National Institute for Health and Care Excellence

Lower Urinary Tract Symptoms Update
Addendum Consultation Table
3rd February – 5 pm 3rd March 2015

Stakeholder	Order No	Document	Section No	Page No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
British Association of Urological Surgeons	1	Addendum	8	7	There is clinical evidence from randomised controlled trials that PDE-5 inhibitors are efficacious for LUTS with a similar reduction in the IPSS compared to alpha blockers.	Thank you for your comment. The committee considered the comparison of PDE5Is vs alpha blockers, very low and low quality evidence indicated that there was no difference in the efficacy of PDE5Is and alpha blockers in the improvement in IPSS symptom score, BII, Qmax and nocturia. There was greater improvement in voiding frequency with alpha blocker compared to PDE5I (please see linking evidence to recommendations – quality of evidence section).
British Association of Urological Surgeons	2	Addendum	8	7	PDE-5 inhibitors offer an option for the co morbid patient with erectile dysfunction and LUTS where there may be side effects related to alpha blockers (retrograde ejaculation or anejaculation) or reduction in libido/erectile dysfunction secondary to 5 alpha reductase inhibitors.	Thank you for your comment. This review focussed on the use of PDE5Is in the treatment of LUTS alone (without erectile dysfunction (ED), therefore ED outcomes, such as retrograde ejaculation and anejaculation, were not reviewed and therefore not taken into account by the committee when making their decision. The recommendation has now been amended to reflect that the evidence assessed in this review applies to men with LUTS who do not have ED. More detail on the potential use of PDE5Is is provided in the section 1.12 "Evidence to Recommendations", trade- off between benefits and harms section, paragraph 3.
British Association	3	Addendum	8	7	An appropriate case scenario could be the use of	Thank you for your comment.

Stakeholder	Order No	Document	Section No	Page No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
of Urological Surgeons					PDE5 inhibitors for LUTS secondary to BPE when patients get significant postural hypotension from alpha blockers, have small prostates (so will not benefit from Finasteride) and do not want surgery. It will be difficult to get the GPs to prescribe for this "niche" indication following this recommendation.	This is a guideline, and therefore cannot consider every clinical situation that may be encountered. Furthermore, the guideline is not a substitute for the judgement of the clinician. The decision to prescribe any pharmacological agent will depend on each individual patient, including their comorbidities and the adverse effects they experience with different pharmacological agents. Paragraph 2 of the other considerations section of the Evidence to Recommendations table in section 1.12 contains some important information: "…the patient representative discussed with the Committee that they would be willing to try PDE5Is if there was demonstrable benefit with the treatment. It was also discussed that a balanced view of the benefits and harms of the medications should be fully explained to a person considering PDE5I treatment, and that the patient should be fully involved in the decision making process with regards to their treatment."
British Association of Urological Surgeons	4	Addendum	8	7	PDE-5 inhibitors should also be offered as second line treatment as opposed to not offered at all on the basis of cost. LUTS is a common condition for men after the age of 50 with bothersome symptoms affecting the individual and the partner. On the basis of quality of life improvement and symptom improvement this is a pharmacological option that should be available.	Thank you for your comment. Clinical and cost effectiveness analysis was undertaken for this question, the decision was not made on cost effectiveness alone. The clinical evidence did not indicate that PDE5Is were any more clinically effective than standard treatment (alpha blockers) for the key outcomes for the treatment of LUTS, and PDE5Is were less clinically effective than alpha blockers with regards to voiding

Stakeholder	Order No	Document	Section No	Page No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						frequency. The Committee considered that, based upon the LUTS–specific outcomes assessed for this review question, PDE5Is should not be prescribed solely for the purpose of treating LUTS alone. This does not affect the prescribing of PDE5Is for men with erectile dysfunction (ED) symptoms. The recommendation has now been amended to reflect this. The rest of the guideline recommends clinically and cost effective treatment options for managing LUTS.
British Association of Urological Surgeons	5	Addendum	8	7	The evidence is Grade A , Level 1 and the use of PDE-5 inhibitors for LUTS has been adopted by the European Association of Urology `guidelines on male LUTS	Thank you for your comment. The recommendation quoted in this comment was based on a meta-analysis by Gacci et al (2012), which was not included in this review because it only reported results for PDE5I vs placebo, and only included 7 studies, compared to the 21 studies that were included in this review. Furthermore, the meta- analysis by Gacci (2012) appears to partly base their recommendation on the outcome of IIEF score, which is not used in this review as it is not a direct LUTS outcome. Gacci et al (2012) also report a mean reduction in IPSS score of -2.8, which using the minimal important differences (MIDs) agreed by the committee for IPSS score in this update does not reach a clinically significant level.

