National Institute for Health and Care Excellence

IP1701/2 Prostatic urethral temporary implant insertion for lower urinary tract symptoms caused by benign prostatic hyperplasia

IPAC date: 14 July 2022

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1	Consultee 1 Company Olympus Medical	1.1	Suggest change from "... shows well-recognised complications in the short term..." to "... is associated with expected, short term, mild, transient, and self-resolving complications..."	Thank you for your comment. Section 1.1 has been changed to remove the term 'well-recognised complications'.
2	Consultee 1 Company Olympus Medical	1.1	There are a number of different established procedures that are used to treat the same condition (i.e., LUTS caused by BPH). No head-to-head randomised clinical trials have been conducted to compare prostatic urethral temporary implant insertion directly with other minimally invasive surgical treatments (MISTs). In the absence of direct head-to-head data, a naïve comparison of MISTs with comparable study design shows that prostatic urethral temporary implant insertion is associated with: - Comparable efficacy improvements from baseline as UroLift (Prostatic Urethral Lift - IPG475/ normal arrangements) and Rezum (Transurethral water vapour ablation – IPG625/ standard arrangements). - Comparable efficacy improvements versus sham as UroLift and Rezum	Thank you for your comment. The IP programme does not assess the efficacy and safety of comparator interventions. Section 1.5 has been changed to include randomised controlled trials against a suitable comparator in the recommendation for further research.

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			- Routinely catheter-free procedure, unlike UroLift and Rezum Question 3 of the Specialist Advice Questionnaire, the expert highlights that "... there is now a significant amount of both safety and efficacy data..."	
3	Consultee 1 Company Olympus Medical	1.1	There are a number of different established procedures that are used to treat the same condition (i.e., LUTS caused by BPH). No head-to-head randomised clinical trials have been conducted to compare prostatic urethral temporary implant insertion directly with other minimally invasive surgical treatments (MISTs). In the absence of direct head-to-head data, a naïve comparison of MISTs with comparable study design shows that prostatic urethral temporary implant insertion is associated with: ▪ Comparable efficacy improvements from baseline as UroLift (Prostatic Urethral Lift - IPG475/ normal arrangements) and Rezum (Transurethral water vapour ablation – IPG625/ standard arrangements). ▪ Comparable efficacy improvements versus sham as UroLift and Rezum ▪ Routinely catheter-free procedure, unlike UroLift and Rezum Comparison of Prostatic urethral temporary implant insertion (iTind) clinical evidence with other MIST clinical evidence. Figure 1. Efficacy comparison1, 3, 4, 5, 6, 7  Olympus Medical. Comment on a text s	Thank you for your comment. Consultee has presented safety and efficacy data for other minimally invasive surgical treatments for the same indication. The IP programme does not assess the efficacy and safety of comparator interventions.

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			Non-comparative, multicenter iTind: Amparore, 2021** — Parameter / 12 mon / 36 mon: IPSS reduction [points] -12.9 / -12.1; Qmax increase [mL/s] 7.3 / 7.5 Urolift: Chin, 2012 — 12 mon / 36 mon: -10.4 / ND; 2.6 / ND Rezum: Dixon, 2016 — 12 mon / 36 mon: -12.5 / ND; 4.6 / ND **Comparative (sham) RCT, multicenter** iTind: Chughtai, 2020 — 12 mon / 36 mon: -9.3 / ND; 3.5 / ND Urolift: Roehrborn, 2017 — 12 mon / 36 mon: -10.6 / -8.8; 4.00 / 3.5 Rezum: Mc Vary, 2019 — 12 mon / 36 mon: -11.60 / -11; 5.50 / 3.5	
4	Consultee 1 Company Olympus Medical	1.1	Figure 2. Post-operative catheterisation comparison2, 4, 5, 6, 7, 8 **Non-comparative, multicenter** 0-3 months / Publications / Total Catheterization / Routine Catheterization Urolift: Chin et al., 2012 — 53% / ND Rezum: Dixon et al., 2016 — 55%** / 23% iTIND: Amparore et al., 2021 — 5% / 0% **Comparative (sham) RCT, multicenter** 0-3 months / Publications / Total Catheterization / Routine Catheterization Urolift: Roehrborn et al., 2013 — 51% / 28.5% Rezum: Mc Vary et al., 2016 — 90% / 61% iTIND: Chughtai et al., 2020 — 0% / 0%	Thank you for your comment. Consultee has presented safety and efficacy data for other minimally invasive surgical treatments for the same indication. The IP programme does not assess the efficacy and safety of comparator interventions.
5	Consultee 1 Company Olympus Medical	1.1	References 1. Roehrborn CG, Barkin J, Gange SN, et al. Five-year results of the prospective randomized controlled prostatic urethral L.I.F.T. study. Can J Urol. 2017;24(3):8802-8813. 2. Chughtai B, Elterman D, Shore N, et al. The iTind Temporarily Implanted Nitinol Device for the Treatment of Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia: A Multicenter, Randomized, Controlled Trial. Urology. 2021;153:270-276. doi:10.1016/j.urology.2020.12.022 3. De Nunzio C, Cantiello F, Fiori C, et al. Urinary and sexual function after treatment with temporary implantable nitinol device (iTind) in men with LUTS:	Thank you for your comment. The references relevant to this procedure (refs. 2, 3 and 4) are included in the key evidence. The other references describe other minimally invasive

