Response to:

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Appraisal consultation document

Mirabegron for treating symptoms of overactive bladder

Prepared by:

Astellas

22nd March 2013

Response to the Appraisal Consultation Document: Mirabegron for treating symptoms of overactive bladder [ID542]
Approved Name of Medicinal Product: mirabegron
Brand Name: Betmiga
Company: Astellas UK

General comments

Astellas welcome the opportunity to review and comment on the Appraisal Consultation Document (ACD) relating to the appraisal of mirabegron for treating symptoms of overactive bladder (OAB).

Astellas believe that patients with OAB should have access to all efficacious medicines available in the UK, and agree with the Appraisal Committee's recommendation for mirabegron use.

We believe that all relevant clinical and cost effectiveness evidence has been taken into account and well interpreted, and that these provisional recommendations represent a sound and suitable basis for guidance to the NHS, which will be greatly appreciated by both clinicians and OAB patients.

Astellas would like to request that the Appraisal Committee considers how the guidance should be interpreted for more vulnerable groups of patients for whom the favourable side effect profile of mirabegron may have a more profound benefit. For example, elderly patients in whom the excess side-effects of antimuscarinics may be distressing, or patients in whom an anticholinergic burden may already be present due to the properties of other medications. Mirabegron offers a differing side-effect profile to the only currently available pharmacological option, which would give clinicians an alternative when antimuscarinics would be less suitable, rather than strictly contraindicated.

Specific comments:

Astellas would like to offer further clarity to some of the issues identified by the ERG in Section 3.45 of the ACD (see Table 1 below).

Table 1: Astellas comments on areas of inaccuracy/uncertainty identified by ERG

Issue identified by ERG	Comment from Astellas
Uncertainty resulting from heterogeneity associated with manufacturer's MTC	We recognise that there is a degree of uncertainty resulting from the heterogeneity of the studies included in the MTC. However, each of the 40 studies (including 18 studies later removed by the ERG) were included as it was felt that they provided information pertinent to the scope. A more restrictive inclusion criteria runs the risk of ignoring potentially relevant evidence. Most importantly, the results of either approach show a broadly similar and intuitive result.
Assumption of variable other-cause discontinuation for mirabegron patients	A key feature of patients prescribed antimuscarinics is their high tendency to discontinue treatment. Discontinuation rates for mirabegron would be under-estimated if clinical trial data were used because investigators were encouraged to keep patients on treatment. However, no real-world data is yet available on likely persistence. As such, we took a conservative approach in assuming that the persistence rate experienced when prescribed mirabegron could be based on that of the comparator antimuscarinics - for which retrospective persistence data is available. Using rates from Wagg *et al.*[a] the annual persistence of mirabegron when compared to tolterodine was based on 28% (because tolterodine has an annual persistence rate of 28%), and the annual persistence of mirabegron when compared to solifenacin was based on 35% (because solifenacin has an annual persistence rate of 35%). If discontinuation is considered to be a product of both efficacy and tolerability, then mirabegron would lie between values associated with solifenacin and tolterodine based on efficacy, and would be likely to demonstrate substantially better persistence based on tolerability. Therefore, we believe that assuming a 28% annual persistence rate for mirabegron (as described in the ERG's analysis) does not represent the most plausible ICER versus all antimuscarinics. The most plausible ICER based on current evidence may be derived from an annual persistence rate somewhere between 28% for tolterodine and 35% for solifenacin based on efficacy data. Please find below the ICERs for mirabegron 50mg vs. tolterodine 4mg ER and solifenacin 5mg with different estimates of persistence rate for mirabegron:

[a] Wagg A, Compion G, Fahey A, Siddiqui E. Persistence with prescribed antimuscarinic therapy for overactive bladder: a UK experience. BJU Int. 2012 Mar 12.

