Appendix D

National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

Mirabegron for the treatment of symptoms associated with overactive bladder

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Astellas Pharma	Astellas support the referral of mirabegron to NICE for single technology appraisal. We believe that this first in class β_3-adrenoceptor agonist represents a significant advancement in treatment of over-active bladder (OAB), given the novel mode of action and efficacy and tolerability profiles. Efficacy has been demonstrated in the general OAB patient population; in patients previously prescribed antimuscarinic treatment; and in patients who have previously discontinued antimuscarinic treatment due to lack of efficacy. Current treatment regimens are limited because of a lack of well-tolerated non-surgical treatment options, and Astellas believe that mirabegron can deliver a superior balance between efficacy and tolerability which will greatly improve patient compliance and outcomes.	Thank you for your comment. No change to scope required.
	Astellas Pharma	Astellas would also like to highlight that this treatment is not included in existing clinical guidelines, or those currently under review (CG40 or 97). A technology appraisal will therefore allow prescribers timely guidance within this high prevalence disease area.	Thank you for your comment. No change to scope required.
	National Clinical Guideline Centre	In response to the question *'Would it be appropriate to refer this topic to NICE for appraisal?'*: Yes	Thank you for your comment. No change to scope required.
	British Geriatrics Society (endorsed by Royal College of Physicians)	Overactive bladder and urgency incontinence are common conditions of older people causing much morbidity and impairment of quality of life. Pharmacological treatment of OAB is currently dependent upon one class of drugs, the antimuscarinics. There are no guidelines within	Thank you for your comment. NICE will only be able to make recommendations on the use of mirabegron for the age groups

Section	Consultees	Comments	Action
		the UK which deal with the specific requirements of older people with lower urinary tract symptoms and urinary incontinence. Both existing guidelines deal with an undifferentiated population of men and women. The efficacy of the antimuscarinics agents is limited by their tolerability and the relatively common occurrence of adverse events such as dry mouth, heartburn, constipation, and blurred vision. Delivering effective treatment as an effective dose is therefore a challenge for clinicians dealing with the elderly. The introduction of Mirabegron, the beta 3 receptor agonist is potentially of value for older people, its use not being associated with such troublesome adverse events.	covered by the marketing authorisation. No change to scope required.
	The Urology Foundation (formerly British Urological Foundation)	Yes, it's entirely appropriate. This is a new mode of action to treat a problem that NICE has focused on quite a lot in the past.	Thank you for your comment. No change to scope required.
Wording	Astellas Pharma	Astellas support the wording of the draft remit.	Thank you for your comment. No change to scope required.
	Astellas Pharma	Astellas would like to clarify the terminology used in the appraisal surrounding OAB. It would be helpful to state that OAB is used as an umbrella term capturing a range of symptoms such as "urge syndrome", "urge-frequency syndrome", "urgency", "urinary frequency", and "urge urinary incontinence". We propose that it would be useful for all stakeholders to be clear on the patient population under scrutiny, and would like to propose that the International Continence Society (ICS) definition is used for future reference to OAB: "*Urgency, with or without incontinence, usually with frequency and nocturia*" [i]	Consultees at the scoping workshop indicated that the International Continence Society definition is widely (often implicitly) used in the UK and that it was not necessary to specify this in the scope. The manufacturer will be able to further define the patient population in its evidence submission. No change to the scope required.
	National Clinical Guideline Centre	In response to the question '*Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider?'*:	Thank you for your comment. No change to scope required.