Stakeholder	Order No	Document	Section No	Page No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
British Association of Urological Surgeons	6	Addendum	8	7	Given that the trials of PDE5i vs alpha blockers which were reviewed found no clinically important differences in symptoms, QoL, nocturia or flow rate between the two agents then PDE5i's can be assumed to be not inferior to alpha blockers with regard to these outcomes.	Thank you for your comment. Please refer to the quality of evidence and trade- off between benefits and harms section of the linking evidence to recommendations table for more detail. Briefly, it describes the following situation: For PDE5Is vs placebo there was no clinically important difference between PDE5Is overall and placebo for IPSS symptom score, IPSS QoL or Qmax. For PDE5Is vs alpha blockers, there was no difference between the drugs for IPSS symptom score, BII, Qmax and nocturia, but alpha blockers were more effective than PDE5Is at improving voiding frequency. The Committee discussed that the evidence presented for PDE5Is vs alpha blockers was not sufficiently powered or analysed as a non-inferiority (or equivalence) trial and therefore cannot be interpreted as showing that PDE5Is are as effective as alpha blockers. It was noted that the evidence for PDE5Is was mostly of very low quality which reduced the confidence in the evidence representing the true effects of the intervention in a LUTS and ED population.
British Association of Urological Surgeons	7	Addendum	8	7	It seems that the decision not to recommend was largely based on cost-effectiveness which is reasonable. It does however remove one valid potential treatment option.	Thank you. The recommendation was based on both clinical and cost effectiveness analysis. There are a number of cost and clinically effective treatments for LUTS that the existing guideline recommends. Please note that this is a guideline, and

Stakeholder	Order No	Document	Section No	Page No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						therefore cannot consider every clinical situation that may be encountered; guidance is not a substitute for the judgement of the clinician. The decision to prescribe any pharmacological agent will depend on each individual patient, including their comorbidities and the adverse effects they experience with different pharmacological agents.
Department of Health	1	General	General	General	I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Thank you
HQT Diagnostics	1	Addendum	General	General	There is evidence that recurrence of Urinary Tract Infection is 4X more likely if Vitamin D is low Suggest test and supplement Vitamin D 25(OH)D to be between 100-150nmol/L Re-test after 3 months Read more at: www.vitamindwiki.com (Search for UTI) http://vitamindwiki.com/tiki-index.php?page_id=4423	Thank you for your comment. Causes of Urinary Tract Infections (UTIs) was not included in the scope of this update, therefore the evidence was not assessed for the link between Vitamin D and UTIs.
HQT Diagnostics	2	Addendum	General	General	One of the factors leading to Urinary Tract Infections is a poor immune system. Advice should be given about diet and lifestyle, with a possible referral to a Registered Dietitian (www.bda.uk.com) or a Nutritional Therapist (www.bant.org.uk) Read more at: http://www.soc.ucsb.edu/sexinfo/article/urinary-tract-infections-utis	Thank you for your comment. Causes of Urinary Tract Infections (UTIs) was not included in the scope of this update, therefore the evidence was not assessed for the link between a poor immune system and UTIs.