<table>
<tr><td></td><td>
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<tr><th></th><th>Mirabegron 50mg vs tolterodine 4mg ER (SCORPIO data)</th><th>Mirabegron 50mg vs solifenacin 5mg (MTC data)</th></tr>
<tr><th>Annual persistence rate for mirabegron</th><th>ICER[1]</th><th>ICER[2]</th></tr>
<tr><td>28%</td><td>£4,383</td><td>£32,571</td></tr>
<tr><td>29%</td><td>£4,397</td><td>£25,665</td></tr>
<tr><td>30%</td><td>£4,411</td><td>£21,383</td></tr>
<tr><td>31%</td><td>£4,423</td><td>£18,470</td></tr>
<tr><td>32%</td><td>£4,435</td><td>£16,359</td></tr>
<tr><td>33%</td><td>£4,446</td><td>£14,758</td></tr>
<tr><td>34%</td><td>£4,456</td><td>£13,504</td></tr>
<tr><td>35%</td><td>£4,465</td><td>£12,493</td></tr>
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[1] based on a tolterodine 4mg ER annual persistence rate of 28%
[2] based on a solifenacin 5mg annual persistence rate of 35%
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<tr><td>Assumption that immediate (that is, within the same cycle) discontinuation as a result of an adverse event would be equivalent to the rate of other-cause discontinuation</td><td>Astellas would like to clarify that we did not use the same probability value for a patient discontinuing due to an AE or discontinuing due to other causes.

The model uses a probability of:

1. immediate discontinuation if a patient experiences an AE regardless of treatment type (90%), and;
2. a probability of a patient discontinuing for causes other than AEs, based on retrospective overall persistence rates from Wagg et al.(as described above) corrected to exclude the proportion of patients discontinuing due to AEs.

The 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 element of the overall discontinuation rate may be linked to the individual efficacy of each comparator.</td></tr>
<tr><td>Possibility of infinite treatment discontinuation and re-initiation, a factor of the ‘lack of memory’ associated with the Markov model</td><td>It is recognised that Markov models are associated with a lack of memory, however, the choice of a Markov model as a basis for this cost-effectiveness analysis was considered most appropriate because:

• Describing a patient’s OAB symptoms as of 1 of 25 health states (5 severity levels of micturition frequency and 5 severity levels of incontinence frequency), allowed a more detailed analysis of the changing costs and benefits experienced by all patients within a general OAB population. While we accept that it was possible that some patients could have unrealistically discontinued and restarted treatment, this structure was still felt to represented the most plausible simulation of a chronic and complicated disease.

• Sensitivity analyses show that assuming that patients never reinitiate treatment after discontinuation had little impact on the results. The ICER</td></tr>
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	for mirabegron vs. tolterodine based on the SCORPIO trial for the overall population, changed from £4,386 to £6,830. • A model with memory would have to be a microsimulation model such as a discrete event simulation model, or Markov model at patient level. Such models have a long running time, which make them impractical for sensitivity analyses, especially probabilistic sensitivity analyses. We opted for a simpler model, with extensive analyses of uncertainty. This approach is supported by Griffin *et al*.[b]
Use of adverse event rates from SCORPIO rather than the manufacturer's safety study TAURUS	Adverse event rates from SCORPIO are generally higher than those in TAURUS and therefore their inclusion in the model provides a more conservative estimate of the ICER for mirabegron. As noted by the ERG in Section 3.50 of the ACD, use of the adverse event rates from TAURUS would actually **decrease** (by £72) the base case ICER from £4,386 to £4,314.
Cost associated with botulinum toxin injections	The cost of botulinum toxin injections used in the model was £1,158 for the initial injection and £964 for re-injections (Nottingham Urology Group)[c]. The ERG identified NHS reference costs for botulinum toxin of £321 and £212. The effect of assuming £321 for the initial injection and £212 for re-injections on the cost-effectiveness of mirabegron was minimal. The ICER increases from £4,386 to £5,196.

Abbreviations: ERG, evidence review group; ICER, incremental cost-effectiveness ratio; MTC, mixed treatment comparison; NHS, National Health Service; PbR, payment by results.

[b] Griffin S, Claxton K, Hawkins N, Sculpher M. Probabilistic analysis and computationally expensive models: Necessary and required? Value Health. 2006 Jul-Aug;9(4):244-52.

[c] http://www.nottinghamurologygroup.co.uk/treatments/bladder-botulinum toxin-injections)