Section	Consultees	Comments	Action
		Yes	
	The Urology Foundation (formerly British Urological Foundation)	Yes, it's entirely appropriate. This is a new mode of action to treat a problem that NICE has focused on quite a lot in the past.	Thank you for your comment. No change to scope required.
Timing Issues	Astellas Pharma	Astellas estimate a positive opinion from the CHMP in October 2012, followed by marketing authorisation in January 2013. Based on this schedule, Astellas support inclusion into NICE's work programme as soon as possible.	Thank you for your comment. No change to scope required.
	National Clinical Guideline Centre	Routine	Thank you for your comment. No change to scope required.
	British Geriatrics Society (endorsed by Royal College of Physicians)	This is a routine, rather than "urgent" matter	Thank you for your comment. No change to scope required.
	The Urology Foundation (formerly British Urological Foundation)	Mirabegron is poised to be promoted at the forthcoming European Association of Urology and UK practitioners will need to know if it is prescribe-able.	Thank you for your comment. No change to scope required.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Astellas Pharma	The draft scope refers to symptoms of OAB as including an "unstoppable" urge to urinate. Astellas would like to suggest changing this terminology to "compelling" in order to include individuals in whom incontinence is not a necessary condition for OAB diagnosis. Often referred to as *dry-OAB*, this condition is thought to describe a majority of OAB diagnoses.	The background section of the scope has been amended to include the wording 'a compelling urge to urinate' to make it clear that the condition includes those with overactive bladder who do not experience

Section	Consultees	Comments	Action
			incontinence.
	Astellas Pharma	The draft scope describes the current OAB treatment pathway in which antimuscarinic treatment is initiated after failure of bladder training and lifestyle advice (as described in NICE CG40 and CG97). Astellas accept this current treatment pathway, but believe it is relevant for the background information to describe the limitations of currently available drug therapy, and implications for OAB patients in whom antimuscarinic treatment fails. Astellas propose the following additional wording: *"One of the challenges faced with the current mainstay pharmacological treatment for OAB (i.e antimuscarinics) is the low persistence with treatment. Patients may stop medication due to an insufficient response to treatment or unacceptable side effects, in particular, dry mouth and constipation. To experience efficacy with any chronic medication it is important that treatment is well tolerated and shown to be taken as prescribed. Persistence with antimuscarinic treatment varies from 17-35% at one year, and those patients who choose to discontinue treatment may accrue both personal and societal costs associated with poor continence control. Surgical treatment such as sacral nerve stimulation, augmentation cystoplasty, urinary diversion or botulinum toxin bladder injection are consequently left as the only other treatment option."*	The purpose of the background section of the scope is to briefly describe the current treatment pathway in the NHS and to contextualise the population, comparators and outcomes defined in the scope. The manufacturer will be able to describe the limitations of these existing therapies in its evidence submission. No change to scope required.
	National Clinical Guideline Centre	Adequate	Thank you for your comment. No change to scope required.
	British Geriatrics Society (endorsed by Royal College of Physicians)	"Overactive bladder is typically caused by spasms of the muscles of the bladder resulting in a sudden and unstoppable urge to urinate, even though the bladder may only contain a small amount of urine" This is a somewhat simplistic statement and does not reflect current understanding of the underlying pathophysiology of the condition	The purpose of the background section of the scope is to contextualise the population, comparators and outcomes defined in the scope. This does not typically include detailed information

Section	Consultees	Comments	Action
			about the pathophysiology (unless it is especially relevant to treatment). The manufacturer will be able to describe condition in more detail in its evidence submission. No change to the scope required.
The technology/ intervention	Astellas Pharma	The draft scope refers to mirabegron as a β_3-adrenoceptor agonist, but does not describe the relevance of this class. Astellas feel that it is relevant to the appraisal scope to include that mirabegron is the first treatment within this new and previously unappraised class. The draft scope refers to Mirabegron as being studied in trials of "*at least 12 weeks*". Astellas would like to clarify that an abstract has been accepted at the European Association of Urology (due 26th February 2012) in which the long-term safety and efficacy of Mirabegron over a 1 year period will be detailed.	The scope should only provide a brief summary of the mechanism of action of a technology. Manufacturers of the technology under consideration are able to expand on its pharmacology in their evidence submissions. Thank you for the additional information regarding forthcoming availability of clinical trial data beyond 12 weeks. No change to the scope required.
	National Clinical Guideline Centre	In response to the question '*Is the description of the technology or technologies accurate?'*: Adequate	Thank you for your comment. No change to scope required.
	British Geriatrics Society (endorsed by Royal College of Physicians)	In response to the question '*Is the description of the technology or technologies accurate?'*: Yes	Thank you for your comment. No change to scope required.
	The Urology Foundation (formerly British Urological	The explanation for OAB symptoms could be better written, even if it is intended for the lay reader. It should certainly mention that "idiopathic" forms a large group.	The background section of the scope has been amended to include the word 'idiopathic'. A

