). No death was considered related to investigational product.
Section 5.2.2.1, p. 146		The company stated in the factual accuracy check pro forma: "*The final guidance for mepolizumab states that patients should "continue treatment if the asthma has responded adequately and assess response each year. An adequate response is defined as: at least 50% fewer asthma exacerbations needing systemic corticosteroids in those people with 4 or more exacerbations in the previous 12 months or a clinically significant reduction in continuous oral corticosteroid use while maintaining or improving asthma control." This is the continuation criteria used within the company model and the [redacted] of patients who respond to mepolizumab is reflective of this.*" The CS reads: "*As the data regarding the percentage of patients responding to*

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		mepolizumab is not specific as to whether it applies to the non mOCS or the mOCS population and it is referenced to the MENSA/DREAM trials it is assumed that this percentage relates to the non mOCS population and an assumption is made that the percentage of responders in the mOCS population is equal that of benralizumab."
Section 5.2.2.1.1, p. 147		In the MEPO appraisal, the annual attrition rate was assumed to be 10% (p. 81, committee papers dated 1 December, 2016).
Section 5.2.6.1.2, p. 159	According to the results of the pooled SIROCCO/CALIMA subgroup analysis shown in Table 20, the marginal annual exacerbation rates for BEN and placebo were 0.85 and 1.83, respectively; the annual rates of ER visits were 0.05 and 0.15 for BEN and placebo, respectively; hospitalisation rates were *not reported*, but the relevant RR was 1.01; and exacerbation rates requiring OCS burst were also missing in the CS. For the BEN vs. SOC comparison, the company's model predicted a twice higher rate of hospitalisation in SOC patients; underestimated the rate of exacerbations requiring ER visit, and overestimated OCS rate in BEN patients.	
Section 5.2.6.3, p. 161		For the comparison vs. SOC, the company assumed that 30.1% and 10.7% of patients in the BEN and SOC arms, respectively, discontinue mOCS at 28 weeks after treatment initiation. In the MEPO comparison, the respective proportions for BEN and MEPO were 20.2% and 9.82%; these proportions were not reported in the company's submission (they were taken from the company's model). In MEPO appraisal, to account for benefits of mOCS sparing, the company applied a reduction of £4,000-£9,000 to the ICER in a scenario analysis, referring to the appraisal of

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		omalizumab (p. 133, committee papers dated 1 December, 2016). In the RESLI appraisal, the model did not incorporate stopping or reducing the dose of oral corticosteroids, because the dose was kept constant in the pivotal trials (p. 13, committee papers dated 3 February, 2017) [8].
Section 5.2.6.5.2, p. 165		Importantly, *only adjustments made to 45-54 and 55-64 age categories for hospital admissions were effectively used in the ERG's base case* since the modelled age at treatment initiation was 50 years. In the updated base case for the MEPO appraisal, mortality rates in hospitalised patients from these age categories were 0.0092 and 0.0152, respectively; the probability of death in patients 65+ was 0.0455 (p. 75, committee papers dated 1 December, 2016). In RESLI appraisal, the asthma mortality was modelled based on Roberts et al. (2013) [2] (p. 32, committee papers dated 20 July, 2017). The authors reported odds ratio estimates from a logistic regression model for asthma-related mortality *within 30 days from hospital admission for asthma.* The following odds ratio estimates were used: - 2.4 for 45-54 age group - 6.3 for 55-64 age category - 12.3 for 65+ patients The 18-24 age group was the reference category.
Section 5.2.7.1, p. 168		Of note, in the RESLI appraisal, utilities reported by Willson et al. (2014) [49] and Lloyd et al. (2007) [16] were used.
Section 5.2.7.2, p. 170		In the revised base case, the respective assumptions were *20.3, 19.2 and 24.4 days*, which were based on the midpoint values between MENSA and Lloyd et al. (2007) (p. 10, committee papers dated 1 December, 2016). In the updated base-case analysis for reslizumab appraisal, the length of severe exacerbations was confidential but definitely less than the model cycle of *4 weeks* (p. 57, committee papers dated 20 July, 2017).