National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

Tadalafil for the treatment of symptoms associated with benign prostatic hyperplasia

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	GlaxoSmithKline	BPH is an under recognized and under treated condition. Issuance of an STA may help to encourage more appropriate screening and treatment. However, none of the comparator treatments, particularly the 5ARIs (which share a proposed severity level indication), have undergone an economic evaluation by NICE which may make it more difficult to assess incremental cost-effectiveness where assumptions and indirect comparisons may be required for multiple therapies.	Thank you for your comment. No change to scope required.
	Eli Lilly and Company	Thank you for the opportunity to provide comments on the draft scope for a potential appraisal of Cialis for the treatment of benign prostatic hyperplasia (BPH). After careful consideration of this topic we suggest that it would not be appropriate for this topic to be referred to NICE for an appraisal. Whilst we are not seeking referral we have provided our comments on the draft scope as requested below.	A formal referral for this topic has been received from the Minister for Health. This topic will be considered through the STA process.
	Pfizer	This topic is appropriate for referral to NICE.	Thank you for your comment. No change to scope required.

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Wording	GlaxoSmithKline	In the absence of an approved licenced indication in England, more detail will be required for the scoping meeting on the proposed population. Clarity is required regarding the proposed patient populations.	The population in the scope 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 a UK marketing authorisation. Attendees at the scoping workshop considered that no changes to the population are required.
	Lilly	We do not consider the current wording of the remit to be appropriate for this appraisal. We suggest changing the remit to say: "To appraise the clinical and cost effectiveness of Cialis (tadalafil) 5mg Once Daily within its licensed indication for the treatment of the signs and symptoms for benign prostatic hyperplasia in adult males, including those with erectile dysfunction."	The brand name has been added to the scope. An appraisal would be conducted within the marketing authorisation for tadalafil's BPH indication so it is not necessary to add the dosage. Further information about the dosage regimen will be provided in the manufacturer's evidence submission during the course of the appraisal.
Timing issues		No issues raised during consultation	None.
Additional comments on the draft remit	GlaxoSmithKline	Desired information for the scoping meeting would be: Indicated severity and how this is defined The dosage and regimen (2.5mg, 5mg, both?) Unmet need in BPH and the ability of tadalafil to address this Symptomology, age, prostate volume, PSA level and any other factors associated with indication	Any appraisal undertaken will be according to the marketing authorisation for tadalafil's BPH indication so it is not necessary to specify these parameters in the scope. No amendment needed.

Comment 2: the draft scope

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Background information		No issues raised during consultation	None.
The technology/ intervention	GlaxoSmithKline	Dosing is unclear - 2.5mg or 5mg. Treatment duration requires defining.	Any appraisal undertaken will be according to the marketing authorisation for tadalafil's BPH indication so it is not necessary to specify the dosage or duration of treatment in the scope. No amendment needed.
	Lilly	We would like to suggest the following corrections to the content of this section: First paragraph – "Tadalafil (Cialis; Eli Lilly and Company) 5mg once daily." The brand name is Cialis and it is important to specify that it is the 5mg Once Daily formulation as opposed to the 10mg or 20mg when required, or 2.5mg once daily formulations. Second paragraph – "It has been studied in clinical trials in comparison with placebo, and with tamsulosin as an active control, for the treatment of the sign and symptoms of BPH in men with and without ED."	The confirmed brand name (Cialis) has been added to the scope. Any appraisal undertaken will be according to the marketing authorisation for tadalafil's BPH indication so it is not necessary to specify the dosage. The description of the clinical trials has been amended in the scope.
	Pfizer	Tadalafil is currently not recommended for use with alpha blockers (in patients who are taking alpha1-blockers concomitant administration of CIALIS may lead to symptomatic hypotension in some patients (see section 4.5). The combination of tadalafil and doxazosin is not recommended.), which may be used widely for BPH. Therefore, any recommendations would need to take this account.	Thank you for your comment. No change to the scope required.
Population	GlaxoSmithKline	The population is ill defined and requires stratification via predominant symptoms (storage/voiding); disease severity (IPSS score); risk of progression	The population in the scope was defined in line with the