Stakeholder	Order No	Document	Section No	Page No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
Lilly UK	1	Addendum	General	General	Lilly would like to respectfully query some of the conclusions of this review with regard the clinical evidence supporting the use of tadalafil in LUTS. Our responses below highlight areas where our clinical evidence may not have been accurately represented. We would like to remind the standing committee that tadalafil is the only PDE5 inhibitor that has regulatory approval for the treatment of LUTS therefore our clinical evidence should be reviewed with this in mind.	Thank you for your comment. Please see detailed responses in sections below for all your comments.
Lilly UK	2	Addendum Draft consultation Guidance	8 25	7 2.5	There is evidence from pooled sub-group data from the Phase III studies demonstrating the effect of tadalafil in men with LUTS, who do not have erectile dysfunction (ED) [1,2]. In men without (ED), tadalafil 5 mg once daily significantly reduced LUTS due to BPH (LUTS-BPH) symptoms and improved quality of life; these changes were similar to those observed in men with ED. The adverse events profile in men without ED was consistent with that of men with ED treated with tadalafil. The results from this integrated analysis of data from three global clinical trials provide evidence tadalafil is an efficacious and well tolerated treatment option, in men with LUTS-BPH, in men with and without ED	Thank you. The review protocol (Appendix C) states that we will only consider meta- analysis and RCTs for inclusion in this review, as these are considered the highest quality of evidence. Therefore any other study types, including post hoc analyses of primary studies that are at high risk of selection bias and attrition bias were not included in this analysis. The post hoc analyses referred to in your comment (references 1 and 2), which were excluded from this review are based on primary studies that were included in this review. The evidence showed that there was no clinically important difference between PDE5Is overall and placebo for IPSS symptom score, IPSS QoL or Qmax. The change in BII with PDE5Is could not be assessed due to a lack of MIDs. With regards to harms, there were increased instances of flushing and headaches in the people taking PDE5Is and there may be increased instances of withdrawals in people taking

Stakeholder	Order No	Document	Section No	Page No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						PDE5Is Sildenafil shows that there is no clinically important improvement in IPSS QoL. Alpha blockers show an improvement in voiding frequency when compared to tadalafil. For all other outcomes (IPSS symptom score, BII, Qmax, nocturia) there was no difference between tadalafil, sildenafil or UK-369,003 and alpha blockers. There was no difference between any PDE5I and alpha blocker with regards to the adverse events of headache, flushing, dizziness and withdrawals due to adverse events. Postural hypotension was not reported for this comparison. There was no difference between tadalafil and solifenacin for IPSS symptom score, IPSS QoL, voiding frequency and nocturia. Qmax had a clinically important improvement with solifenacin compared to tadalafil. There was no difference in the incidence of headaches between the tadalafil and antimuscarinic groups. This review addressed the effectiveness of tadalafil at improving outcomes for LUTS; therefore the outcomes of ejaculation disorders, ejaculatory function, erectile function, and sexual satisfaction (which are ED outcomes) were not assessed in this review. Please refer to the protocol for the clinical question (Appendix C) for further detail. The recommendation in this update is applicable to men with LUTS only, not for those with ED or ED related symptoms;

Stakeholder	Order No	Document	Section No	Page No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						therefore tadalafil remains a treatment option for men with ED or ED related symptoms. The guidance also recommends other treatments for LUTS (such as alpha blockers) which are clinically and cost effective.
Lilly UK	3	Addendum Draft consultation guidance	8 18	7 1.4.10	We note that the response to the review question does not take into account the broader clinical effectiveness of tadalafil and the clinical effectiveness of tadalafil in patients that are experiencing adverse events or may have contraindications with other treatments. Tadalafil could be alternatively considered in patients experiencing bothersome adverse events when taking alpha-blockers, for example ejaculation disorders [3, 4]. Tadalafil improves ejaculatory function, erectile function, and sexual satisfaction in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia and erectile dysfunction [5]. Patients at risk for cataract-surgery should be considered for tadalafil as alpha-blockers may cause interoperative complications, IFIS, intra-operative floppy iris syndrome [6].	The population of the studies included did not exclude people who had previously received other pharmacological treatment for LUTS, that is, the included population were not necessarily treatment naïve, therefore the response to tadalafil from people not responding to other treatments for LUTS was implicitly addressed. Patients at risk for cataract surgery were not identified a priori as a specific subgroup and therefore no separate recommendations have been made on this population. Furthermore, interoperative complications, IFIS, intra-operative floppy iris syndrome were not considered critical or important outcomes affecting the population with LUTS as a whole by the Committee as these are rare in the LUTS population. Please refer to the question protocol (Appendix C). The aim of this question was to assess the efficacy of tadalafil in the treatment of LUTS only, and therefore outcomes that reflected any improvement in LUTS were selected by topic experts and the committee, and only these were reported. No ED outcomes were included in this review as the efficacy of tadalafil at improving ED