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			6-month interim results of the MT-06-study. World J Urol. 2021;39(6):2037-2042. doi:10.1007/s00345-020-03418-2 4. Amparore D, Fiori C, Valerio M, et al. 3-Year results following treatment with the second generation of the temporary implantable nitinol device in men with LUTS secondary to benign prostatic obstruction. Prostate Cancer Prostatic Dis. 2021;24(2):349-357. doi:10.1038/s41391-020-00281-5 5. Chin PT, Bolton DM, Jack G, et al. Prostatic urethral lift: two-year results after treatment for lower urinary tract symptoms secondary to benign prostatic hyperplasia. Urology. 2012;79(1):5-11. doi:10.1016/j.urology.2011.10.021 6. Dixon CM, Cedano ER, Pacik D, et al. Two-year results after convective radiofrequency water vapor thermal therapy of symptomatic benign prostatic hyperplasia. Res Rep Urol. 2016;8:207-216. doi:10.2147/RRU.S119596 7. McVary KT, Rogers T, Roehrborn CG. Rezūm Water Vapor Thermal Therapy for Lower Urinary Tract Symptoms Associated with Benign Prostatic Hyperplasia: 4-Year Results From Randomized Controlled Study. Urology. 2019;126:171-179. doi:10.1016/j.urology.2018.12.041 8. Roehrborn CG, Gange SN, Shore ND, et al. The prostatic urethral lift for the treatment of lower urinary tract symptoms associated with prostate enlargement due to benign prostatic hyperplasia: the L.I.F.T. Study. J Urol. 2013;190(6):2161-2167. doi:10.1016/j.juro.2013.05.116	surgical treatments, which have separate IP guidance.
6	Consultee 1 Company Olympus Medical	1.5	Porpiglia, 2018; Amparore, 2021, Chughtai, 2021 and De Nunzio, 2020, report details of patient selection, including size of prostate. Prostate Volume [ml], <60ml (Porpiglia, 2018), <75ml (Amparore, 2021), 25-75ml (Chughtai, 2021). <120ml (De Nunzio, 2020). Prostate size (ml/cm3) was also reported. 29.5 ± 7.4 (Porpiglia, 2018), 37 (IQR 16-65) (Amparore, 2021), 43.4 ± 15.5 (Chughtai, 2021) and 37.68 (IQR 15-80ml) (De Nunzio, 2021).	Thank you for your comment. The committee considered that more evidence is needed before the procedure can be used under standard arrangements, and this should include patient details such as prostate size.

