NICE National Institute for Health and Care Excellence

# Single Technology Appraisal

# Pentosan polysulfate sodium for treating bladder pain syndrome [ID1364]

# Committee Papers

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**SINGLE TECHNOLOGY APPRAISAL**

# Pentosan polysulfate sodium for treating bladder pain syndrome [ID1364]

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*Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.*

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal

## Pentosan polysulfate sodium for treating bladder pain syndrome

## Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

**Definitions:**

**Consultees –** Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

**Clinical and patient experts and NHS commissioning experts** – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

**Commentators –** Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

**Public –** Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

**Please note:** Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

## Comments received from consultees

| Consultee | Comment [sic] | Response |
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| Consilient Health | Section 3.5 – "It recognised that pentosan polysulfate sodium could be given at different points in the treatment pathway but it would tend to be used before bladder instillations."<br><br>We agree that pentosan polysulfate sodium (PPS) and bladder instillations are all part of the treatment pathway for patients with IC/BPS; however the ACD does not fully recognise the positioning of PPS within that pathway. PPS would only be considered as an option for the treatment of patients when 'best supportive care' (BSC), which is typically started in primary care, has failed; PPS is not as an alternative to BSC. In addition, the ACD does not recognise that PPS can only be given once the patient has been referred to secondary care. In this case, patients can be offered either PPS or bladder instillations as second-line treatment, as PPS has been shown to be an effective and cost-effective alternative to bladder instillations.<br><br>The ACD states that some patients would refuse bladder instillations because of their invasive nature and would instead choose best supportive care. Whilst we agree with this statement, it should be recognised that this would apply to a very small number of patients. As stated in our submission, consensus among clinical experts at an advisory board was that <5% BPS patients are contraindicated to or refuse bladder instillations. This was accepted by the ERG and its clinical expert.<br><br>If patients discontinue bladder instillations because of apparent symptom resolution, they will not receive PPS as further treatment would not be required. If their symptoms recur, patients would be offered either a bladder instillation or PPS. As described by our advisory board (Appendix M of the company submission), patients that fail on one type of bladder instillation would typically be offered alternative bladder instillations in an attempt to find one that works for the patient. Given the lack of treatment options for this condition, if both PPS and the various bladder installations ultimately fail in secondary care, patients may be tried again on best supportive care/palliative care as a last resort prior to surgery. | Comments noted. The committee considered the positioning of pentosan polysulfate sodium in the treatment pathway. Please see the Final Appraisal Document (FAD) for a summary of these considerations and details of how the pathway has been incorporated into the recommendations (see FAD sections 3.4, and 3.20 to 3.24). |

| Consultee | Comment [sic] | Response |
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| | In summary, PPS can be used as an alternative to bladder instillations as second-line therapy after BSC has failed, but is not an alternative to BSC. | |
| Consilient Health | Sections 3.7-3.8<br><br>The company base case uses the Bucher method to source treatment response rates, recognising that there was considerable heterogeneity in the trials to allow for a robust indirect comparison. As highlighted by the ERG, neither the Bucher method nor a Bayesian network meta-analysis (NMA) are ideal for comparing PPS and bladder instillations due to challenges with both approaches. The ERG expressed a preference for a Bayesian NMA. Both the ERG and Consilient Health conducted a Bayesian NMA using the same clinical data included in the original submission. We consider that all methods have limitations and that any differences in the methods are mainly centred around the handling of heterogeneity. Therefore, there was no ideal method to be used in this particular case. | Comments noted. The committee acknowledged that both the Bucher method and Bayesian approach are valid methods of analysis in this setting (see FAD section 3.8). The committee considered the company and ERG Bayesian analyses. It preferred the ERG analysis as it better characterised the uncertainty in comparing active treatments (see FAD section 3.9). |
| Consilient Health | Section 3.9 – "In the company's updated analysis, it included the placebo arms of the bladder instillation trials which gave an 18.9% estimated response rate".<br><br>This statement is inaccurate. The company base case analysis uses a 15.8% placebo response rate which is in line with the 16% recognised as reasonable by the committee. The quoted 18.9% was used in a scenario analysis submitted by the company using a Bayesian NMA approach. | Comments noted. This has been corrected in the FAD (see FAD section 3.10). |
| Consilient Health | Section 3.10 – Missing data on utility values<br><br>The ACD states that the ERG's preferred method to account for the missing data relating to recent treatment with bladder instillation is multiple imputation. As previously stated, the missing data for the variable 'received bladder instillations in the previous 6 months' are not missing at random. There were statistically significant differences in the EQ-5D scores and ages of those who responded to this question. No other variables, with a clinically plausible explanation, were found to explain the missingness for this variable.<br><br>A multiple imputation analysis would therefore use EQ-5D score and age to predict the response to 'received bladder instillations in the previous 6 months'. However, the imputed bladder instillation variable would then be used in the analysis to predict the EQ-5D score (with ICSI score and age), i.e. the EQ-5D value and bladder instillation variable would be dependent on each other. Therefore, we consider it inappropriate to conduct multiple imputation for this variable. | Comments noted. The committee were made aware of the responses from the patient survey about quality of life associated with PPS treatment. It considered approaches for handling missing data and concluded that missing data was not adequately accounted for (see FAD section 3.11). |

| Consultee | Comment [sic] | Response |
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| | In addition, the ACD states that "It also highlighted that the patient survey did not collect data on utilities associated with pentosan polysulfate treatment."<br><br>As PPS was previously only available through unlicensed import in the UK, it was anticipated that very few patients would be receiving treatment with PPS in current clinical practice. Therefore, the survey did not ask a specific question about treatment with PPS. Conversely, bladder instillations are part of standard care of IC/BPS and a specific question was therefore included. However, a free text field was included in the survey which asked patients to report oral medications that they were currently receiving. Only [redacted] of the [redacted] patients in the survey who stated that they were on any oral medication for their BPS reported treatment with PPS in this time period. With so few patients reporting treatment with PPS it would not have been possible to robustly include a covariate for PPS treatment in the mapping model. | |
| Consilient Health | Sections 3.11-3.12 – Bladder instillations utility decrement<br><br>Bladder instillations are an invasive and uncomfortable procedure, and have been associated with adverse effects (as also portrayed in the patient cases studies we submitted in the original company submission, Appendix N). This was noted by the NICE clinical experts as stated in the ACD. Clinical experts confirmed the likelihood of reduced quality of life with bladder instillations, highlighting in particular the potential for an increase in urinary tract infections (UTIs) as well as the fact that the efficacy following an instillation wanes over time, which can leave the patient in increasing pain prior to each treatment. This is summarised in Appendix M of the company submission and was also mentioned by the clinical expert participating in this appraisal process. UTIs are known to be associated to bladder instillations and are considered the commonest side effect (alongside bladder pain) by the British Association of Urological Surgeons (BAUS 2017). As noted by the patient and clinical experts in the committee meeting, UTIs in patients with IC/BPS are significantly different from those experienced by the general population both in duration and severity.<br><br>The ACD underappreciates the potential for a negative impact on patients' quality of life associated with the use of bladder instillations, arising from the: inconvenience and lifestyle disruption of attending regular hospital outpatient clinics; discomfort of administration; and waning efficacy between doses. Of note, these features of | Comments noted. The committee considered the evidence for a utility decrement associated with bladder instillations. They concluded that there was insufficient evidence to assume a direct link between bladder instillations and UTIs and that any associated decrement is likely to be short-lived (see FAD section 3.12). The committee considered that the Cervigni et al. study was not generalisable to the population in the PPS marketing authorisation (see FAD section 3.12). The committee noted that it is not appropriate to include a utility decrement for bladder instillations (see FAD section 3.13). |