Stakeholder	Order No	Document	Section No	Page No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
					This guidance also does not recognise that tadalafil has advantages when comparing sexual adverse events [5]. Treatment satisfaction has also been proven to be significantly improved with tadalafil vs placebo, in comparison to no significant improvement in satisfaction with tamsulosin vs placebo [7].	symptoms was not being assessed in this review. Outcomes related to cataract surgery were not chosen as critical outcomes because the committee did not consider it to be a critical issue and considered that the incidence of floppy iris syndrome was very rare and therefore would not be captured in RCT evidence.
Lilly UK	4	Addendum	12	5	Re Dmochowski (2010) - This study was designed as a urodynamic safety study. The primary end point of this study was change in pdetQmax from baseline to week 12 and the study was specifically powered to detect changes in pdetQmax rather than secondary urodynamic or efficacy measures. Therefore this study should not be included to assess clinical efficacy as measured by IPSS or Qmax results. In addition, tadalafil 20mg is not a licensed dose for the treatment of LUTS-BPH.	Thank you for your comment. Any study that matches our review protocol was included in the review, irrespective of the primary end point of the study. Dmochowski (2010) had a population, Intervention, comparator and outcomes that matched the question protocol and was therefore included in the review. The quality of the evidence from this study, including any limitations, was taken into account when assessing the evidence using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) tool. The fact that the study had pdetMax as a primary outcome was not considered as part of the GRADE assessment, please refer to Appendix H of the addendum document for full details of the GRADE assessment of this study. Our review protocol (Appendix C) states that the interventions will be PDE5Is, it does not state that only studies using licensed doses will be analysed. The aim of the review is to

Stakeholder	Order No	Document	Section No	Page No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						assess the efficacy of PDE5Is for LUTS at all doses, therefore Dmochowski (2010) was included.
Lilly UK	5	Addendum	12	5	Re Egerdie (2012) - In this study, tadalafil 2.5mg significantly improved IIEF-EF (vs placebo), but did not significantly improve IPSS; whereas 5 mg improved both IIEF-EF and IPSS. This demonstrates the effect of tadalafil on LUTS is independent of the effect in ED.	Thank you for your comment. As per the review protocol (Appendix C), the review question was addressing the efficacy of tadalafil of LUTS only. ED outcomes were not being addressed in this question, therefore IIEF-EF was not included as an outcome, and the effect of tadalafil on IIEF-EF was not considered by the committee in the decision making process. With regards to the claim of effect shown by the Egerdie (2012) study, this is only indirect qualitative postulation of the effect which did not scientifically prove an independent effect of tadalafil on LUTS, we need data on a LUTS only population to draw this kind of conclusion.
Lilly UK	6	Addendum	12-13 14	5 4	Kim (2011), Takeda (2014) and Yokoyama (2012) are all studies in Asian patient populations. We question why these have been included to assess efficacy of tadalafil as these are of a different patient population to the UK population. Furthermore, in Yokayama (2012) tamsulosin is an active control and the dose used for tamsulosin in this study is not a licensed dose in UK.	Thank you for your comment. There are no physiological differences in an Asian population that would lead this population to be excluded from the review protocol. As per our review protocol (Appendix C), tamsulosin was agreed by the committee to be a valid comparator to PDE5Is, and therefore the inclusion of Yokoyama (2012) in this review question is valid. Our review protocol (Appendix C) states which comparators will be considered, it does not state that only studies using licensed doses will be analysed. The aim of the review is to assess the efficacy of PDE5Is compared