Section	Consultees	Comments	Action
	Foundation)		more detailed description of symptoms associated with overactive bladder can be provided by the manufacturer in its evidence submission.
	Pfizer UK	Mirabegron was studied using tolterodine as an active control, and not a comparator.	The manufacturer's submission will clearly describe the design of the clinical trials. No change to scope required.
Population	Astellas Pharma	Astellas agree that the population defined within the draft scope is appropriate, assuming that the definition of OAB extends to all patients captured within the ICS definition as detailed above.	Thank you for your comment. No change to scope required.
	Astellas Pharma	*"Is mirabegron likely to be used to treat people with overactive bladder who - are treatment naive or; have previously received treatment with an antimuscarinic drug or; both populations?"* Many patients discontinue currently available antimuscarinic treatment due to dissatisfaction with efficacy and/or tolerability. Astellas intends to demonstrate that mirabegron has significant and clinically relevant efficacy and tolerability advantages to support use in patients for whom previous antimuscarinic therapy has failed**.**	Thank you for your comment. If evidence allows, subgroups based on previous treatment experience (treatment naïve compared with previously-treated patients) should be considered in the manufacturer's evidence submission. The other considerations section of the scope has been updated to include this proposed subgroup.
	Astellas Pharma	*"Are there any subgroups of people in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately?"* Astellas intend to fully explore the clinical and cost-effectiveness benefits of mirabegron in other patient subgroups, however at this time, we are unable to access data stratified into relevant subgroups to perform any such preliminary analyses.	Thank you for your comment. The Committee will consider any patient subgroups depending on evidence availability during the course of the appraisal. At the scoping workshop, attendees

Section	Consultees	Comments	Action
			considered that if evidence allows, subgroups according to gender and according to previous treatment experience (treatment naive compared with previously treated patients) should be considered in the manufacturer's evidence submission. The 'other considerations' section of the scope has been updated to include these proposed subgroups.
	National Clinical Guideline Centre	It is important to consider separately patients with neurogenic detrusor overactivity and those with idiopathic detrusor overactivity as the pathophysiological processes underlying the two conditions may differ. In studies where urodynamic investigations are not being undertaken, the separation can be made on the basis of clinical diagnosis e.g. patients with multiple sclerosis would be neurogenic and patients without neurological disease would be idiopathic.	Thank you for your comment. During the scoping workshop, the manufacturer confirmed that it is unlikely that there will be evidence to support dividing the population into these subgroups because the clinical trials excluded patients with neurogenic detrusor activity. No change to the scope required.
	British Geriatrics Society (endorsed by Royal College of Physicians)	As far as subgroups of people for whom technology might be expected to be more clinically effective and cost-effective, then the elderly or frail elderly would constitute such a population. There are good data showing that these people are vastly under treated for overactive bladder. Additionally there is a theoretical interaction between antimuscarinic treatment and the cholinesterase inhibitors. However, there are currently no research data available for Mirabegron in this frail older population.	Thank you for your comment. NICE can only make recommendations on the use of mirabegron for the age groups specified in the marketing authorisation. No change to the scope required.
	Pfizer UK	The questions for consultation suggest that mirabegron may be	The population in the scope