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		(PSA, prostate volume)	patient population in the pivotal clinical trials and according to the population that is likely to be covered by a UK marketing authorisation. Attendees at the scoping workshop considered that if evidence permits, subgroups according to disease severity (IPSS) should be evaluated. This proposed subgroup has been added to the scope.
	Lilly	The population would be better defined as "Adult men with signs and symptoms of benign prostatic hyperplasia, including those with erectile dysfunction." Clinical evidence to date is not limited to those men with moderate to severe symptoms and does not exclude those with ED as suggested in the draft scope.	The draft scope specifies "People with moderate to severe symptoms of benign prostatic hyperplasia", which does not exclude those who have both BPH and ED, or people who are transgendered. NICE clinical guideline 97 (LUTS) recommends that pharmacological treatment should be offered only to men with bothersome symptoms when conservative management options have been unsuccessful or are not appropriate. Therefore men with mild symptoms will not be considered in this appraisal.
	Pfizer	Tadalafil trials for BPH have high proportions of ED patients made up 60-70% and therefore this appraisal is restricted to ED patients with BPH symptoms.	Thank you for your comment. The draft scope specifies

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		Need to be careful about use spreading to ED - doctors can use this recommendation to gain access for their patients with ED.	"People with moderate to severe symptoms of benign prostatic hyperplasia", which does not exclude those who have both BPH and ED, or people who are transgendered. If evidence permits, a subgroup analysis according to the presence or absence of erectile dysfunction should be undertaken by the manufacturer. The scope has been amended to include this subgroup.
Comparators	GlaxoSmithKline	NICE guidelines (CG97) describe LUTS comparators. The selection of which comparators are most appropriate will be determined by the positioning of tadalafil.	Thank you for your comment. The comparators in the scope were amended following consultees' input at the scoping workshop, where it was determined that alpha blockers were the sole relevant comparator.
	Lilly	The appropriate comparator is alpha-blockers. Additionally, PDE5 inhibitors (PRN) and anticholinergics may be used in combination with alpha blockers and as such they may also be considered comparators. The exact combination of comparators is dependent upon the patient population and the symptoms presented: those with BPH and with/without ED and whether the lower urinary tract symptoms (LUTS) are those of storage or voiding. Note, some alpha-blockers are contraindicated with PDE5 inhibitors and PDE5 inhibitors are not licensed for BPH, and would only be used for the control of	Thank you for your comment. The comparators in the scope were amended following consultees' input at the scoping workshop, where it was determined that alpha blockers were the sole relevant comparator.

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		the ED symptoms. 5-alpha reductase inhibitors (5-ARI) are not relevant comparators. They are used either later in the treatment pathway or to reduce the size of an enlarged prostate. Active surveillance is not an appropriate comparator as NICE guidelines recommend offering drug treatment to men with bothersome LUTS when conservative management options have been unsuccessful or are not appropriate. References: NCGC. The management of lower urinary tract symptoms in men. Full guideline. Clinical Guideline 97. London: NICE; June 2010 NICE. Lower Urinary Tract Symptoms. CG97. London: NICE; May 2010	
Outcomes	GlaxoSmithKline	Outcome measures need to incorporate symptom improvement, symptom progression and disease progression to acute urinary retention and surgery. Long term symptom progression may be another outcome to consider.	Thank you for your comment. The scope has been amended to include long-term as well as short-term symptom control.
	Lilly	We agree with the outcomes suggested for BPH symptoms and physiological measures. However we also consider the draft scope should include outcome measure for erectile function (International Index of Erectile Function (IIEF) and Sexual Encounter Profile (SEP)).	The draft scope has been amended to include erectile function as an outcome. A scope does not specify the method or scale of outcome evaluation. This information will be included in the manufacturer's evidence submission.
	Pfizer	International Prostate Symptom Score should be added.	A scope does not specify the method or scale of outcome evaluation. This information will be included in the manufacturer's evidence submission. No amendment to