Stakeholder	Order No	Document	Section No	Page No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						to other treatments for LUTS at all doses.
Lilly UK	7	Addendum	12 14	5 4	Oelke (2012) –This study assesses tadalafil or tamsulosin vs placebo for LUTS-BPH. Tamsulosin is an active control. This study shows comparable efficacy of tadalafil and tamsulosin and comparable improvements of Qmax (both vs placebo). Only tadalafil improves erectile function and orgasmic function [(5)]. Lilly does not believe this comparable efficacy and improvement has been taken into consideration in this guidance. Liguori (2009) – Tadalafil 20mg alternate days is not a licensed dose or dose regimen for LUTS-BPH. Also Singh 2014 – tadalafil 10mg not a licensed dose for LUTS-BPH. Roehrborn (2008) –This is a dose finding study, of which three of the included doses are not licensed for LUTS-BPH.	Thank you for your comment. As per our review protocol (Appendix C), the efficacy of PDE5Is on LUTS was being assessed, not the effect of PDE5Is on ED; therefore no ED outcomes (including erectile function and orgasmic function) were considered in the decision making process. Our review protocol (Appendix C) states that the interventions will be PDE5Is, it does not state that only studies using licensed doses will be analysed. The aim of the review is to assess the efficacy of PDE5Is for LUTS at all doses. Therefore Liguori (2009) and Roehrborn (2008) matched the review protocol and were included in this review question.
Lilly UK	8	Addendum	12	5	Pinggera (2014) was designed and powered to assess prostate blood flow. Lilly question why this study has been included to assess adverse events.	Thank you for your comment. Any study that matched the review protocol was included in the review, irrespective of the primary end point of the study. Pingerra (2014) had a population, intervention, comparator and outcomes that matched the review protocol and was therefore included in the review. The quality of the evidence from this study, including any limitations, was taken into account when assessing the evidence using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) tool. The full GRADE assessment is in Appendix H of the addendum document,

Stakeholder	Order No	Document	Section No	Page No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						which details the reasons for downgrading the quality of evidence contributed by this study; the reason put forward by the stakeholder was not a reason for downgrading the quality of the evidence.
Lilly UK	9	Addendum	13	5	UK-369,003 is not a licensed molecule. Lilly question why this molecule has been included in this review	Thank you for your comment. The review protocol for this question (Appendix C) states that the intervention was PDE5Is, this includes all PDE5Is, whether licensed or not licensed. UK-369,003 was being used as an experiment formulation under the name Gisadenafil for the treatment of LUTS symptoms and is therefore a valid intervention included in the review question.
Lilly UK	10	Addendum	12	5	Combination therapy has not been assessed in this review. Lilly believes there is evidence demonstrating the effectiveness of tadalafil/finasteride combination therapy [8, 9]. Casabe (2013) [8] represents a certain group of patients with LUTS-BPH i.e. those with an enlarged prostate who might benefit from a therapy with a 5ARI and the addition of an alpha blocker for early symptom relief. The alpha blocker alleviates symptoms, but does not reduce prostate size. The 5ARI's reduce prostate size, and due to the mode of action, effects on LUTS are only seen after 6 to 9 months on therapy. The 5ARI's also have some sexual adverse effects [10]. The co-administration of tadalafil/finasteride provides early improvement in LUTS in men with BPH and prostatic enlargement. Tadalafil/finasteride co-administration also improves erectile function in men who have comorbid erectile dysfunction. The combination of 5ARI with alpha blocker or with PDE5i is	Thank you for your comment. The review protocol for this question (Appendix C) states that only monotherapy with PDE5Is will be addressed in this particular update. Therefore, the combination of tadalafil and finasteride was excluded from the review question and the study Casabe (2013) was not included in the analysis. Combination therapy is covered by a different clinical area with a separate clinical question, the evidence in this area was not considered in need of updating at this time.

Stakeholder	Order No	Document	Section No	Page No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
					recommended in the EAU guidelines [11]. Tadalafil/finasteride combination was well tolerated and most adverse events were mild/moderate in the six month study [8,9]	
Lilly UK	11	Addendum	16	25-26	Lilly does not agree with the following statement: "There is very low quality evidence that suggests there may be no clinically important difference between tadalafil and placebo in the critical outcome of IPSS (symptom score)". There is evidence demonstrating a clinically important difference between tadalafil and placebo. Unlike alpha blocker studies, several tadalafil studies included a 4 week placebo run-in period. As patients with symptoms of BPH-LUTS often experience an improvement in symptoms during the blinded placebo run-in phase of BPH-LUTS therapies, it may be helpful for clinicians to know not only the typically reported improvement in symptom scores of treated versus placebo subjects post randomization, but also the total improvement in symptom score from the time of blinded placebo run-in until the study endpoint. The latter total improvement score may better reflect what an individual patient experiences in real-world clinical practice, and is rarely reported. Since patients in clinical practice are not treated with a placebo run-in period as in clinical studies, the analysis also aimed at identifying the magnitude of improvement when considering this additional placebo effect. The Nickel study [12] demonstrated that patients achieve a clinically meaningful improvement in BPH-LUTS symptoms. Tadalafil 5mg once daily resulted in a significantly greater proportion of 1) Patients ≥3 point IPSS improvement (71.1% vs 56% for tadalafil and placebo	Thank you for your comment. This evidence statement was agreed by the committee following a discussion of all evidence relating to the outcomes and from the studies included in this review. We consider that effects post randomisation are more appropriate measures and are less prone to risk of bias. We do not believe that the inclusion of data through the run in period is appropriate.