Section	Consultees	Comments	Action
		considered for use in those for whom treatment with previous anti-muscarinic treatments have failed. It is our understanding the clinical data for mirabegron are insufficient to support appraisal in this population. The pivotal studies for mirabegron recruited from an "all-comers" population, and were not sufficiently powered to detect statistically significant differences in post-hoc subgroups, such as non-responders to previous anti-muscarinic treatment. Similarly, efficacy in those intolerant to anti-muscarinic treatment has not been described in the clinical trials.	was defined in line with the patient population in the pivotal clinical trials and according to the population that is likely to be covered by the UK marketing authorisation. If evidence allows, additional subgroup analyses according to previous treatment experience (treatment naive compared with previously treated patients) will be considered. The 'other considerations' section of the scope has been updated to include these proposed subgroups.
Comparators	Astellas Pharma	The draft scope lists seven antimuscarinic options currently available to UK prescribers as potential comparators for mirabegron. While Astellas agree that these are all valid, we would like to propose that tolterodine, oxybutynin and solifenacin are the key comparators given their dominance of the UK market (89.6% of total antimuscarinic prescriptions). Astellas has conducted phase 3 clinical trials of mirabegron including tolterodine and placebo. In the interests of a succinct and relevant submission, we would like to propose that the appraisal base case addresses clinical and cost-effectiveness versus tolterodine. Astellas have investigated the possibility of presenting additional data versus alternative comparators via an indirect comparison, however a preliminary literature search was unable to identify any additional trials reporting outcomes within a previously treated population. Astellas believe that darifenacin, propiverine, fesoterodine, and	The comparators in the scope were amended following consultees' input at the scoping workshop, where it was determined that darifenacin and propiverine were not relevant comparators because they were not used routinely in UK clinical practice. However, it was felt that trospium is used for certain patients with OAB and that use of fesoterodine is growing so these comparators should remain in the scope.

Section	Consultees	Comments	Action
		trospium should be excluded due to their limited use in routine clinical practice, demonstrated by their low share of total antimuscarinic prescriptions (0.2%, 1.1%, 3.7%, and 4.6%, respectively). "Best alternative care" is likely to be limited to antimuscarinic treatment with tolterodine, oxybutynin or solifenacin.	
	Astellas Pharma	The draft scope poses a series of further questions regarding comparators*:* *"Have the most appropriate comparators for mirabegron for the treatment of overactive bladder been included in the scope?"* Astellas are satisfied that all appropriate active comparators are captured within the draft scope.	The comparators in the scope were amended following consultees' input at the scoping workshop, where it was determined that darifenacin and propiverine were not relevant comparators because they were not used routinely in UK clinical practice. However, it was felt that trospium is used for certain patients with OAB and that use of fesoterodine is growing so these comparators should remain in the scope.
	Astellas Pharma	"*Are all the comparators listed routinely used in clinical practice?"* As above, Astellas would like to propose that darifenacin, propiverine, fesoterodine, and trospium are not routinely used in clinical practice.	The comparators in the scope were amended following consultees' input at the scoping workshop, where it was determined that darifenacin and propiverine were not relevant comparators because they were not used routinely in UK clinical practice. However, it was felt that trospium is used for certain patients with OAB and

Section	Consultees	Comments	Action
			that use of fesoterodine is growing so these comparators should remain in the scope.
	Astellas Pharma	*"Are other antimuscarinic treatments, such as flavoxate, propantheline or duloxetine also used routinely for overactive bladder?"* Astellas does not consider flavoxate a suitable comparator given its very low use in clinical practice (antimuscarinic prescription market share of 0.7%). Astellas does not consider propantheline or duloxetine to be relevant comparators since neither is licensed for the treatment of OAB and both have low use in clinical practice.	At the scoping workshop, consultees agreed flavoxate, propantheline and duloxetine were not used in routine clinical practice and that they did not represent relevant comparators. Therefore, they have not been added to the scope.
	Astellas Pharma	*"Is botulinum toxin type A (bladder injection) an appropriate comparator?* Astellas consider botulinum toxin type A (bladder injection) to be an invasive procedure, more appropriately categorised with surgical options later in the treatment pathway such as sacral nerve stimulation, augmentation cystoplasty, or urinary diversion (as detailed in CG40 and CG97). Such procedures are delivered in a secondary care setting and may be appropriate for a much narrower patient population than those suitable for pharmaceutical treatment. Astellas believe that it is clinical practice for pharmaceutical options to be exhausted before considering such invasive procedures. Since the benefits of mirabegron are aimed at an earlier stage in the treatment pathway, we do not consider botulinum toxin injections an appropriate comparator. Furthermore, botulinum toxin type A does not have a licence for treatment of OAB.	At the scoping workshop, consultees agreed botulinum toxin type A was not a relevant comparator because it would be used at a later stage in the treatment pathway. Consequently this has not been added to the scope.
	National Clinical Guideline Centre	Appropriate	Thank you for your comment. No change to scope required.
	British Geriatrics Society (endorsed by Royal College of Physicians)	Consider BTX A as comparator. Consider bladder retraining and urgency suppression techniques as comparators. There are data on the efficacy of behavioural treatments of OAB in adults and in older people which should be included in the analysis. Bladder retraining should be	At the scoping workshop, consultees agreed botulinum toxin type A was not a relevant comparator because it would

