19 November 2012

NHS
National Institute for Health and Clinical Excellence

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Re: Single Technology Appraisal – Mirabegron for the treatment of overactive bladder

The Evidence Review Group (BMJ-Technology Assessment Group (BMJ-TAG)) and the technical team at NICE have now had an opportunity to take a look at submission received on 24 October by Astellas. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **17:00, 03 December 2012**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments, or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact [redacted]

[redacted]

Yours sincerely

[redacted]
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

A1: priority question

For the following outcomes listed in the final scope:

- symptoms of urgency;
- urinary frequency;
- frequency of urge urinary incontinence;
- nocturia;
- health-related quality of life (EQ-5D).

a) Please provide data from SCORPIO comparing the effectiveness of mirabegron 50 mg versus tolterodine by completing tables such as the one below.

Number of micturitions per 24 hours	**Mirabegron 50 mg**
178-CL-046 (SCORPIO)	**N=473**
Mean difference vs tolterodine	
SE	
95% CI	

b) Please provide the efficacy results of the trials DRAGON, 178-CL-045, 178-CL-048, and TAURUS (please provide results from the 3 month and 12 month time points for TAURUS), for mirabegron 25 and 50 mg versus placebo and versus 4 mg tolterodine by completing tables such as the one below.

Outcome	Placebo	Mirabegron 25 mg	Mirabegron 50 mg	Tolterodine SR 4 mg
178-CL-044 (DRAGON)				
Adjusted mean CFB				
SE				
95% CI				
Mean difference vs placebo	N/A			
SE	N/A			
95% CI	N/A			
Mean difference vs tolterodine				N/A
SE				N/A
95% CI				N/A
178-CL-045				
Adjusted mean CFB				N/A
SE				N/A
95% CI				N/A
Mean difference vs placebo				N/A
SE				N/A
95% CI				N/A
178-CL-048				
Adjusted mean CFB		N/A		
SE		N/A		
95% CI		N/A		
Mean difference vs placebo	N/A	N/A		
SE	N/A	N/A		
95% CI	N/A	N/A		
Mean difference vs tolterodine		N/A		N/A
SE		N/A		N/A
95% CI		N/A		N/A
178-CL-049 (TAURUS) 3 months				
Adjusted mean CFB	N/A	N/A		
SE	N/A	N/A		
95% CI	N/A	N/A		
Mean difference vs tolterodine	N/A	N/A		N/A
SE	N/A	N/A		N/A
95% CI	N/A	N/A		N/A

Outcome	Placebo	Mirabegron 25 mg	Mirabegron 50 mg	Tolterodine SR 4 mg
p-value	N/A	N/A		N/A
178-CL-049 (TAURUS) 12 months				
Adjusted mean CFB	N/A	N/A		
SE	N/A	N/A		
95% CI	N/A	N/A		
Mean difference vs tolterodine	N/A	N/A		N/A
SE	N/A	N/A		N/A
95% CI	N/A	N/A		N/A

A2 – definitions of incontinence and urge incontinence

Please clarify the definitions used in the submission and each of the trials of incontinence, and urge incontinence.

A3 – assessment of level of urgency

Please clarify what scale or questionnaire was used to assess level of urgency in each of the 7 trials.

A4 – endpoint and final visit definitions

The ERG is unable to locate definitions for the terms “endpoint” and “final visit” within the manufacturer’s submission. Please provide definitions for: (i) endpoint, as presented in Table 21; and (ii) final visit, as presented in Table 22. In addition, please clarify how missing values were handled for the analysis of baseline to endpoint and baseline to final visit analysis.

A5 – WinBUGS code

Please provide the working WinBUGS code populated with the appropriate data set for each outcome.

A6 – MTC outcomes in tabular format

Please provide the results from the MTCs for all the outcomes in a tabulated format, as in the example table below.

Micturitions	Mean difference vs mirabegron 50 mg	95% Credible Interval
Tolterodine 4 mg		
Fesoderodine 4 mg		
Fesoderodine 8 mg		
Oxybutynin 10 mg		
Placebo		
Solifenacin 1 mg		
Solifenacin 5 mg		
Trospium 60mg		

A7 – additional MTC outcomes

Please provide DIC, residual deviance and number of effective parameters in the MTC, for each of the outcomes assessed.