Stakeholder	Order No	Document	Section No	Page No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
					respectively) (odds ratio [95%CI]: 1.9(1.5, 2.4); p<0.001) 2) Tadalafil patients (61.7%) compared to placebo patients (45.5%) achieving ≥25% improvement in total IPSS from randomization to endpoint (odds ratio [95% CI]: 2.0 (1.6, 2.5); p<0.001) as compared to placebo In addition, EAU guidelines on the treatment and follow-up of non-neurogenic male LUTS make the following grade A recommendation, with 1b level of evidence: "Phosphodiesterase type 5 inhibitors reduce moderate-to-severe (storage and voiding) LUTS in men with or without erectile dysfunction. Only tadalafil (5 mg once daily) has been licensed for the treatment of male LUTS in Europe" (11).	Thank you for your comment. The Nickel study referred to in this comment was published after the literature search for this guideline was completed and therefore was not included in the review. Additionally, this is a post – hoc analysis and would not have met inclusion criteria for this review. The EAU guidelines appear to be based on a meta-analysis by Gacci et al., (2012) which only compares tadalafil to placebo, and only includes 7 studies (this review includes 21 studies). The Gacci et al., (2012) study also considers ED outcomes as evidence for efficacy, and appears to use lower thresholds for clinically meaningful of improvement in IPSS score compared to this review,
Lilly UK	12	Addendum	16	33-35	There is evidence demonstrating that tadalafil statistically significantly improves maximum urinary flow rate in men with LUTS-BPH. A pooled post hoc analysis (13) characterized changes in the maximum urinary flow rate using integrated data from 4 international, placebo controlled studies of tadalafil once daily for LUTS. This integrated analysis revealed a statistically significant Q_{max} improvement for tadalafil (5mg) vs placebo. The numerical difference in the maximum urinary flow rate from baseline between tadalafil and placebo increased with increased voided volume.	Thank you for your comment. As per our review protocol (Appendix C), post hoc analyses were not included study types for this review question. The post hoc analyses referred to in your comment (reference 13), which were excluded from this review are based on primary studies that were included in this review. Please see our response to your comment (ID 6) for further information on inclusion criteria for this review question.
Lilly UK	13	Addendum	17	38	Of the 5 studies assessed, 3 includes studies in which tamsulosin is an active control (Oelke, Kim,	Thank you for your comment. Any study that matched the question review protocol was

Stakeholder	Order No	Document	Section No	Page No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
					Yokoyama). It also includes Asian patient populations' studies that Lilly believes are not relevant to UK population (Kim, Yokoyama). The Kumar and Liguori use inappropriate unlicensed doses.	included in the review. The comparator Tamsulosin (used in Oelke, Kim & Yokoyama) was included as a comparator in this review protocol and therefore these studies are included in the clinical review. Our protocol (Appendix C) did not specify that studies including an Asian population should be excluded from this review. Furthermore, there is no sound medical or physiological reason for excluding an Asian population from this review. Therefore Kim & Yokoyama are included in the review. Our review protocol (Appendix C) states that the interventions will be PDE5Is, it does not state that only studies using licensed doses will be analysed. The aim of the review is to assess the efficacy of PDE5Is for LUTS at all doses. Therefore the Kumar and Liguori studies matched the review protocol and were included in this review question. The quality of the evidence from these studies, including any limitations, was taken into account when assessing the evidence using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) tool.
Lilly UK	14	Addendum	14 18	4 14/15	Maselli (2010) is a single centre study, with 68 patients, and did not adequately report randomisation or blinding. Lilly question how these conclusions can be made based on this evidence	Thank you for your comment. Any study that matched the question review protocol was included in the review. Maselli (2010) had a population, intervention and comparator that matched the question review protocol. The review protocol (Appendix C) did not state that a study needed a minimum number of