Section	Consultees	Comments	Action
		included as a comparator. Flavoxate is not recommended for treatment of overactive in many of the current guidelines. Additionally the evidence for duloxetine in overactive bladder is of low quality and it is not in routine use.	be used at a later stage in the treatment pathway. Consequently this has not been added to the scope. NICE guidance recommends that non-pharmacological interventions (such as bladder training) should be offered before drug therapy where appropriate. Consultees at the scoping workshop agreed that non-pharmacological options would be offered before or as an adjunct to drug therapy and were not relevant comparators. Moreover, they agreed flavoxate and duloxetine were not used in routine clinical practice and that they did not represent relevant comparators. Therefore, they have not been added to the scope.
	The Urology Foundation (formerly British Urological Foundation)	The scope asked whether botulinum toxin A (bladder injection) should also be listed as an appropriate comparator? BTX-A is really the “next stage up” – it requires an invasive process (the detrusor injection of the agent) and may result in the need for the patient to perform clean intermittent self catheterisation. Neither mirabegron nor oral anti-muscarinics require either of those. Although NICE 40 “specifies that non-proprietary oxybutynin should be offered first” this was quite controversial at the time and since then other adverse information about oxybutynin has emerged such that it is	At the scoping workshop, consultees agreed botulinum toxin type A was not a relevant comparator because it would be used at a later stage in the treatment pathway. Consequently this has not been added to the scope.

Section	Consultees	Comments	Action
		widely regarded as not the best first option.	A range of antimuscarinic drugs is listed in the scope to allow for the fact that oxybutynin might not be used as first-line drug therapy. No change to the scope is required.
	Pfizer UK	The 2011 Cochrane review of anticholinergic drugs for overactive bladder states that "any new anticholinergic therapies, after their safely has been established, should be compared to either oxybutynin or tolterodine to establish if they have similar or better efficacy or side effect profile than either of these 'standard' drug therapies."[1] Mirabegron was studied using tolterodine as an active control, and not a comparator. It should be noted that tolterodine did not show a significant difference against placebo. Therefore there are no head-to-head data to support the equivalence or superiority of mirabegron against an antimuscarinic. [1.] Madhuvrata P,Cody JD, EllisG,HerbisonGP,Hay-Smith EJC.Which anticholinergic drug for overactive bladder symptoms in adults. *Cochrane Database of Systematic Reviews* 2012, Issue 1. Art. No.: CD005429. DOI: 10.1002/14651858.CD005429.pub2.	Thank you for your comment. These issues will be considered during the course of the appraisal. No change to scope required.
Outcomes	Astellas Pharma	Astellas support that outcomes detailed in the draft scope capture all relevant clinical and quality of life measures directly relevant to the NHS.	Thank you for your comment. No change to scope required.
	National Clinical Guideline Centre	Appropriate but should include long-term data as continuation rates for drugs looking at overactive bladders are low for anticholinergic medications. Emphasis needs to be put on clinically useful benefit as other drug treatments often offer improvements which are of marginal usefulness.	Thank you for your comment. These issues will be considered during the course of the appraisal. No change to scope required.
	British Geriatrics Society (endorsed	Should be "urgency" incontinence Add "nocturia"	Existing NICE guidance uses the term 'urge incontinence' so