A8 – subgroup data

Using the example table below, please provide subgroup data of men, women, previously treated, and treatment naive for the following outcomes listed in the final scope:

- symptoms of urgency;
- urinary frequency;
- frequency of urge urinary incontinence;
- nocturia;
- health-related quality of life (EQ-5D).

for the individual trials:

- 178-CL-044 (DRAGON);
- 178-CL-045;
- 178-CL-046 (SCORPIO);
- 178-CL-047 (ARIES);
- 178-CL-048;
- 178-CL-049 (TAURUS);
- 178-CL-074 (CAPRICORN).

Outcome	Placebo	Mirabegron 25 mg	Mirabegron 50 mg	Tolterodine SR 4 mg
Study				
Men				
Adjusted mean CFB				
SE				
95% CI				
Women				
Adjusted mean CFB				
SE				
95% CI				
Treatment naive				
Adjusted mean CFB				
SE				
95% CI				
Previously treated				
Adjusted mean CFB				
SE				
95% CI				

A9 – additional references

Please provide references and full publications for the studies excluded from the MTC based on any of the exclusion criteria listed below (Section 6.7.2):

- sub-analysis;
- pooled analysis;
- not a major publication;
- not appropriate population for analysis.

A10 – discrepancies in patient flow

In the patient flow diagrams throughout the submission (Figure 2, 4, 5, and 32) the number of patients assessed for eligibility minus the number of patients who received placebo run-in study drug do not equal the number of patients who discontinued during screening. Please clarify these discrepancies.

Section B: Clarification on cost-effectiveness data

B1 – test of correlation

Please clarify which test (p192) was carried out to investigate potential correlation between the number of micturitions and incontinence episodes per day used to inform the overall severity of OAB. In addition please provide the estimate of correlation (0 or otherwise) obtained from the test.

B2 – logistic regressions

For the logistic regressions used to obtain the probability of transition between severity levels for each symptom (micturitions and incontinence) please provide the following details:

a) the rationale for using a regression analysis to obtain these probabilities;
b) the rationale for choosing a multinomial logistic regression model;
c) the rationale/evidence base for selecting: treatment, symptom severity in previous month, gender and age as explanatory variables;
d) on what basis the null hypothesis of proportional odds was rejected;
e) which test (and the p-value obtained) was used to determine the level of interaction between treatment and severity (in the previous month).

B3 – linear regression models

For the linear regression models used to estimate utility (based on EQ-5D and OAB-5D data) please provide the following details:

a) the rationale for using regression analyses to obtain these parameters;
b) the rationale for choosing a linear regression model;
c) the rationale/evidence base for selecting: age, gender, and country (as random effect) as explanatory variables;
d) how correlation between changes in the number of micturitions and incontinence episodes in utility estimation was tested (pg 196);
e) results of the sensitivity test of the two models, which estimated utility changes from baseline to week 12 (pg 209).

B4 – model rationale

Please clarify the rationale for using a repeated regression model to estimate the disutility associated with AEs.

B5 – explanatory variable rationale

Please provide the rationale/evidence base for selecting gender, age and severity of symptoms (incontinence, urgency, micturition), and random effect of geographical region as explanatory variables.

B6 – model of change in symptoms

Regarding the calculation of modelled change in symptoms (carried out as part of the calibration approach; p197), please clarify whether the word "group" in the following sentence "*The mean change in frequency of symptom episodes (micturitions or incontinence) was estimated within each **group** based on data from the mirabegron 50mg arm of the SCORPIO study*." refers to treatment group or each group of the 25 symptom severity groups defined.

B7 – beta coefficients

The beta coefficients informing the regression model used to derive transition probabilities for other antimuscarinic treatments are presented in Table 170, based on optimisation techniques applied to beta coefficients obtained from the mirabegron 50 mg arm of SCORPIO. Please provide the beta coefficients derived from optimisation using:

a) the coefficients for tolterodine ER 4 mg;
b) the coefficients for solifenacin 5 mg.

In addition, please clarify why the coefficients for solifenacin used in the base case model were derived from optimisation on mirabegron coefficients in the base case, rather than regression analysis of data from study 905-CL-015.

Adverse events rates

B8 – dry mouth

Table 85 of the submission reports the probabilities of dry mouth at 12 weeks (based on results of SCORPIO) with mirabegron 50 mg and tolterodine 4 mg as 2.5% and 10.1%, respectively. However, the ERG notes that the rate of dry mouth reported for mirabegron 50 mg and tolterodine 4 mg throughout the clinical section of the submission were 1.8% and 9.5%. Please clarify this potential discrepancy.

B9 - constipation

Please clarify where the rates of constipation recorded in SCORPIO are in the clinical section of the submission.