| Consultee | Comment [sic] | Response |
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| | treatment are not short-lived but are ongoing. Therefore, considering that UTIs are not the only potential negative effects associated with bladder instillations, we consider the decrement of [redacted] found in the survey to be reflective of this fact.<br><br>Evidence from Cervigni et al. (2017) does not include a utility decrement for bladder instillations; nonetheless, they indicate that the quality of life (QoL) difference between patients at baseline and after 6 months of treatment may be greater than what is currently modelled in the company cost-effectiveness model for patients pre-response assessment/non-responders and responders. Using QoL evidence from this paper in the cost-effectiveness model resulted in incremental quality-adjusted life-year (QALY) differences that are similar to those in the company base-case (which includes a bladder instillation utility decrement). | |
| Consilient Health | Section 3.12 – "The committee noted that the utility score for patients having subsequent bladder instillations was counter-intuitive when compared against the utility score for people whose condition did not respond to treatment having best supportive care."<br><br>The utility of subsequent treatments used in the economic model is a weighted average of the utility of responders and non-responders to bladder instillations. Since the treatment response rate to bladder instillations is 20-30%, the weighted average is mainly driven by the utility score of non-responders. | Comments noted. The committee and ERG acknowledged the potential reasons for the utility score modelled for patients having subsequent bladder instillations (see FAD section 3.13). |
| Consilient Health | Section 3.12 – "The patient and clinical experts explained that both bladder instillations and pentosan polysulfate sodium may be associated with decrements"<br><br>Unlike bladder instillations which are invasive, PPS is an oral treatment and its administration would not be expected to be associated with a disutility. Furthermore, the adverse effects of bladder instillations are acknowledged by clinical experts and the NICE committee. No specific adverse effects of PPS have been suggested by the clinical or patient experts, or the committee. Therefore, it is unclear what evidence supports this statement in the ACD. | Comments noted. The committee noted the comments from patient and clinical experts regarding the potential impact on quality of life with PPS treatment (see FAD section 3.3). |
| Consilient Health | Section 3.13 – Frequency of bladder instillation administration<br><br>The manufacturers' recommendations for administration of bladder instillations is typically weekly for 4 weeks then increased to once every 4 weeks. This was also discussed at an advisory board in September 2018 with 9 urology/urogynaecology consultants or specialist nurses. The advisory board agreed that treatment should be tailored to the individual patient's needs, and frequency of bladder instillations was typically guided by when the patient experienced a return of painful symptoms. | Comments noted. The committee acknowledged the variance in bladder instillation administration based on individual patient needs and noted the manufacturer's recommendation. The committee noted the evidence from clinical experts and concluded that administration intervals would be different for first-time and subsequent bladder instillations (see FAD section 3.14). |

| Consultee | Comment [sic] | Response |
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| | This leads to a degree of variability in the dosing frequency of bladder instillations in clinical practice; while some patients are able to tolerate a longer interval than 4 weeks, others unfortunately require even more frequent instillations.<br><br>Feedback from 11 UK experts was obtained and has previously been presented. The feedback from these 11 respondents again shows that there is a degree of variability in clinical practice and while intervals of longer than 4 weeks are used in some patients, there is a not insignificant minority (10-30%) that require more frequent instillations.<br><br>The effect of a bladder instillation wanes over time following the dose and, increasingly, the pain returns before the patient receives their next dose. Therefore, extending the interval between instillations is not without adverse consequences for patients and their quality of life.<br><br>Overall, there is variability in clinical practice with regard to frequency of bladder instillations, with some patients requiring instillations more often than 4 weekly and some less often. Applying an administration frequency of 6 weeks for bladder instillations is likely to be inaccurate and not representative of a substantial proportion of the BPS patient population. Furthermore, a 4-week administration frequency is in line with manufacturer recommendations. | |
| Consilient Health | Section 3.14 – Long-term use of bladder instillations<br><br>Evidence from an advisory board included in our evidence submission indicates that current clinical practice for patients whose symptoms cannot be handled by best supportive care is to cycle through multiple bladder instillation cycles. As stated in section 3.1 of the ACD, BPS is incurable and as a result many patients will require long-term treatment. There is insufficient evidence to support a specific symptom resolution/condition relapse pattern that would enable us to model the long-term treatment pathway more granularly. In addition, any modelling scenarios would need to consider assumptions about intermittent use of either bladder instillations or PPS.<br><br>Recognising the aforementioned uncertainty, we believe our updated PAS discount, which offers an ICER below the lower end of the NICE threshold band, is accounting for this fact, making PPS a cost-effective use of NHS resources.<br><br>Section 3.14 of the ACD states that '…best supportive care becomes a more relevant comparator if more patients stop treatment with bladder instillations.' We | Comments noted. The committee considered that in clinical practice bladder instillations would not continue indefinitely and most would stop within 5 years making best supportive care a more relevant comparator for people who stop treatment with bladder instillations (see FAD section 3.15).<br>The committee considered the positioning of pentosan polysulfate sodium in the treatment pathway and how the pathway has been incorporated into the recommendations (see FAD sections 3.4, and 3.20 to 3.24). |

| Consultee | Comment [sic] | Response |
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| | disagree with this statement as PPS is positioned as an alternative to bladder instillations in secondary care for patients who have already failed best supportive care, i.e. as second-line therapy.<br><br>For patients who receive bladder instillations and then discontinue due to apparent symptom resolution, continued treatment with bladder instillations or PPS would not be appropriate. At such a time that symptoms return, patients could then be considered for active treatment again with PPS (or bladder instillations) as PPS is an effective and cost-effective alternative to bladder instillations.<br><br>As reported by the company's advisory board and accepted by the ERG, the number of patients for whom bladder instillations are contraindicated or not tolerated is a very small (<5%) proportion of the already small IC/BPS population. If patients fail treatment with bladder instillations and/or PPS, best supportive care may be tried again as palliative therapy prior to last-resort surgery. Therefore, PPS is positioned only when best supportive care has failed and cannot be considered an alternative to best supportive care. | |
| Consilient Health | Section 3.15 – Inpatient resource use<br><br>Disease-related costs in the cost-effectiveness model were sourced from the survey of 252 patients included in our evidence submission. Prior use of bladder instillations was not a coefficient in the regression used to relate ICSI values to costs; therefore, background disease-related costs did not vary per treatment. Questions directed to patients inquiring about their healthcare visits were strictly phrased in relation to their interstitial cystitis/bladder pain syndrome. The total number of visits (in the previous 6 months) per type and as a percentage of total healthcare visits are reported below.<br><br>Inpatient visits = 67 (3% of total healthcare visits)<br>Outpatient visits = 796 (39% of total healthcare visits)<br>GP visits = 840 (42% of total healthcare visits)<br>Nurse visits = 318 (16% of total healthcare visits)<br><br>Therefore, we consider that a 3% inpatient visits figure is in line with the committee expectations. | Comments noted. The committee considered the inpatient resource use costs and concluded that although it may be overestimated in the company's model, the ICER was not sensitive to this parameter (see FAD section 3.16). |