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7	Consultee 1 Company Olympus Medical	2.4	Suggest change from "…Insertion and removal of the device are both done as day-case procedures…" to "…Insertion and removal of the device are both done as day-case or outpatient procedures…" Chughtai, 2021 demonstrated that the device can be conducted in patients under sedation or local anaesthesia in an ambulatory or outpatient setting. All procedures were performed in an outpatient setting (De Nunzio, 2020).	Thank you for your comment. Section 2.4 has been changed to note that removal of the device is done as a day-case **or outpatient** procedure. Amparore 2021, which includes UK data, states 'The device is implanted under direct vision through a standard rigid 19F-22F cystoscope under light intravenous sedation and removed in outpatient setting through an open-ended 22F Foley catheter with topical anaesthesia.' This detail has been added to the overview.
8	Consultee 1 Company Olympus Medical	3.2	Suggest addition of "preservation of sexual function" as a key safety/ or efficacy outcome. Preservation of ejaculatory function is of major importance to men when pursuing treatments for LUTS secondary to BPH. TURP is associated with rates of retrograde ejaculation of 38.2-89.0% and impotence rates of 13.0-14.0%, while laser prostatectomy has retrograde ejaculation rates of 50-76.6% and impotence rates of 5.2-7.9%. Both surgical and pharmacologic sexual side effects contribute to the undertreatment of men with BPH. One major advantage of prostatic urethral temporary implant insertion procedure is the preservation of sexual function. Chughtai, 2021 demonstrated that subjects with the device, did not	Thank you for your comment. Section 3.2 has been changed to include preservation of sexual function as a key efficacy outcome.

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			experience de novo erectile dysfunction or retrograde ejaculation. A prospective study, also showed sexual function was preserved in all device subjects at 6 months (Nunzio, 2020). One professional expert also highlighted "...impact on SHIM (Sexual Health Inventory for Men) …" as a key efficacy/ safety outcome (Question 15 of the Specialist Advice Questionnaire).	
9	Consultee 1 Company Olympus Medical	3.3	Suggest removal of 'urinary incontinence' as a key safety outcome. Urinary incontinence – if occurring – would be reported as an adverse event. 1 case of transient incontinence due to device displacement (3.1%) (Porpiglia, 2018). 6 patients (8.4%) observed transient incontinence which resolved after device removal (Nunzio, 2021). It's important to highlight that they were TRANSIENT and self-resolving (I.e., not urinary incontinence). De Nunzio, 2021 demonstrated that urinary continence was preserved in all 70 subjects, using validated questionnaires (incontinence Symptom Index questionnaire (ISI)). No cases of urinary or transient incontinence were reported in Chughtai, 2021 and Amparore, 2020. Important to highlight that one expert highlighted that - to their knowledge - "...there have been no incidences of incontinence..." (Question 14 of specialist advice questionnaires).	Thank you for your comment. Section 3.3 has been changed to remove 'urinary incontinence' from the key safety outcomes.

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10	Consultee 1 Company Olympus Medical	3.5	It's worth highlighting the below for context. Chughtai, 2021 demonstrated a powerful placebo effect that resulted in non-statistically significant improvement in prostatic urethral temporary implant versus the sham arm at the time of unblinding at 3 months. A meta-analysis found significant improvements in AUA-SS (American Urology Association Symptom Score) and Qmax at 3 months in the sham arm of randomized controlled trials in BPH trials [1]. AUA-SS improved an average of 27%, similar to the improvement in IPSS of 28.9% in the prostatic urethral temporary implant sham arm. Whilst the sham effect is large, this improvement is similar to Prostatic Urethral Lift (PULs) sham arm improvement of 24.2% [2] and Rezum's sham arm improvement of 20% [3]. 1. C Welliver, M Kottwitz, P Feustel, K. McVary Clinically and Statistically Significant Changes Seen in Sham Surgery Arms of Randomized, Controlled Benign Prostatic Hyperplasia Surgery J. Urol, 194 (2015), pp. 1682-1687 doi.org/10.1016/j.juro.2015.06.091 2 - CG Roehrborn, SN Gange, ND Shore, et al. (2013). The prostatic urethral lift for the treatment of lower urinary tract symptoms associated with prostate enlargement due to benign prostatic hyperplasia: the L.I.F.T. Study. J Urol, 190 (6) (2013), pp. 2161-2167, 10.1016/j.juro.2013.05.116. 3 - KT McVary, T Rogers, CG. Roehrborn Rezūm Water Vapor Thermal Therapy for Lower Urinary Tract Symptoms Associated With Benign Prostatic Hyperplasia: 4-Year Results from Randomized Controlled Study Urology, 126 (2019), pp. 171-179, 10.1016/j.urology.2018.12.041	Thank you for your comment. Section 3.5 of the draft guidance states: 'The committee noted that there: • is only 1 device for this procedure and the technology is evolving • was a sizeable placebo effect associated with the procedure in some of the studies.' The committee considered the evidence for prostatic urethral temporary implant insertion and noted there was a sizeable placebo effect in the randomised controlled trial by Chughtai et al.,2021. The IP programme does not assess the efficacy and safety of comparator interventions.