Stakeholder	Order No	Document	Section No	Page No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						participants to be included in the review. Inadequate reporting of randomisation and blinding was not a reason for exclusion in the protocol; however, study quality (including adequacy of randomisation and blinding) was taken into account when assessing the evidence using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) tool.
Lilly UK	15	Addendum	18 20	11-19 12-19	Lilly believes that PDE5i's and antimuscarinics should not be compared. Antimuscarinics are only licensed for overactive bladder syndrome, not for LUTS-BPH.	Thank you for your comment. The BNF lists the indications of the antimuscarinic drug Solifenacin (which is used in the study) as urinary frequency, urgency and urge incontinence, all of which are features of LUTS. The topic experts and the committee agreed that antimuscarinics was a valid comparator to be included in this review protocol.
Lilly UK	16	Addendum	20	25	Re quality of evidence – population: the tadalafil trial populations for Lilly sponsored studies were mostly composed of men with both LUTS and ED but ED was **not** an inclusion criteria in the LUTS-BPH studies except one (Egerdie). Because it's a common comorbidity and majority of these patients will present with co-existing ED, secondary erectile function measures were included. Egerdie (2011) demonstrated an independent effect on IPSS from IIEF-EF results. There is evidence available in a pooled analysis that demonstrates significant improvement in IPSS, BII and IPSS-QoL scores when compared with placebo in patients with LUTS-BPH without ED, similar to that in LUTS-BPH patients with ED [1, 2, 3].	Thank you for your comment. The wording used here does not imply that ED was an inclusion criteria of the studies included in the review, but rather emphasises the fact that the majority of the population of the included studies in the review included people with both LUTS and ED. It is understood that many patients present with LUTS and ED as coexisting conditions; however, the review question that was addressed here was specifically to address the effectiveness of PDE5Is on LUTS symptoms, not ED symptoms. Therefore ED outcomes were not taken into consideration when the committee made the decision about the use of PDE5Is for treating men with LUTS symptoms only.

Stakeholder	Order No	Document	Section No	Page No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						The references and outcomes reported here refer to post hoc analyses which were not included in this review, please see our response to your comment (ID 6) for more detail on included study criteria.
Lilly UK	17	Addendum	21	25	Re trade-off between benefits and harms. Lilly do not agree with the following statement "the Committee were concerned that any improvements in the subjective patient outcomes of IPSS symptom score, IPSS QoL and BII may be confounded by improvement in ED, rather than LUTS specific improvement alone; therefore leading to uncertainty in the benefits of PDE5Is in managing LUTS alone in men with LUTS." Lilly believe that there is evidence demonstrating improvement in LUTS alone [1,2]. There is also evidence available that demonstrates that improvement in LUTS symptoms is not confounded by ED [14,15]	Thank you for your comments. The committee based their recommendations and decisions upon the evidence review presented to them, with LUTS- specific outcomes (agreed by the committee members a priori) as indicators of the efficacy of PDE5Is in the treatment of the symptoms of LUTS. The committee explicitly stated their reasoning for their decision in the linking evidence to recommendations section. The committee based their decisions upon the best evidence available to them. As stated in comment ID 6, the post hoc analyses from which data are presented here (references 1 and 2) were not included in this review for the committee's consideration (refer to Appendix C for study inclusion criteria). Reference 14 (Brock et al., (2014) was not included in the review as it was a post hoc analysis, and therefore this data was not presented to the committee (see comment ID 6 and review protocol in Appendix C for more detail on this). Reference 15 (Egerdie, 2012) was included in the review, and the LUTS-specific outcomes of IPSS, BII and Qmax