Section	Consultees	Comments	Action
	by Royal College of Physicians)		changing to 'urgency incontinence' would not be appropriate. The consultees discussed the relevance of nocturia as a clinical outcome and agreed that this should be included if evidence permits. The scope has been amended accordingly.
Economic analysis	Astellas Pharma	Astellas support the use of the NICE reference case in demonstrating the cost-effectiveness of mirabegron. A new model will be commissioned based on an accepted structure developed by Kobelt *et al*, in which different health states represent different levels of OAB severity and stages of therapeutic management. This Markov model will describe 12 monthly cycles within a 1 year time horizon to estimate incremental cost per quality adjusted life years (QALYs) gained. We believe that all important differences in costs and outcomes will be reflected within this time horizon.	Thank you for your comment. No change to scope required.
	British Geriatrics Society (endorsed by Royal College of Physicians)	Appropriate	Thank you for your comment. No change to scope required.
	The Urology Foundation (formerly British Urological Foundation)	The proposed time horizon "should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared" sounds a good idea but gives no clue as to how long that might be – months or years?	Thank you for your comment. More information about how to determine an appropriate time horizon can be found in the 'Guide to methods of technology appraisal' (2008), which is available on the NICE website. No change to scope required.

Section	Consultees	Comments	Action
Equality and Diversity	Astellas Pharma	Astellas would like to propose that the initial choice of pharmaceutical treatment for OAB is based on the relative importance of their side-effect profiles for individuals. Costs associated with failing OAB treatment can be borne outside of the NHS/PSS remit. Astellas would like to highlight that it is common for patients who fail or who cannot tolerate their therapy to manage symptoms by supplying their own incontinence pads, and where such patients have a low income, these out-of-pocket expenses represent a higher proportion of their total income. Astellas would like to propose that this appraisal is mindful of the potential out-of-pocket expenses incurred when current treatment options fail, in particular in those with lower incomes who may be unfairly burdened by a need to purchase ancillary supplies.	The NICE reference case stipulates appraisals should take an NHS/PSS perspective. All patients have the same treatment choices, irrespective of income and mirabegron would be expected to provide a similar benefit in all socioeconomic groups. Socioeconomic status is a characteristic which is not currently protected under equality legislation; however, the Committee will be mindful of the out of pocket expenses during the course of the appraisal. No amendment to the scope is required.
	British Geriatrics Society (endorsed by Royal College of Physicians)	There appear to be no issues in the current scope which are relevant to quality or disability. The medication should be applicable to all individuals with the condition of interest. The introduction of Mirabegron onto the market can certainly be considered an advance in treatment in OAB. It is the first of a new class of agents which with some proven efficacy. Consider frail older people as additional group who are under-represented and under-treated.	Thank you for your comment. The Committee will consider these issues during the course of the appraisal. NICE can only make recommendations on the use of mirabegron for the age groups covered by the marketing authorisation. No amendment to the scope is required.
Innovation	Astellas Pharma	*Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?* Astellas believe that this new class of β_3-adrenoceptor agonists will	Thank you for your comment. The Committee will consider the innovative nature of mirabegron during the course of the appraisal. No