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11	Consultee 1 Company Olympus Medical	3.5	There was a powerful placebo effect in one study (Chughtai, 2021). Suggest change from "…was a sizeable placebo effect associated with the procedure in some of the studies…" to "…was a sizeable placebo effect associated with the procedure in one study…".	Thank you for your comment. Section 3.5 has been changed as suggested.
12	Consultee 1 Company Olympus Medical	3.6	Suggest addition of "…those looking to preserve sexual function…" as people who may benefit from this procedure. Preservation of ejaculatory function is of major importance to men when pursuing treatments for LUTS secondary to BPH. One major advantage of prostatic urethral temporary implant is the preservation of sexual function. No prostatic urethral temporary implant subjects experienced de novo erectile dysfunction or retrograde ejaculation (Chughtai, 2020). This is similar to a prospective study showing sexual function was preserved in all prostatic urethral temporary implant subjects at 6 months of follow-up (De Nunzio, 2020). A professional expert highlighted that a group of patients who would particularly benefit from this procedure are those "…seeking a treatment alternative to both medication and standard resecting procedures such a TURP or laser, with the desire to avoid negative impact upon sexual function and ensure a rapid return to normal activities…".	Thank you for your comment. A committee comment has been added to note that preservation of sexual function may be a benefit of the procedure.
13	Consultee 1 Company Olympus Medical	Overview – efficacy summary	Suggest inclusion of the Amparore, 2021 as most relevant and informative. In the single-arm trial of 81 patients, from baseline to 24 months 5 (6.2%) patients required drug therapy. No additional patients underwent alternative treatments (either medical or surgical) between 24 and 36 months (Amparore, 2021).	Thank you for your comment. The following text from Amparore 2021 has been added to the overview: 'From baseline to 24 months, 5 (6.2%) patients needed drug therapy and 8 (8.6%) patients

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				had surgical retreatment. No additional patients had alternative treatments (either medical and surgical) between 24 and 36 months.'
14	Consultee 1 Company Olympus Medical	Overview – safety summary	The phrasing of the overall safety summary is misrepresentative of the published evidence and reads ambiguously. Suggested summary: In the prostatic urethral temporary implant group, there was only a total of 5 procedure- and/or device-related SAEs observed in 3 patients. Only 3 SAEs were found to be possibly related to the device. Most AEs were mild, anticipated, and all but 2 resolved within 1-4 weeks. In addition, all procedures were performed without serious perioperative AEs. The author concludes that AEs were limited to mild events at a low rate (Chughtai, 2021). No intraoperative complications were reported, and all patients were discharged without a catheter on the same day of the procedure. The rate of post-operative adverse events was low, with all complications grade as I or II according to the Clavien-Dindo system, self-limiting and resolved within 30 days. No new procedure or device related adverse events were reported as any of the other follow-up points out to 3 years (Amparore, 2021). Overall, 75 complications were detected in 70 patients. All complications except for one, were graded as I or II according to the Clavien-Dindo system and were self-limiting, with 75% of patients recovering from all their AEs within 7 days (De Nunzio, 2020).	Thank you for your comment. The 'Overall' paragraph at the beginning of the safety section was intended to describe the overall rate of adverse events reported in Chughtai 2021 as 'serious adverse events' and 'all adverse events'. It was not intended to be an overall summary of safety events reported by the different studies. The title of this paragraph has been changed to 'unspecified adverse events'. Chughtai 2021 was the only paper that reported a general rate of adverse events without specifying what they all were. Adverse events in the other studies are described under the relevant subheading.