## Comments received from clinical experts and patient experts

| Nominating organisation | Comment [sic] | Response |
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| British Association of Urological Surgeons | The British Association of Urological Surgeons (BAUS) would strongly recommend that the decision not to support the use of oral Pentosan Polysulfate Sodium (PPS) is reconsidered. Bladder pain syndrome (BPS) is a chronic and extremely debilitating condition which is very difficult to treat. Patient 'phenotypes' and exact symptoms can vary considerably and treatments need to be targeted on an individual basis. BAUS have significant concerns that if this treatment, which is highly effective for some patients to the point where they rely on it to control their condition, is made inaccessible, many vulnerable people will suffer, including patients who are currently only managing their symptoms by taking this medication. There are only limited other medications and minimally invasive options for the BPS patient group, and removal of oral PPS from practice will mean that patients will be at risk of progressing to major, irreversible surgery such as formation of an ileal conduit, which is associated with significant risks and complications. | Comments noted. The committee acknowledged that bladder pain syndrome is challenging to manage and affects quality of life (see FAD section 3.1). They also acknowledged that there is an unmet need for effective treatment options that can be used instead of invasive bladder instillations (see FAD section 3.3). |
| British Association of Urological Surgeons | BAUS raises concerns that in the absence of other reliably effective universal treatments for BPS patients, that patient options will become even more limited, and that existing patients who are managed on PPS will have to be withdrawn from an effective treatment. BAUS request that this drug is made available to clinicians, even if it is considered a second-line or a 'later' options for patients with BPS. | Comments noted. The committee have considered the evidence for PPS. It is recommended for treating BPS only after an inadequate response to standard oral treatments, it is not offered in combination with bladder instillations, any previous treatment with bladder instillations was not stopped because of lack of response, and it will only be given in secondary care (see FAD section 3.24). |
| British Association of Urological Surgeons | BAUS appreciate that there are cost implications to the use of oral PPS, however, withdrawal of this drug is likely to increase patient contact and appointments in both primary and secondary care, with cost implications associated with this. Whilst other drugs are available, such as amitriptyline, this is a class of drug with anticholinergic properties, and there have been significant concerns about using this class of drug recently, as prolonged use or use of combinations of drugs with anticholinergics properties has an association with the onset of cognitive impairment and dementia [Gray S 2015]. Alternative drug options include cimetidine and hydroxyzine, which again have anticholinergic properties and risks. | Comments noted. The committee have considered the evidence for PPS. It is recommended for treating BPS only after an inadequate response to standard oral treatments, it is not offered in combination with bladder instillations, any previous treatment with bladder instillations was not stopped because of lack of response, and it will only be given in secondary care (see FAD section 3.24). |
| British Association of Urological Surgeons | Alternative common treatments, such as bladder instillations, are not tolerated or not effective in all BPS patients. In addition, bladder instillations are associated with increased costs as they are generally provided in nurse | Comments noted. The committee have considered the evidence for PPS. It is recommended for treating BPS only after an inadequate response to |

| Nominating organisation | Comment [sic] | Response |
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| | lead clinics, where multiple visits are required, and have an inherent risk of urinary tract infection, which would then require diagnostic tests and treatment, adding to the potential costs of this management. Oral PPS is a useful, non-invasive alternative. BAUS request that oral PPS is not excluded on the basis of cost. | standard oral treatments, it is not offered in combination with bladder instillations, any previous treatment with bladder instillations was not stopped because of lack of response, and it will only be given in secondary care (see FAD section 3.24). |
| British Association of Urological Surgeons | In the supporting documentation, oral PPS was compared to intravesical bladder instillations, which may be a flawed comparison as they have different routes of administration. BAUS would also comment that the evidence for most BPS therapies is not strong, but we rely on the full armamentarium of medical options to manage the BPS patient, to try to regain their quality of life and activities of daily living. | Comments noted. The committee have considered the evidence for PPS. It is recommended for treating BPS only after an inadequate response to standard oral treatments, it is not offered in combination with bladder instillations, any previous treatment with bladder instillations was not stopped because of lack of response, and it will only be given in secondary care (see FAD section 3.24). |
| British Association of Urological Surgeons | **International guideline recommendations:**<br>The following are an example of the internationally recognised organisations and groups which have previously published or have current online guidance on BPS:<br>• European Association of Urology (EAU) 2016<br>• American Urological Association (AUA) 2014<br>• Japanese Urological Association (JUA) 2009<br>• Agency for Healthcase Research and Quality (AHRQ) 2014<br>• Royal College of Obstetricians and Gynaecologists (RCOG) 2016<br>• Canadian Urological Association (CUA) 2016<br>• International Society of the Study of BPS (ESSIC) 2008<br>• Bladder Pain Syndrome Committee of ICS 2017<br>• East Asian Guideline 2016<br>• International Urogynaecology Association (IUGA) 2012<br>• International Association for the Study of Pain 2011<br>• NICE (DMSO & PPS) 2014-5<br>• International consultation on Incontinence (ICI-RS) 2011<br><br>Of the most important guidelines to UK urology clinical practice, the EAU and AUA guidelines both recommend the use of oral PPS for BPS patients. A summary of international guidelines regarding treatments for BPS patients is also available [Malde S 2018]. | Comments noted. The committee considered the use of international guidelines in clinical practice (see FAD section 3.4).<br>Comments noted. The committee have considered the evidence for PPS. It is recommended for treating BPS only after an inadequate response to standard oral treatments, it is not offered in combination with bladder instillations, any previous treatment with bladder instillations was not stopped because of lack of response, and it will only be given in secondary care (see FAD section 3.24). |
| British Association of Urological Surgeons | The EAU [Engeler D 2019] performed a meta-analysis of 3 randomised control trials (RCTs) and give a 1a level of evidence and a strong recommendation (i.e. benefits outweigh drawbacks; most will want it) and | Comments noted. The committee have considered the evidence for PPS. It is recommended for treating BPS only after an inadequate response to |

