National Institute for Health and Clinical Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Mirabegron for the treatment of symptoms associated with overactive bladder

Please find enclosed the ERG report prepared for this appraisal.

You are asked to check the ERG report from *BMJ-TAG* to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 5pm, *18th January 2013* using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The attached proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 UK brand name

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 9 of the ERG report describes the brand names of mirabegron in Japan (Betanis™) and the US (Myrbetriq™), but not the brand name that will be used in Europe.	Astellas propose that the Committee use the UK brand name - Betmiga™	To maintain consistency, and avoid confusion when discussing mirabegron in the UK.	Not a factual inaccuracy; no change required. The ERG thanks the manufacturer for their comment. The ERG chose to specify the brand names of mirabegron as licensed in the USA and Japan. The ERG acknowledges the manufacturer's point but does not consider this to be a factual error.

Issue 2 European licence update

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 9 and 147 of the ERG report discuss the licence status of mirabegron in Europe. Mirabegron has been awarded a marketing authorisation since the manufacturer submission was sent to NICE.	Astellas suggest that the text is amended to: **"The European Commission granted marketing authorisation for Betmiga (mirabegron) for the symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in patients with overactive bladder (OAB) syndrome on 21st December 2012"**	To maintain accuracy	Not a factual inaccuracy; no change required. At the time of writing of the ERG report, mirabegron had not been awarded marketing authorisation. On page 24 of the ERG report, the ERG highlights that "The manufacturer anticipates that the European Medicines Agency (EMA) will issue

			marketing authorisation in late January 2013."

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 10 of the ERG report states "In addition to the three trials submitted as direct clinical evidence, the manufacturer identified publications on 40 trials in OAB..."	Astellas would like to clarify that the three trials submitted as direct clinical trial evidence are actually part of the 40. Astellas suggest rewording this sentence.	To maintain accuracy	The ERG thanks the manufacturer for highlighting this inaccuracy. The sentence has been amended to read "Including the three trials submitted as direct clinical evidence, the manufacturer identified publications on 40 trials in OAB evaluating interventions listed as comparators of interest in the scope and that were used to construct networks to evaluate the comparative clinical effectiveness of mirabegron."

Issue 4 Formatting

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Boxes 10 and 12 within the ERG report are obscuring some text below	Re-format	Several lines of text of the ERG report are unreadable	Not a factual inaccuracy; no change required.

			The ERG thanks the manufacturer for highlighting this potential formatting problem. The text around Boxes 10 and 12 is visible in the ERG's local version of the report. NICE is aware of the issue.

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 101 of the ERG report states **"Furthermore, the ERG notes that although the manufacturer has disaggregated discontinuation as a result of an AE and discontinuation as a result of other-causes, in some instances the same probability is used for both. In particular, the probability of other-cause discontinuation is used to inform the probability of immediate discontinuation (i.e. within the same cycle) as a result of an AE. The probability of other-cause discontinuation was assumed to be treatment specific and in the manufacturer's base case (primary and secondary), was derived from the published	Astellas would like to clarify that we did not use the same probability value for discontinuing due to an AE or discontinuing due to other causes. The model uses a probability of immediate discontinuation if a patient experiences an AE regardless of treatment type (90%) and a probability of a patient discontinuing for causes other than AEs (based on overall persistence data from Wagg et al corrected to exclude the proportion of patients discontinuing due to AEs). This rate was different for each comparator, and mirrored in the mirabegron arm to isolate the effect of AEs. The most likely reason for discontinuation other than AEs is a lack of efficacy and therefore it is intuitive that this discontinuation rate may be linked to the individual efficacy of each comparator. A persistence rate of 28% was used for the analyses versus tolterodine (based on the	To maintain accuracy	Not a factual inaccuracy, no change required, In the statement made by the ERG, that the model uses the same probability of discontinuation as a result of AEs and discontinuation as a result of other causes, the ERG is referring to the probability of **immediate** discontinuation as a result of an adverse event. That is, the probability that informs the transition from, for example, the "Mirabegron 2nd month" health state to the "Next line of therapy B1 Start" health state (i.e. Transition_Matrix MICT:CZ15). The ERG notes that the 90% probability of

literature to exclude discontinuation as a result of AEs." Similarly: Page 114 of the ERG report states **"Moreover, the ERG notes that the manufacturer reported that 28% of mirabegron patients were observed to persist with treatment after 12 months; although, it is unclear which data the manufacturer used to inform this statement."**	persistence rate of tolterodine in the Wagg et al study) however, the persistence rate of mirabegron in analyses versus other comparators should be changed to match their respective persistence rates. We presented this method as a highly conservative approach to predicting the real life persistence rate of mirabegron. Expert opinion has reported that a much higher persistence rate would be expected with mirabegron given its efficacy and tolerability profile from the key phase three studies. Astellas propose that the sensitivity analysis in which a persistence rate of 28% is assumed for mirabegron versus all comparators is reviewed, and that expert opinion is sought to inform the most clinically plausible estimate for the persistence rate of mirabegron.		discontinuation referred to by the manufacturer is that which informs, for example, the transitions from the "Mirabegron w/AE 2nd month" health state to the "Next line of therapy B1 Start" health state (i.e. Transition_Matrix MICT:CZ40). The ERG would like to thank the manufacturer for clarifying the data on which the statement in the MS "28% of patients continue treatment beyond 12 months" (MS; pg 200) is based. However, at the time of writing the ERG report, this was unclear. Furthermore, based on evidence from the ERG's MTC, the ERG does not agree that it is conservative (i.e., biased against mirabegron) to assume a persistence rate equivalent to tolterodine.

Issue 6 Balance of the report

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 132 of the ERG report the tornado diagram which presents the deterministic sensitivity analysis of the manufacturer's base case is described inappropriately. The current text reads ***"the ERG notes that most of the analyses returned ICER estimates of less than £17,000 per QALY gained."***	Astellas would like to clarify that "most" of the ICERs are less than £10,000 per QALY gained, with only three of the thirty analyses presented approaching £17,000 per QALY gained. The current description therefore implies that mirabegron is less cost-effective under many sensitivity analyses than the data shows. Astellas suggest that the text is amended to ***"the ERG notes that most of the analyses returned ICER estimates of less than £10,000 per QALY gained, with the three most sensitive parameters increasing the ICER to up to £17,000 per QALY gained"***	To fairly represent the data.	Not a factual inaccuracy, no change required.

Issue 7 Interpretation of dominance

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 146, the description of the ERG's sensitivity analyses are open to misinterpretation. The current text reads **"The ERG notes that the impact of each sensitivity analysis on the ICERs for mirabegron 50 mg versus solifenacin 5 and 10 mg was highly variable, with ICERs ranging from £573 to the**	Astellas would like to clarify that the text "**dominance of solifenacin**" may be misinterpreted to mean that mirabegron is dominated by solifenacin rather than solifenacin is dominated by mirabegron Astellas suggest that the text is amended to **"...ICERs ranging from £573 to solifenacin being dominated..."**	To maintain a clear report and fairly represent the data.	The ERG thanks the manufacturer for highlighting this inaccuracy. The sentence was intended by the ERG to be read as the dominance of solifenacin over mirabegron as a result of misreading the results table. The text has therefore been amended to read "The ERG notes that the impact of each sensitivity

dominance of solifenacin in the comparison of mirabegron 50 mg versus solifenacin 10 mg."			analysis on the ICERs for mirabegron 50 mg versus solifenacin 5 and 10 mg was highly variable, with ICERs ranging from £573 to £32,572".