Section	Consultees	Comments	Action
		have a significant impact on health related benefits within a treatment pathway which is currently frustrated by poor efficacy and tolerability. The management of OAB is based on finding a treatment option for patients which provides the right balance of efficacy and tolerability. Antimuscarinics have been shown to fail to achieve such a balance in many patients, reflected by the general low persistence with treatment. For patients in whom the desired efficacy is not achieved with antimuscarinic treatment, or for those who are unable to tolerate their medication there are currently no further pharmacological treatment options, leaving surgery or symptom management via incontinence pads as the only options. Astellas intends to demonstrate that mirabegron has significant and clinically relevant efficacy and tolerability advantages to support use in patients for whom previous antimuscarinic therapy has failed.	amendment to the scope is required.
	National Clinical Guideline Centre	Yes this is a new class of drug.	Thank you for your comment. The innovative nature of mirabegron will be considered during the course of the appraisal. No change to scope required.
	The Urology Foundation (formerly British Urological Foundation)	*Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?* Yes.	Thank you for your comment. No change to scope required.
Other considerations	Pfizer UK	It will be important to consider the side effect profile of mirabegron, as profiles differ widely among anti-muscarinics. Distinctions will need to be made between tolerability and efficacy at any doses considered.	These issues will be considered during the course of the appraisal. No change to scope required.
	British Geriatrics Society (endorsed by Royal College of	Mirabegron is likely to be used in a progressive nature by clinicians. Certainly it is more likely to be used as an adjunctive treatment or for those people who have been proven intolerant of antimuscarinics in the	These issues will be considered during the course of the appraisal. If evidence

Section	Consultees	Comments	Action
	Physicians)	first instance agents. As confidence with the drug increases, there may be a greater use in those who are treatment naive.	allows, subgroup analyses according to previous treatment experience (treatment naive compared with previously treated patients) will be considered. The scope has been updated to include these proposed subgroups.
Questions for consultation	Astellas Pharma	*Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* OAB adversely affects many aspects of patients' quality of life. OAB has been shown to have significant social, psychological, occupational, domestic, and physical stigmas[ii], as well as a strong association with depression. OAB patients become anxious in unfamiliar environments: they focus on and may be preoccupied with such concerns as locating the closest bathroom, looking for aisle seating, and estimating the amount of time until their next work break. Embarrassment, frustration, anxiety, annoyance, depression, and fear of odour can have a negative impact on daily activities, such as travel, physical activity, interpersonal relationships, and sexual function, resulting in social isolation. Such activity may be associated with costly management of absenteeism, presenteeism, and depression. Nocturia is often experienced by people with OAB diminishing quality of sleep and resulting in fatigue and increased risk of fall and hip fracture in elderly, osteoporotic female patients. Costs of fractures and nursing home admission also contribute to NHS costs *Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.* Astellas have collected patient reported outcome data using both the	These issues will be considered during the course of the appraisal. The Committee will also consider any benefits of mirabegron which are likely to have been inadequately captured in the QALY calculation. Nocturia has been added as an outcome measure, if evidence allows.

Section	Consultees	Comments	Action
		EQ5D and the OABq instruments. We intend to use this data to inform our health economic model where appropriate, and will report health benefits which are not captured by the QALY calculation separately.	
	National Clinical Guideline Centre	*Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* No.	Thank you for your comment. No change to scope required.
	The Urology Foundation (formerly British Urological Foundation)	*Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* Yes. *Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.* Tyagi, P., Tyagi, V. & Chancellor, M. Mirabegron: a safety review. Expert Opin Drug Saf. 2011 Mar;10(2):287-94 This review includes references to publications to date.	Thank you for your comment. No change to scope required.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope:

Healthcare Improvement Scotland
Medicines and Healthcare products Regulatory Agency

NATIONAL INSTITUTE FOR HEALTH CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Mirabegron for the treatment of symptoms associated with overactive bladder

Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	Proposal made by:		Action taken: Removed/Added/Not included/Noted	Justification:
1.	Cystits and Overactive Bladder Foundation	NICE Secretariat		Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria. Therefore the **Cystits and Overactive Bladder Foundation** have been added to the matrix under consultee **'patient' groups**.