| Nominating organisation | Comment [sic] | Response |
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| | states in its recommendations that oral PPS is effective for pain and related symptoms of BPS.<br><br>The AUA [Hanno PM 2015] advice that oral PPS is administered as an overall second-line therapy in the management pathway of BPS (after conservative management) and works effectively as a first line drug option.<br><br>The most recently published results of a systematic review of RCTs on the treatment of BPS [van Ophoven 2019], demonstrated that oral PPS lead to a statistically significant improvement in the patient's overall response assessment ($p<0.001$), pain ($p=0.009$) and urinary urgency symptoms ($p=0.005$). They conclude that their meta-analysis shows that oral PPS is 'efficacious compared to placebo in the treatment of bladder pain, urinary urgency and frequency of micturition' and a good option for the treatment of BPS. Furthermore, systematic review of oral therapies for BPS (which forms the basis of the Brazilian guidelines) [Santos 2017], conclude that oral PPS should be considered one of the best oral drugs for the treatment of BPS symptoms. Generally, after review of all studies on BPS treatments, effects from oral PPS have been reported as having a 'positive' effect on pain [Giannantoni A 2012].<br><br>Oral PPS is particularly effect for 'ulcer' forms of BPS [Fritjofsson A 1987], and its efficacy may be enhanced if provided in combination with bladder instillations [Nickel JC 2015; Van Ophoven A 2005]. | standard oral treatments, it is not offered in combination with bladder instillations, any previous treatment with bladder instillations was not stopped because of lack of response, and it will only be given in secondary care (see FAD section 3.24). |
| British Association of Urological Surgeons | In summary, BAUS strongly recommend that further consideration is made for allowing clinicians access to oral PPS for BPS patients, and feel that if patients are deprived of access to this drug, that there is potential for detriment to the health and well-being of this vulnerable patient group. | Comments noted. The committee have considered the evidence for PPS. It is recommended for treating BPS only after an inadequate response to standard oral treatments, it is not offered in combination with bladder instillations, any previous treatment with bladder instillations was not stopped because of lack of response, and it will only be given in secondary care (see FAD section 3.24). |
| Bladder Health UK | Has all of the relevant evidence been taken into account?<br><br>Although the scientific evidence has been taken into account, we would just like to reiterate that from a patient point of view, Interstitial Cystitis/Bladder Pain Syndrome is a very difficult disease to treat as different treatments | Comments noted. The committee have considered the evidence for PPS. It is recommended for treating BPS only after an inadequate response to standard oral treatments, it is not offered in combination with bladder instillations, any previous |

| Nominating organisation | Comment [sic] | Response |
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| | benefit different patients. Therefore, the more treatment options available the better. | treatment with bladder instillations was not stopped because of lack of response, and it will only be given in secondary care (see FAD section 3.24). |
| Bladder Health UK | Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?<br><br>Not able to comment. | Comment noted. |
| Bladder Health UK | Are the recommendations sound and a suitable basis for guidance to the NHS?<br><br>Given that Pentosan Polysulphate is not being recommended within its marketing authorisation for treating Interstitial Cystitis/Bladder Pain Syndrome, we are disappointed. It would appear that the recommendations within the application are sound and the negative decision is based purely on cost-effectiveness. The outcome of this decision is denying this small cohort of patients who would have benefited from this treatment the opportunity to do so. | Comments noted. The committee have considered the evidence for PPS. It is recommended for treating BPS only after an inadequate response to standard oral treatments, it is not offered in combination with bladder instillations, any previous treatment with bladder instillations was not stopped because of lack of response, and it will only be given in secondary care (see FAD section 3.24). |
| Bladder Health UK | Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?<br><br>No. | Comment noted. |
| J Goddard | Section 1 I am pleased to note the committee agrees that clinical trials suggest that pentosan polysulfate sodium may be more effective at relieving pain than placebo and that comparison of clinical trials suggests that pentosan polysulfate sodium may have a moderate benefit over best supportive care and bladder instillations. | Thank you for your comments. |
| J Goddard | Section 3.1 I am pleased to note the committee agrees that IC/BPS is very challenging to manage and causes extreme pain, which disrupts normal living. | Thank you for your comments. |
| J Goddard | Section 3.2 I am pleased to note that the committee agrees there will be a small overall number of patients in the UK requiring this treatment. | Thank you for your comments. |

| Nominating organisation | Comment [sic] | Response |
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| J Goddard | Section 3.3 I am pleased to note that the committee agrees there is an unmet need for effective treatment options and options are few. | Thank you for your comments. |
| J Goddard | Section 3.2.1 I am sorry to read that despite the above conclusions the committee feel that pentosan polysulfate sodium is not recommended due to cost. I can only emphasize the difficulty the clinician faces in treating these patients with the limited options available and the dramatic effect it has on the quality of life of those patients in which it has an effect. I fully appreciate the lack of good quality evidence, however, due to the nature of this rare condition I believe it is unlikely higher quality data will easily or quickly become available. I also appreciate that for simplicity the committee wished to compare pentosan polysulfate sodium directly to an alternative single treatment but I wish to remind the committee that this is just one part of a multimodal approach to the management of these patients that requires a balanced, empirical and often repetitive management plan. In some cases treatment partially alleviates their suffering and allows them to take part in some normality of life. I have seen the difference it makes; I do hope that at some point in the future other clinicians and patients will have opportunity to see the same. | Comments noted. The committee have considered the evidence for PPS. It is recommended for treating BPS only after an inadequate response to standard oral treatments, it is not offered in combination with bladder instillations, any previous treatment with bladder instillations was not stopped because of lack of response, and it will only be given in secondary care (see FAD section 3.24). |

## Summary of comments received from members of the public

| Question | Comments | Response |
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| Has all of the relevant evidence been taken into account? | Yes | Comment noted. |
| | European Urology Guidelines Chronic Pelvic pain<br>Pentosane polysulphate improves global assessment and QoL score in PPS. - level 1b evidence<br>https://uroweb.org/guideline/chronic-pelvic-pain/#5 | Comments noted. The committee considered the use of international guidelines in clinical practice (see FAD section 3.4). |
| Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? | Yes if you only work in a cost based manner | Comments noted. The committee have considered the evidence for PPS. It is recommended for treating BPS only after an inadequate response to standard oral treatments, it is not offered in combination with bladder instillations, any previous treatment with bladder instillations was not stopped |

| Question | Comments | Response |
|---|---|---|
| | | because of lack of response, and it will only be given in secondary care (see FAD section 3.24). |
| | Burden of bladder pain;<br>The Burden of Bladder Pain in Five European Countries: A Cross-sectional Study<br>Urology. Volume 99, January 2017, Pages 84-91 | Comments noted. The committee have considered the evidence for PPS. It is recommended for treating BPS only after an inadequate response to standard oral treatments, it is not offered in combination with bladder instillations, any previous treatment with bladder instillations was not stopped because of lack of response, and it will only be given in secondary care (see FAD section 3.24). |
| Are the recommendations sound and a suitable basis for guidance to the NHS? | No - they are unclear and do not fully describe recommendations for BPS patients without Hunner's lesions or glomerlations | Comment noted. Technologies are only appraised within their marketing authorisation. The committee considered the scope for PPS which only includes people with BPS with glomerulations or Hunner's lesions (see FAD section 2). |
| | It would be useful to keep this option. | Comment noted. |
| Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? | No | Comment noted. |
| | Painful bladder / IC is not fully understood disease / syndrome, with a range of symptoms and suggestive theories.<br>A number of these patient when the disease is controlled and no effect on QOL are managed at the community by primary care. However, majority have significant symptoms which impacted on QOL . There are no treatment pathways, but suggestions. However, most of these patient end up with a urologist or urogynecologist who has a specific interest is such complex patient, with link to pain team and psychologist. We have a close link with York University and involved in painful bladder /Interstitial cystitis research.<br>In our trust in York Teaching Hospital, we use Pentosane polysulphate as a treatment option, as well as bladder instillation. The choice tend to be a discussion between the consultant and the patient (risk, side effect, convenience, and duration of treatment). Patients given written information for both options (mostly from FDA approval application) and bladder instillation, with link to main charities. These two option are for potential treatment, rather than best supportive care. | Comments noted. The committee have considered the evidence for PPS. It is recommended for treating BPS only after an inadequate response to standard oral treatments, it is not offered in combination with bladder instillations, any previous treatment with bladder instillations was not stopped because of lack of response, and it will only be given in secondary care (see FAD section 3.24). |

