NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Mirabegron for treating symptoms of overactive bladder

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Astellas UK	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.	Thank you for your comment. Comment noted. The Committee noted that withdrawal rates due to adverse events did not differ in the mirabegron and tolterodine tartrate arms of the TAURUS trial and the manufacturer did not provide additional evidence of mirabegron having a lower rate of adverse events in older patients. The Committee concluded that there was no evidence to support a different recommendation for older people. With respect to people who had a high cholinergic burden from other medications, the Committee concluded that normal prescribing practice would involve an assessment of existing medications and potential drug interactions, and it was not necessary to specify this in the guidance. (see FAD section 4.20).
Astellas UK (continued)	***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.	The Committee was aware of the uncertainties in the manufacturer's and ERG's MTCs (see FAD section 4.11, 4.17, and 4.19). The Committee concluded that the MTCs indicated that mirabegron, like antimuscarinic drugs, offers modest improvements compared with placebo, but it was more uncertain whether it had equivalent efficacy to all antimuscarinic drugs.

Consultee	Comment	Response
Astellas UK (continued)	***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.*[1] 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: **[table not reproduced in this document]**	The Committee discussed the uncertainties in the persistence rates of mirabegron and antimuscarinic drugs (see FAD section 4.5). The Committee concluded that there was no clear evidence that persistence rates with mirabegron would differ from current pharmacological treatments.

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

Consultee	Comment	Response
Astellas UK (continued)	***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*** 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: 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 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.	The Committee was aware that the discontinuation rate in the model was based on persistence rates derived from Wagg et al, and discontinuation rates set at 90% based on expert opinion (see FAD section 3.35 and 3.47). The Committee concluded that there was no clear evidence that persistence rates with mirabegron would differ from current pharmacological treatments (see FAD section 4.5).

Consultee	Comment	Response
Astellas UK (continued)	***Possibility of infinite treatment discontinuation and re-initiation, a factor of the 'lack of memory' associated with the Markov model*** 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 represent 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 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.[2]	Comment noted. The Committee noted the ERG's comment that the manufacturer's model was accurate and transparent, and The Committee concluded that the base-case analyses were similar for the manufacturer and the ERG, and were likely to be robust. (see FAD section 4.16).

[2] 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.

Consultee	Comment	Response
Astellas UK (continued)	***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.	Comment noted.
Astellas UK (continued)	***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)[3]. 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.	Comment noted.

Comments received from clinical specialists and patient experts

None received.

Comments received from commentators

None received.

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

Comments received from members of the public

Role*	Section	Comment	Response
Pharmaceutical Industry	**Section 4** (Consideration of the evidence)	Allergan requests NICE to revise section 4.15; BOTOX® at a 100U dose is an effective option for OAB shown to deliver meaningful benefits for patients who are inadequately managed with antimuscarinic drugs and has an acceptable safety and tolerability profile. BOTOX® 100U has been evaluated in large multicenter placebo-controlled phase III trials for OAB. The first accepted manuscript is published by the Journal of Urology at http://www.jurology.com/article/S0022-5347(12)05849-1/abstract. The dose would be different for other products as Botulinum toxins are not interchangeable. In the two pivotal phase III studies patients treated with 100U exhibited significant improvements in all OAB-related efficacy measures, translating into substantial HRQOL improvements. A positive opinion for BOTOX® 100U for OAB was received in Europe on 18/12/2012 via the Mutual Recognition Procedure with Ireland as the reference member state. **[Commercial in confidence information removed]**. An abstract describing the interim results of long-term safety and efficacy will be presented at the May 2013 American Urological Association congress.	Thank you for your comment. Botulinum toxin injection was not listed as a comparator in the scope, and is not currently licensed as a treatment for overactive bladder.
Other - UK Patient support group for bladder illness	**Notes**	The COB Foundation is the largest patient support charity for bladder illness in the UK. We support patients suffering with all forms of cystitis, overactive bladder and continence issues. Our membership patient database gives us direct information from those suffering with overactive bladder and we fully understand their treatment pathways and the current options available to them.	Comment noted. Thank you for your comment.
Other - UK Patient support group for bladder illness (continued)	**Section 1** (Appraisal Committee's preliminary recommendations)	The COB Foundation supports the recommended treatment option of Mirabegron to those who cannot tolerate antimuscarinic drugs or for whom it proves ineffective. Our patient database tells us that there are many who cannot tolerate the side effects of antimuscarinic drugs, therefore the introduction of Mirabegron is a viable alternative treatment option. For those who are currently receiving Mirabegron for any other conditions where it proves beneficial, should certainly continue with their treatment.	Comment noted. Thank you for your comment.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
Other - UK Patient support group for bladder illness	**Section 2** (The technology)	Mirabegron may also prove to be an effective alternative treatment option for those suffering with other bladder conditions such as interstital cystitis or painful bladder syndrome, pelvic pain syndrome and any other conditions that require the bladder to relax therefore reducing discomfort and pain.	Comment noted. Thank you for your comment. The technology appraisals programme only considers indications that have received regulatory approval.
Other - UK Patient support group for bladder illness	**Section 3** (The manufacturer's submission)	The COB Foundation recognises that Astellas Pharma have provided ethical clinical data and research to support the use of Mirabegron.	Comment noted. Thank you for your comment.
Other - UK Patient support group for bladder illness	**Section 4** (Consideration of the evidence)	The impact of overactive bladder illness on an individual's life cannot be understated. Patients suffering with this life debilitating illness could be helped by the introduction of this medication. We therefore endorse the release of Mirabegron as a viable treatment option.	Comment noted. Thank you for your comment.
Other - UK Patient support group for bladder illness	**Section 6** (Proposed recommendations for further research)	The COB Foundation is a stakeholder and will be commenting on the development of these guidelines.	Comment noted. Thank you for your comment.
Other - UK Patient support group for bladder illness	**Section 7** (Related NICE guidance)	The COB Foundation is a support group for those suffering with debilitating bladder illness and would prefer that the review date be brought forward if possible.	Comment noted. Thank you for your comment.
NHS Professional	**Section 1** (Appraisal Committee's preliminary recommendations)	There is definitely a need for an alternative to anti muscarinic drugs.	Comment noted. Thank you for your comment.
NHS Professional	**Section 3** (The manufacturer's submission)	In section 3.40 it gives solifenacin 10mg a QALY of £340 but solifenacin 5mg £12493 is this right?	Comment noted. Thank you for your comment. The incremental cost effectiveness ratios presented are correct