2.	Multiple Sclerosis Resource	NICE Secretariat		Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria. Therefore the Multiple Sclerosis Resource have been added to the matrix under consultee **'patient' groups.**
3.	Multiple Sclerosis Society	NICE Secretariat		Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria. Therefore the Multiple Sclerosis Society have been added to the matrix under consultee **'patient' groups.**
4.	Multiple Sclerosis Trust	NICE Secretariat		Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria. Therefore the Multiple Sclerosis Trust have been added to the matrix under consultee **'patient' groups.**

5.	Parkinson's UK	NICE Secretariat		Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria. Therefore the Parkinson's UK have been added to the matrix under consultee **'patient' groups.**
6.	Stroke Association	NICE Secretariat		Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria. Therefore the Stroke Association have been added to the matrix under consultee 'patient' groups.
7.	Association for Continence Advice	NICE Secretariat		Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria. Therefore the Association for Continence Advice have been added to the matrix **under consultee 'professional' groups**.

8.	Association of British Neurologists	NICE Secretariat		Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria. Therefore the Association of British Neurologists have been added to the matrix **under consultee 'professional' groups**.
9.	British Association for Nursing in Cardiovascular Care	NICE Secretariat		Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria. Therefore the British Association for Nursing in Cardiovascular Care have been added to the matrix **under consultee 'professional' groups**.
10.	British Atherosclerosis Society	NICE Secretariat		Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria. Therefore the British Atherosclerosis Society have been added to the matrix **under consultee 'professional' groups**.

11.	British Cardiac Intervention Society	NICE Secretariat		Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria. Therefore the British Cardiac Intervention Society have been added to the matrix **under consultee 'professional groups**.
12.	British Cardiovascular Society	NICE Secretariat		Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria. Therefore the British Cardiovascular Society have been added to the matrix **under consultee 'professional' groups**.
13.	British Heart Foundation	NICE Secretariat		Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria. Therefore the British Heart Foundation have been added to the matrix **under consultee 'professional' groups**.

14.	British Nuclear Cardiology Society	NICE Secretariat		Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria. Therefore the British Nuclear Cardiology Society have been added to the matrix **under consultee 'professional' groups**.
15.	British Society of Cardiovascular Imaging	NICE Secretariat		Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria. Therefore the British Society of Cardiovascular Imaging **have been added to the matrix under consultee 'professional' groups**.
16.	British Society of Urogynaecology	Astellas and BGS		Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria. Therefore the British Society of Urogynaecology have been added to the matrix **under consultee 'professional' groups**.

17.	College of Emergency Medicine	NICE Secretariat		Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria. Therefore the College of Emergency Medicine have been added to the matrix **under consultee 'professional' groups**.
18.	National Heart Forum (UK)	NICE Secretariat		Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria. Therefore the National Heart Forum (UK) have been added to the matrix **under consultee 'professional' groups**.
19.	Primary Care Cardiovascular Society	NICE Secretariat		Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria. Therefore Primary Care Cardiovascular Society have been added to the matrix **under consultee 'professional' groups**.

20.	Royal College of Obstetricians and Gynaecologists	Astellas		Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria. Therefore the Royal College of Obstertricians and Gynaecologists have been added to the matrix **under consultee 'professional' groups**.
21.	Society for Cardiological Science and Technology [BCS affiliated]	NICE Secretariat		Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria. Therefore the Society for Cardiological Science and Technology [BCS affiliated] have been added to the matrix **under consultee 'professional' groups**.
22.	United Kingdom Continence Society	Astellas		Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria. Therefore the United Kingdom Continence Society have been added to the matrix **under consultee 'professional' groups**.

23.	Vascular Society	NICE Secretariat		Added	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria. Therefore the Vascular Society have been added to the matrix **under consultee 'professional' groups**.
24.	Amdipharm (propiverine)	NICE Secretariat		Removed	This organisation's are no longer closely related to the appraisal topic and as per our inclusion criteria. Therefore the Amdipharm (propiverine) has been removed to the matrix under 'comparator' manufacturers.
25.	Novartis Pharmaceuticals UK (darifenacin)	NICE Secretariat		Removed	This organisation's interests are closely related to the appraisal topic and as per our inclusion criteria. Therefore Novartis Phamaceuticals UK (darifenacin) have been added to the matrix **under 'comparator' manufacturer**.