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			the scope required.
Economic analysis	GlaxoSmithKline	Published cost effectiveness studies in BPH are typically life-time Markov models. Longer term follow up (>2 years) is required to assess symptom and disease progression.	Thank you for your comment. No amendment to the scope required.
	Lilly	We agree with the description of the economic analysis.	Thank you for your comment. No amendment to the scope required.
Equality and Diversity		No issues raised during consultation	None
Innovation	Lilly	We consider this technology innovative because: Tadalafil offers a new mechanism of action to treat the signs and symptoms associated with BPH compared to current available treatments. Tadalafil has shown benefits in clinical studies for the simultaneous treatment of the symptoms of BPH and ED which are common co-morbid conditions in the older male. This is a unique feature compared to current treatments which treat each respective condition singularly.	Thank you for your comment. Aspects of innovation should be described in the evidence submissions. The Committee will consider the innovative nature of tadalafil during the course of the appraisal. No amendment to the scope required.
Other considerations	Royal College of Pathologists	The draft scope (Appendix B) refers to men with lower urinary tract symptoms (LUTS), presumed due to benign prostatic hyperplasia (BPH) who also have raised serum PSA being eligible for treatment with tadalafil in comparison with other existing agents. Whilst raised serum PSA of itself should not necessarily prompt biopsy, some kind of clinical nomogram-based risk assessment aimed in particular at not overlooking the possibility of high risk prostate cancer should be considered before embarking on treatment for presumed BPH. This is particularly important because some therapeutic agents could induce changes in histological appearances that could impact on histological interpretation, should a subsequent biopsy become necessary. An example of the other clinical considerations regarding whether or not a biopsy should be performed in patients who have raised serum PSA is given in NICE clinical guidance 58 (2008), section 3.1	Thank you for your comment. No amendment to the scope required.
	GlaxoSmithKline	Partner HRQL/utility	Thank you for your comment.

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			The outcomes listed in the scope are not exhaustive and do not prohibit the manufacturer from providing information on further outcomes. No amendment to the scope required.
	Lilly	We consider the patient population with ED and BPH to be a relevant subgroup.	Thank you for your comment. The scope has been amended to state that subgroups with BPH with or without ED will be evaluated, if evidence permits.
Questions for consultation	GlaxoSmithKline	Impact upon PSA and prostate cancer detection may be relevant. Secondary benefits of improvements in sexual dysfunction are relevant. The quality of life of partners of men with BPH is known to be adversely affected. The utility decrement associated with partner HRQL could be considered for inclusion in the QALY calculations. Utility data is sparse for the comparator treatments, though a time trade-off study has been performed to elicit values for the IPSS. Any EQ-5D data available from the tadalafil trials?	Thank you for your comment. These issues will be considered during the course of the appraisal. No amendment to the scope required.
	GlaxoSmithKline	There is a utility decrement associated with sexual dysfunction over and above the BPH base value. It would be expected that tadalfil would prove more cost-effective in a sub-group of men with BPH would are also experiencing erectile dysfuction (perhaps as a result of 5ARI monotherapy [given the alpha-blocker contraidication]).	Thank you for your comment. These issues will be considered during the course of the appraisal. No amendment to the scope required.
	Lilly	There are potential compliance/adherence benefits when considering the use of tadalafil for the simultaneous treatment of ED and BPH. It is not clear how well the QALY can describe the bothersome and inconvenience of BPH symptoms (disrupted sleep, risk of incontinence). Similarly, it is not clear how well the QALY can describe some of the key	Thank you for your comment. These issues will be considered during the course of the appraisal. No amendment to the scope required.

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		features of ED treatment such as impact on male self-esteem, partner's self-esteem and sexual satisfaction (both patient and partner) which are difficult to capture with standard utility tools.	
Additional comments on the draft scope.	GlaxoSmithKline	Will tadalafil be marketed as "Cialis" in BPH with a commensurate price across indications? Was EQ-5D or another appropriate preference based measure of utility captured in the tadalafil trials for BPH?	Thank you for your comment. These issues will be considered during the course of the appraisal. No amendment to the scope required.

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

Department of Health
Men's Health Forum
Prostate Action
Royal College of Nursing
Royal College of Physicians

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

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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.	Add Allied Health Board Professionals to general commentators.	NICE Secretariat		Added	Allied Health Board Professionals meets the inclusion criteria and has a close interest in this appraisal topic therefore this organisation has been added to the matrix as a general commentator.
2.	Add The Urology Foundation to professional group consultees.	NICE Secretariat		Added	The Urology Foundation meets the inclusion criteria and has a close interest in this appraisal topic therefore this organisation has been added to the matrix as a professional group consultee.

3.	Remove Prostate Cancer UK from patient/carer group consultees.	NICE Secretariat		Removed	This organisation's interests are not closely related to the appraisal topic and as per our inclusion criteria. Prostate Cancer UK has not been included in the matrix of consultees and commentators.
4.	Remove Men's Health Forum from patient/carer group consultees.	NICE Secretariat		Removed	The Men's Health Foundation has requested to be removed from this and all future matrices.