| Question | Comments | Response |
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| | As there are limited treatment options (for patients without Hunner's Ulcer), Pentosane polysulphate is effected in some patient and bladder instillation in others. In addition, there are other group that all options are not effective and considered surgery. | |
| Other comments | Sodium pentosan polysuphate is the only oral agent approved by the FDA specifically for the management of bladder pain syndrome. Many women do not respond adequately to other analgesics or to bladder instillations and many do not wish to consider instillation or are unable to hold them in for the required length of time.<br>BPS can be highly distressing and severly impair quality of life and is ofen difficult or even impossible to manage adequately. without the ability to prescribe elmiron evan 3rd or 4th line therapy, management strategies will be even more limited.<br>this guidelines does not make it clear if it we can still use this treatment in newly diagnosed patients with mild to mod or mod to severe pain without hunner's lesions or glomerulations. It also is not clear that it can be used in those in line with its marketing authorization that are intolerant of other oral agents and refuse / or cannot have instillations. | Comments noted. The committee have considered the evidence for PPS. It is recommended for treating BPS only after an inadequate response to standard oral treatments, it is not offered in combination with bladder instillations, any previous treatment with bladder instillations was not stopped because of lack of response, and it will only be given in secondary care (see FAD section 3.24). |
| | | |

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**Pentosan polysulfate sodium for treating bladder pain syndrome [ID1364]**

**Consultation on the appraisal consultation document – deadline for comments** 5pm on Thursday 1 August 2019. **email:** NICE DOCS

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| | Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.<br><br>The Appraisal Committee is interested in receiving comments on the following:<br>• has all of the relevant evidence been taken into account?<br>• are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?<br>• are the provisional recommendations sound and a suitable basis for guidance to the NHS?<br><br>NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:<br>• could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology;<br>• could have any adverse impact on people with a particular disability or disabilities.<br><br>Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced. |
| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | Consilient Health |
| **Disclosure** Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | Nothing to disclose |
| **Name of commentator person completing form:** | Michael Ho |

| **Comment number** | **Comments**<br><br>Insert each comment in a new row. |
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**Pentosan polysulfate sodium for treating bladder pain syndrome [ID1364]**

**Consultation on the appraisal consultation document – deadline for comments** 5pm on Thursday 1 August 2019. **email:** NICE DOCS

| | Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
|---|---|
| 1 | Section 3.5 – "It recognised that pentosan polysulfate sodium could be given at different points in the treatment pathway but it would tend to be used before bladder instillations."<br><br>We agree that pentosan polysulfate sodium (PPS) and bladder instillations are all part of the treatment pathway for patients with IC/BPS; however the ACD does not fully recognise the positioning of PPS within that pathway. PPS would only be considered as an option for the treatment of patients when 'best supportive care' (BSC), which is typically started in primary care, has failed; PPS is not as an alternative to BSC. In addition, the ACD does not recognise that PPS can only be given once the patient has been referred to secondary care. In this case, patients can be offered either PPS or bladder instillations as second-line treatment, as PPS has been shown to be an effective and cost-effective alternative to bladder instillations.<br><br>The ACD states that some patients would refuse bladder instillations because of their invasive nature and would instead choose best supportive care. Whilst we agree with this statement, it should be recognised that this would apply to a very small number of patients. As stated in our submission, consensus among clinical experts at an advisory board was that <5% BPS patients are contraindicated to or refuse bladder instillations. This was accepted by the ERG and its clinical expert.<br><br>If patients discontinue bladder instillations because of apparent symptom resolution, they will not receive PPS as further treatment would not be required. If their symptoms recur, patients would be offered either a bladder instillation or PPS. As described by our advisory board (Appendix M of the company submission), patients that fail on one type of bladder instillation would typically be offered alternative bladder instillations in an attempt to find one that works for the patient. Given the lack of treatment options for this condition, if both PPS and the various bladder installations ultimately fail in secondary care, patients may be tried again on best supportive care/palliative care as a last resort prior to surgery.<br><br>In summary, PPS can be used as an alternative to bladder instillations as second-line therapy after BSC has failed, but is not an alternative to BSC. |
| 2 | Sections 3.7-3.8<br><br>The company base case uses the Bucher method to source treatment response rates, recognising that there was considerable heterogeneity in the trials to allow for a robust indirect comparison. As highlighted by the ERG, neither the Bucher method nor a Bayesian network meta-analysis (NMA) are ideal for comparing PPS and bladder instillations due to challenges with both approaches. The ERG expressed a preference for a Bayesian NMA. Both the ERG and Consilient Health conducted a Bayesian NMA using the same clinical data included in the original submission. We consider that all methods have limitations and that any differences in the methods are mainly centred around the handling of heterogeneity. Therefore, there was no ideal method to be used in this particular case. |
| 3 | Section 3.9 – "In the company's updated analysis, it included the placebo arms of the bladder instillation trials which gave an 18.9% estimated response rate".<br><br>This statement is inaccurate. The company base case analysis uses a 15.8% placebo response rate which is in line with the 16% recognised as reasonable by the committee. The quoted 18.9% was used in a scenario analysis submitted by the company using a Bayesian NMA approach. |
| 4 | Section 3.10 – Missing data on utility values<br><br>The ACD states that the ERG's preferred method to account for the missing data relating to recent |