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						were included in the review.
Lilly UK	18				**References** 1. Brock et al BJU International BJU Int. 2013 Nov;112(7):990-7 Tadalafil once daily in the treatment of lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH) in men without erectile dysfunction 2. Porst et al Urology. 2014 Mar; 83 (3):684. Efficacy and safety of tadalafil 5mg once daily for lower urinary tract symptoms suggestive of benign prostatic hyperplasia: subgroup analyses of pooled data from 4 multinational, randomized, placebo-controlled clinical studies. 3. Flomax MR (tamsulosin) APC http://www.medicines.org.uk/emc/medicine/22738#UNDESIRABLE_EFFECTS 4. Gacci et al. J Sex Med 2014; 11:1554–1566. Impact of medical TX for male LUTS due to BPH: A systematic review and meta-analysis 5. Giuliano et al. J Sex Med. 2013 Mar;10 (3):857-65. Tadalafil once daily improves ejaculatory function, erectile function, and sexual satisfaction in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia and erectile dysfunction: results from a randomized, placebo- and tamsulosin-controlled, 12-week double-blind study 6. Oelke et al. 2014 Sep; 13 (9):1187-97. Cardiovascular and ocular safety of α1-adrenoceptor antagonists in the treatment of male lower urinary tract symptoms 7. Oelke et al. BJU Int. 2014 Oct; 114 (4):568-75. Treatment satisfaction with tadalafil or	Thank you for providing this list of references. We have given consideration (include/ exclude (reasons already stated above)/ information only) to all of these documents (please see list of excluded studies in the appendices of the Addendum) with the following exceptions: 8. Casabe (2013)- included a combination of tadalafil + finasteride which was excluded from the review protocol. 9. Glina (2015) – this was a combination study of tadalafil + finasteride (exclusion criteria) and was published after the information sciences department had run the searches for this review question (27/08/2014). 12. Nickel (2014) – this study was published after the information sciences department had run the searches for this review question (27/08/2014). Additionally, this is a post hoc analysis which was excluded from this review question.

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					tamsulosin vs placebo in men with lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH): results from a randomised, placebo-controlled study 8. Casabé et al. J Urol. 2014 Mar; 191 (3):727-33. Efficacy and Safety of the Coadministration of Tadalafil Once Daily with Finasteride for 6 Months in Men with Lower Urinary Tract Symptoms and Prostatic Enlargement Secondary to Benign Prostatic Hyperplasia 9. Glina et al. J Sex Med. 2015 Jan; 12 (1):129-38. Sexual function in men with lower urinary tract symptoms and prostatic enlargement secondary to benign prostatic hyperplasia: results of a 6-month, randomized, double-blind, placebo-controlled study of tadalafil coadministered with finasteride 10. Finasteride (Proscar) and dutasteride SPC. http://www.medicines.org.uk/emc/medicine/1190#UNDESIRABLE_EFFECTS dutasteride (Avodart) http://www.medicines.org.uk/emc/medicine/11618#UNDESIRABLE_EFFECTS 11. Oelke M et al, EAU Guidelines on the treatment and follow-up of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. Eur Urol 2013;64:118-140 12. Nickel et al BJU Int. 2014 Sep 5. doi: 10.1111/bju.12926. [Epub ahead of print]. Proportion of tadalafil-treated patients with clinically meaningful improvement in lower 1 urinary tract symptoms associated with benign prostatic hyperplasia – integrated data 2 from 1499 study participants.	

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					13. Roehrborn et al Journal of Urology. April 2014; 191, 1045-1050. Effects of Tadalafil Once Daily on Maximum Urinary Flow Rate in Men with Lower Urinary Tract Symptoms Suggestive of Benign Prostatic Hyperplasia 14. Brock et al J Urol. 2014 Feb;191 (2):405-11 Direct Effects of Tadalafil on Lower Urinary Tract Symptoms versus Indirect Effects Mediated through Erectile Dysfunction Symptom Improvement: Integrated Data Analyses from 4 Placebo Controlled Clinical Studies 15. Egerdie et al. J Sex Med 2012 Jan;9(1):271-81.Tadalafil 2.5 or 5 mg administered once daily for 12 weeks in men with both erectile dysfunction and signs and symptoms of benign prostatic hyperplasia: results of a randomized, placebo-controlled, double-blind study.	
NHS Choices	1	General	General	General	The Digital Assessment Service welcome the update and have no comments on its content as part of the consultation.	Thank you
NHS England	1	General	General	General	I have sort advice from a urology specialist. I don't think the suggestions are contentious.	Thank you
Royal College of Pathologists	1	Addendum, NICE version, Appendices	General	General	Thank you for asking us to review the documents. I have no comments to add.	Thank you

Registered stakeholders