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15	Consultee 1 Company Olympus Medical	Overview – p9	Suggest change from "...Urinary incontinence because of device displacement..." to "... Transient incontinence because of device displacement..." 1 case of transient incontinence due to device displacement (3.1%) (Porpiglia, 2018). It's important to highlight that they were TRANSIENT and self-resolving (I.e., not urinary incontinence).	Thank you for your comment. This adverse event has been described as it was described in the paper. The next sentence states that it resolved after the device was removed on day 1 after insertion.
16	Consultee 1 Company Olympus Medical	Overview – p10	Suggested inclusion of Chughtai, 2021, Porpigilia, 2018 and De Nunzio, 2020. Retreatment (at 12 months): 10% (12/118) - 6 men (4.7%) had an alternative BPH surgery during the 12-month follow up due to deterioration of symptoms [prostatic urethral temporary implant insertion did not complicate any of the alternative surgeries]. - 6 men (4.7%) required medication for LUTS secondary to BPH (Chughtai, 2021) Retreatment: 0% (0/70) - No patients required reintervention at 6 months (De Nunzio, 2021). Retreatment: 9% (3/32) - No patients required adjunctive surgical treatments during the 3-year follow-up period. - Whilst all patients discontinued BPH-related medical therapy after the	Thank you for your comment. Additional details on reinterventions have been added to safety summary of the overview. The need for medication is described in the efficacy section of the overview.

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			implantation, 3 patients (9%) resumed therapy within 12 or 24 months of treatment (Porpigilia, 2018).	
17	Consultee 1 Company Olympus Medical	Overview – p9	Suggest change from "...urinary incontinence..." to "...Transient incontinence..." Urinary incontinence – if occurring – would be reported as an adverse event. 1 case of transient incontinence due to device displacement (3.1%) (Porpiglia, 2018). 6 patients (8.4%) observed transient incontinence which resolved after device removal (Nunzio, 2021). It's important to highlight that they were TRANSIENT and self-resolving (I.e., not urinary incontinence). De Nunzio, 2021 demonstrated that urinary continence was preserved in all 70 subjects, using validated questionnaires (incontinence Symptom Index questionnaire (ISI)). No cases of urinary or transient incontinence were reported in Chughtai, 2021 and Amparore, 2020.	Thank you for your comment. The title 'urinary incontinence' has been changed to 'transient urinary incontinence' – both events that are described are transient.
18	Consultee 1 Company Olympus Medical	General	Longer term follow-up data (up to 6.6-years) for the MT02 study (Amparore, 2021) is to be published as a conference abstract at the American Urology Association (AUA) meeting May 2022. The abstract reports clinical efficacy up to 79-months for the MT02 study with implantation of the temporary implantable nitinol device (iTind; Medi-Tate Ltd®, Israel) in men with lower urinary tract symptoms (LUTS) due to benign prostatic obstruction.	Thank you for your comment. Conference abstracts are not normally considered adequate to support decisions on efficacy and are not generally selected for presentation in the

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			Link: https://www.auajournals.org/doi/10.1097/JU.0000000000002669.06	overview, unless they contain important safety data.
19	Consultee 1 Company Olympus Medical	Overview -p21	Suggestion to add "…this is a 6-month interim report of the first 70 subjects. The study will go on to follow up for 36-months with 200 patients in total…"	Thank you for your comment. The suggested wording has been added to the study details in the overview.
20	Consultee 1 Company Olympus Medical	General	Longer term follow-up data (up to 6.6-years) for the MT02 study (Amparore, 2020) is to be published as a conference abstract at the American Urology Association (AUA) meeting May 2022. The abstract reports clinical efficacy up to 79-months for the MT02 study with implantation of the temporary implantable nitinol device (iTind; Medi-Tate Ltd®, Israel) in men with lower urinary tract symptoms (LUTS) due to benign prostatic obstruction. Link: https://www.auajournals.org/doi/10.1097/JU.0000000000002669.06	Thank you for your comment. Conference abstracts are not normally considered adequate to support decisions on efficacy and are not generally selected for presentation in the overview, unless they contain important safety data.

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