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| | treatment with bladder instillation is multiple imputation. As previously stated, the missing data for the variable 'received bladder instillations in the previous 6 months' are not missing at random. There were statistically significant differences in the EQ-5D scores and ages of those who responded to this question. No other variables, with a clinically plausible explanation, were found to explain the missingness for this variable.<br><br>A multiple imputation analysis would therefore use EQ-5D score and age to predict the response to 'received bladder instillations in the previous 6 months'. However, the imputed bladder instillation variable would then be used in the analysis to predict the EQ-5D score (with ICSI score and age), i.e. the EQ-5D value and bladder instillation variable would be dependent on each other. Therefore, we consider it inappropriate to conduct multiple imputation for this variable.<br><br>In addition, the ACD states that "It also highlighted that the patient survey did not collect data on utilities associated with pentosan polysulfate treatment."<br><br>As PPS was previously only available through unlicensed import in the UK, it was anticipated that very few patients would be receiving treatment with PPS in current clinical practice. Therefore, the survey did not ask a specific question about treatment with PPS. Conversely, bladder instillations are part of standard care of IC/BPS and a specific question was therefore included. However, a free text field was included in the survey which asked patients to report oral medications that they were currently receiving. Only [redacted] of the [redacted] patients in the survey who stated that they were on any oral medication for their BPS reported treatment with PPS in this time period. With so few patients reporting treatment with PPS it would not have been possible to robustly include a covariate for PPS treatment in the mapping model. |
| 5 | Sections 3.11-3.12 – Bladder instillations utility decrement<br><br>Bladder instillations are an invasive and uncomfortable procedure, and have been associated with adverse effects (as also portrayed in the patient cases studies we submitted in the original company submission, Appendix N). This was noted by the NICE clinical experts as stated in the ACD. Clinical experts confirmed the likelihood of reduced quality of life with bladder instillations, highlighting in particular the potential for an increase in urinary tract infections (UTIs) as well as the fact that the efficacy following an instillation wanes over time, which can leave the patient in increasing pain prior to each treatment. This is summarised in Appendix M of the company submission and was also mentioned by the clinical expert participating in this appraisal process. UTIs are known to be associated to bladder instillations and are considered the commonest side effect (alongside bladder pain) by the British Association of Urological Surgeons (BAUS 2017). As noted by the patient and clinical experts in the committee meeting, UTIs in patients with IC/BPS are significantly different from those experienced by the general population both in duration and severity.<br><br>The ACD underappreciates the potential for a negative impact on patients' quality of life associated with the use of bladder instillations, arising from the: inconvenience and lifestyle disruption of attending regular hospital outpatient clinics; discomfort of administration; and waning efficacy between doses. Of note, these features of treatment are not short-lived but are ongoing. Therefore, considering that UTIs are not the only potential negative effects associated with bladder instillations, we consider the decrement of [redacted] found in the survey to be reflective of this fact.<br><br>Evidence from Cervigni et al. (2017) does not include a utility decrement for bladder instillations; nonetheless, they indicate that the quality of life (QoL) difference between patients at baseline and after 6 months of treatment may be greater than what is currently modelled in the company cost-effectiveness model for patients pre-response assessment/non-responders and responders. Using QoL evidence from this paper in the cost-effectiveness model resulted in incremental quality-adjusted life-year (QALY) differences that are similar to those in the company base-case (which includes a bladder instillation utility decrement). |

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| 6 | Section 3.12 – "The committee noted that the utility score for patients having subsequent bladder instillations was counter-intuitive when compared against the utility score for people whose condition did not respond to treatment having best supportive care."<br><br>The utility of subsequent treatments used in the economic model is a weighted average of the utility of responders and non-responders to bladder instillations. Since the treatment response rate to bladder instillations is 20-30%, the weighted average is mainly driven by the utility score of non-responders. |
| 7 | Section 3.12 – "The patient and clinical experts explained that both bladder instillations and pentosan polysulfate sodium may be associated with decrements"<br><br>Unlike bladder instillations which are invasive, PPS is an oral treatment and its administration would not be expected to be associated with a disutility. Furthermore, the adverse effects of bladder instillations are acknowledged by clinical experts and the NICE committee. No specific adverse effects of PPS have been suggested by the clinical or patient experts, or the committee. Therefore, it is unclear what evidence supports this statement in the ACD. |
| 8 | Section 3.13 – Frequency of bladder instillation administration<br><br>The manufacturers' recommendations for administration of bladder instillations is typically weekly for 4 weeks then increased to once every 4 weeks. This was also discussed at an advisory board in September 2018 with 9 urology/urogynaecology consultants or specialist nurses. The advisory board agreed that treatment should be tailored to the individual patient's needs, and frequency of bladder instillations was typically guided by when the patient experienced a return of painful symptoms. This leads to a degree of variability in the dosing frequency of bladder instillations in clinical practice; while some patients are able to tolerate a longer interval than 4 weeks, others unfortunately require even more frequent instillations.<br><br>Feedback from 11 UK experts was obtained and has previously been presented. The feedback from these 11 respondents again shows that there is a degree of variability in clinical practice and while intervals of longer than 4 weeks are used in some patients, there is a not insignificant minority (10-30%) that require more frequent instillations.<br><br>The effect of a bladder instillation wanes over time following the dose and, increasingly, the pain returns before the patient receives their next dose. Therefore, extending the interval between instillations is not without adverse consequences for patients and their quality of life.<br><br>Overall, there is variability in clinical practice with regard to frequency of bladder instillations, with some patients requiring instillations more often than 4 weekly and some less often. Applying an administration frequency of 6 weeks for bladder instillations is likely to be inaccurate and not representative of a substantial proportion of the BPS patient population. Furthermore, a 4-week administration frequency is in line with manufacturer recommendations. |
| 9 | Section 3.14 – Long-term use of bladder instillations<br><br>Evidence from an advisory board included in our evidence submission indicates that current clinical practice for patients whose symptoms cannot be handled by best supportive care is to cycle through multiple bladder instillation cycles. As stated in section 3.1 of the ACD, BPS is incurable and as a result many patients will require long-term treatment. There is insufficient evidence to support a specific symptom resolution/condition relapse pattern that would enable us to model the long-term treatment pathway more granularly. In addition, any modelling scenarios would need to consider assumptions about intermittent use of either bladder instillations or PPS.<br><br>Recognising the aforementioned uncertainty, we believe our updated PAS discount, which offers an ICER below the lower end of the NICE threshold band, is accounting for this fact, making PPS a cost-effective use of NHS resources. |

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| | Section 3.14 of the ACD states that '…best supportive care becomes a more relevant comparator if more patients stop treatment with bladder instillations.' We disagree with this statement as PPS is positioned as an alternative to bladder instillations in secondary care for patients who have already failed best supportive care, i.e. as second-line therapy.<br><br>For patients who receive bladder instillations and then discontinue due to apparent symptom resolution, continued treatment with bladder instillations or PPS would not be appropriate. At such a time that symptoms return, patients could then be considered for active treatment again with PPS (or bladder instillations) as PPS is an effective and cost-effective alternative to bladder instillations.<br><br>As reported by the company's advisory board and accepted by the ERG, the number of patients for whom bladder instillations are contraindicated or not tolerated is a very small (<5%) proportion of the already small IC/BPS population. If patients fail treatment with bladder instillations and/or PPS, best supportive care may be tried again as palliative therapy prior to last-resort surgery. Therefore, PPS is positioned only when best supportive care has failed and cannot be considered an alternative to best supportive care. |
| 10 | Section 3.15 – Inpatient resource use<br><br>Disease-related costs in the cost-effectiveness model were sourced from the survey of 252 patients included in our evidence submission. Prior use of bladder instillations was not a coefficient in the regression used to relate ICSI values to costs; therefore, background disease-related costs did not vary per treatment. Questions directed to patients inquiring about their healthcare visits were strictly phrased in relation to their interstitial cystitis/bladder pain syndrome. The total number of visits (in the previous 6 months) per type and as a percentage of total healthcare visits are reported below.<br><br>Inpatient visits = 67 (3% of total healthcare visits)<br>Outpatient visits = 796 (39% of total healthcare visits)<br>GP visits = 840 (42% of total healthcare visits)<br>Nurse visits = 318 (16% of total healthcare visits)<br><br>Therefore, we consider that a 3% inpatient visits figure is in line with the committee expectations. |

Insert extra rows as needed

**Checklist for submitting comments**

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright

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reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.

- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

**Note:** We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Kate Moore
Project Manager – Technology Appraisals
National Institute for Health and Care Excellence

29th July 2019

Dear Kate,

**Commercial in Confidence**
**Subject: ID1364 Pentosan Polysulfate Sodium – revision of PAS following 1st committee meeting**

In response to the Appraisal Consultation Document which summarised the committee's recommendations, we have taken a decision to update the level of discount offered in our confidential PAS to [redacted]. Please find below the corresponding ICERs for the company base-case (as this was presented in the committee meeting) and the ERG preferred base-case.

*Table 1. Company base-case ICER with updated PAS price – vs Bladder Instillations*

| Treatment | Total Cost | Total QALYs | Incremental Cost | Incremental QALYs | ICER per QALY |
|---|---|---|---|---|---|
| BIs | [redacted] | [redacted] | [redacted] | [redacted] | Dominant |
| PPS | [redacted] | [redacted] | | | |

*Note: probabilistic ICER using 10,000 simulations (as per ERG's preference)*

*Table 2. ERG-preferred base-case ICER with updated PAS price – vs Bladder Instillations*

| Treatment | Total Cost | Total QALYs | Incremental Cost | Incremental QALYs | ICER per QALY |
|---|---|---|---|---|---|
| BIs | [redacted] | [redacted] | [redacted] | [redacted] | £18,489 |
| PPS | [redacted] | [redacted] | | | |

*Note: probabilistic ICER using 10,000 simulations (as per ERG's preference)*

*Table 3. Company base-case ICER with updated PAS price – vs Best Supportive Care*

| Treatment | Total Cost | Total QALYs | Incremental Cost | Incremental QALYs | ICER per QALY |
|---|---|---|---|---|---|
| BSC | [redacted] | [redacted] | [redacted] | [redacted] | £52,264 |
| PPS | [redacted] | [redacted] | | | |

*Note: probabilistic ICER using 10,000 simulations (as per ERG's preference)*

*Table 4. ERG-preferred base-case ICER with updated PAS price – vs Best Supportive Care*

| Treatment | Total Cost | Total QALYs | Incremental Cost | Incremental QALYs | ICER per QALY |
|---|---|---|---|---|---|
| BSC | [redacted] | [redacted] | [redacted] | [redacted] | £49,747 |
| PPS | [redacted] | [redacted] | | | |

*Note: probabilistic ICER using 10,000 simulations (as per ERG's preference)*

As shown in the result tables, using the updated PAS price, the ICER for the primary analysis versus bladder instillations drops below the lower bound of the NICE cost-effectiveness threshold of £20,000 per additional QALY gained in both the company and the ERG preferred base-cases (with the 7 issues identified at the technical engagement stage addressed). All assumptions, other than the PAS, are the same as those presented to NICE in the company response to the technical engagement (company preferred base case) and the ERG analysis (ERG preferred base case). In their assessment, the committee also noted that in clinical practice bladder instillations would not be likely used for a period longer than 5 years. Advice from our clinical experts, and as the committee concluded in the ACD, is that bladder pain syndrome is incurable, and therefore it is likely that the symptoms of those discontinuing treatment would reappear and either treatment would recommence, or patients are likely to suffer long term decrement to their quality of life. There is, however, insufficient published evidence and considerable clinical uncertainty and variability in the long-term treatment pathway, which prevents robust modelling of this scenario. Recognising this, we believe our updated PAS discount, which is offering an ICER below the lower end of the NICE threshold band, accounts for this, and that PPS is a cost-effective use of NHS resources.

Please note that PPS is being positioned as an alternative to bladder instillations and will be available only in a secondary care setting (i.e. not in place of other oral treatments used in a first-line setting). As highlighted in our evidence dossier, and confirmed in the ERG report, the number of patients for whom bladder instillations are contraindicated or who refuse bladder instillations, and who whose BPS would therefore be managed with best supportive care only, is very small. Therefore, we have presented only the analyses compared to bladder instillations.

In light of the updated confidential PAS discount for PPS, we would encourage NICE to reconsider their assessment of our technology, prior to a potential 2nd committee meeting, in order to accelerate the appraisal process and simplify the next steps. We have also contacted NHS England and are currently in the process of officially updating the level of discount in the confidential PAS.

Please get back to me if you have any questions.

Yours sincerely

[redacted]
Consilient Health

| | |
|---|---|
| **Name** | [redacted] |
| **Organisation** | Bladder Health UK |
| **Comments on the ACD:** | |

**Has all of the relevant evidence been taken into account?**
*Although the scientific evidence has been taken into account, we would just like to reiterate that from a patient point of view, Interstitial Cystitis/Bladder Pain Syndrome is a very difficult disease to treat as different treatments benefit different patients. Therefore, the more treatment options available the better.*

**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**
*Not able to comment.*

**Are the recommendations sound and a suitable basis for guidance to the NHS?**
*Given that Pentosan Polysulphate is not being recommended within its marketing authorisation for treating Interstitial Cystitis/Bladder Pain Syndrome, we are disappointed. It would appear that the recommendations within the application are sound and the negative decision is based purely on cost-effectiveness. The outcome of this decision is denying this small cohort of patients who would have benefited from this treatment the opportunity to do so.*

**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?**
*No*

British Association of Urological Surgeons (BAUS) response and comments on:
**Appraisal consultation document on Pentosan polysulfate sodium for treating bladder pain syndrome**

**BAUS representative:** [redacted] 9th July 2019

**Comments:**
The British Association of Urological Surgeons (BAUS) would strongly recommend that the decision not to support the use of oral Pentosan Polysulfate Sodium (PPS) is reconsidered. Bladder pain syndrome (BPS) is a chronic and extremely debilitating condition which is very difficult to treat. Patient 'phenotypes' and exact symptoms can vary considerably and treatments need to be targeted on an individual basis. BAUS have significant concerns that if this treatment, which is highly effective for some patients to the point where they rely on it to control their condition, is made inaccessible, many vulnerable people will suffer, including patients who are currently only managing their symptoms by taking this medication. There are only limited other medications and minimally invasive options for the BPS patient group, and removal of oral PPS from practice will mean that patients will be at risk of progressing to major, irreversible surgery such as formation of an ileal conduit, which is associated with significant risks and complications.

BAUS raises concerns that in the absence of other reliably effective universal treatments for BPS patients, that patient options will become even more limited, and that existing patients who are managed on PPS will have to be withdrawn from an effective treatment. BAUS request that this drug is made available to clinicians, even if it is considered a second-line or a 'later' options for patients with BPS.

BAUS appreciate that there are cost implications to the use of oral PPS, however, withdrawal of this drug is likely to increase patient contact and appointments in both primary and secondary care, with cost implications associated with this. Whilst other drugs are available, such as amitriptyline, this is a class of drug with anticholinergic properties, and there have been significant concerns about using this class of drug recently, as prolonged use or use of combinations of drugs with anticholinergics properties has an association with the onset of cognitive impairment and dementia [Gray S 2015]. Alternative drug options include cimetidine and hydroxyzine, which again have anticholinergic properties and risks.

Alternative common treatments, such as bladder instillations, are not tolerated or not effective in all BPS patients. In addition, bladder instillations are associated with increased costs as they are generally provided in nurse lead clinics, where multiple visits are required, and have an inherent risk of urinary tract infection, which would then require diagnostic tests and treatment, adding to the potential costs of this management. Oral PPS is a useful, non-invasive alternative. BAUS request that oral PPS is not excluded on the basis of cost.

In the supporting documentation, oral PPS was compared to intravesical bladder instillations, which may be a flawed comparison as they have different routes of administration. BAUS would also comment that the evidence for most BPS therapies is not strong, but we rely on the full armamentarium of medical options to manage the BPS patient, to try to regain their quality of life and activities of daily living.

**International guideline recommendations:**
The following are an example of the internationally recognised organisations and groups which have previously published or have current online guidance on BPS:

- European Association of Urology (EAU) 2016
- American Urological Association (AUA) 2014
- Japanese Urological Association (JUA) 2009
- Agency for Healthcase Research and Quality (AHRQ) 2014
- Royal College of Obstetricians and Gynaecologists (RCOG) 2016
- Canadian Urological Association (CUA) 2016
- International Society of the Study of BPS (ESSIC) 2008
- Bladder Pain Syndrome Committee of ICS 2017
- East Asian Guideline 2016
- International Urogynaecology Association (IUGA) 2012
- International Association for the Study of Pain 2011
- NICE (DMSO & PPS) 2014-5
- International consultation on Incontinence (ICI-RS) 2011

Of the most important guidelines to UK urology clinical practice, the EAU and AUA guidelines both recommend the use of oral PPS for BPS patients. A summary of international guidelines regarding treatments for BPS patients is also available [Malde S 2018].

The EAU [Engeler D 2019] performed a meta-analysis of 3 randomised control trials (RCTs) and give a 1a level of evidence and a strong recommendation (i.e. benefits outweigh drawbacks; most will want it) and states in its recommendations that oral PPS is effective for pain and related symptoms of BPS.

The AUA [Hanno PM 2015] advice that oral PPS is administered as an overall second-line therapy in the management pathway of BPS (after conservative management) and works effectively as a first line drug option.

The most recently published results of a systematic review of RCTs on the treatment of BPS [van Ophoven 2019], demonstrated that oral PPS lead to a statistically significant improvement in the patient's overall response assessment ($p<0.001$), pain ($p=0.009$) and urinary urgency symptoms ($p=0.005$). They conclude that their meta-analysis shows that oral PPS is 'efficacious compared to placebo in the treatment of bladder pain, urinary urgency and frequency of micturition' and a good option for the treatment of BPS. Furthermore, systematic review of oral therapies for BPS (which forms the basis of the Brazilian guidelines) [Santos 2017], conclude that oral PPS should be considered one of the best oral drugs for the treatment of BPS symptoms. Generally, after review of all studies on BPS treatments, effects from oral PPS have been reported as having a 'positive' effect on pain [Giannantoni A 2012].

Oral PPS is particularly effect for 'ulcer' forms of BPS [Fritjofsson A 1987], and its efficacy may be enhanced if provided in combination with bladder instillations [Nickel JC 2015; Van Ophoven A 2005].

In summary, BAUS strongly recommend that further consideration is made for allowing clinicians access to oral PPS for BPS patients, and feel that if patients are deprived of access to this drug, that there is potential for detriment to the health and well-being of this vulnerable patient group.

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NICE National Institute for Health and Care Excellence

**Pentosan polysulfate sodium for treating bladder pain syndrome [ID1364]**

**Consultation on the appraisal consultation document – deadline for comments** 5pm on Thursday 1 August 2019 **email:** NICE DOCS

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| | Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.<br><br>The Appraisal Committee is interested in receiving comments on the following:<br>• has all of the relevant evidence been taken into account?<br>• are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?<br>• are the provisional recommendations sound and a suitable basis for guidance to the NHS?<br><br>NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:<br>• could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology;<br>• could have any adverse impact on people with a particular disability or disabilities.<br><br>Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced. |
| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | |
| **Disclosure** Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | |
| **Name of commentator person completing form:** | [redacted] |

| **Comment number** | **Comments**<br><br>Insert each comment in a new row. |
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NICE National Institute for Health and Care Excellence

**Pentosan polysulfate sodium for treating bladder pain syndrome [ID1364]**

**Consultation on the appraisal consultation document – deadline for comments** 5pm on Thursday 1 August 2019 **email:** NICE DOCS

| | Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
|---|---|
| 1 | Section 1 I am pleased to note the committee agrees that clinical trials suggest that pentosan polysulfate sodium may be more effective at relieving pain than placebo and that comparison of clinical trials suggests that pentosan polysulfate sodium may have a moderate benefit over best supportive care and bladder instillations. |
| 2 | Section 3.1 I am pleased to note the committee agrees that IC/BPS is very challenging to manage and causes extreme pain, which disrupts normal living. |
| 3 | Section 3.2 I am pleased to note that the committee agrees there will be a small overall number of patients in the UK requiring this treatment. |
| 4 | Section 3.3 I am pleased to note that the committee agrees there is an unmet need for effective treatment options and options are few. |
| 5 | Section 3.2.1 I am sorry to read that despite the above conclusions the committee feel that pentosan polysulfate sodium is not recommended due to cost. I can only emphasize the difficulty the clinician faces in treating these patients with the limited options available and the dramatic effect it has on the quality of life of those patients in which it has an effect. I fully appreciate the lack of good quality evidence, however, due to the nature of this rare condition I believe it is unlikely higher quality data will easily or quickly become available. I also appreciate that for simplicity the committee wished to compare pentosan polysulfate sodium directly to an alternative single treatment but I wish to remind the committee that this is just one part of a multimodal approach to the management of these patients that requires a balanced, empirical and often repetitive management plan. In some cases treatment partially alleviates their suffering and allows them to take part in some normality of life. I have seen the difference it makes; I do hope that at some point in the future other clinicians and patients will have opportunity to see the same. |

Insert extra rows as needed

**Checklist for submitting comments**

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

**Note:** We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be

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unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

# Comments on the ACD received from the public through the NICE Website

| | |
|---|---|
| **Name** | [redacted] |
| **Organisation** | King's College Hospital |
| **Comments on the ACD:** | |

**Has all of the relevant evidence been taken into account?**
*Yes*

**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**
*Yes if you only work in a cost based manner*

**Are the recommendations sound and a suitable basis for guidance to the NHS?**
*No - they are unclear and do not fully describe recommendations for BPS patients without Hunner's lesions or glomerlations*

**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?**
*No*

**General comment:**
*Sodium pentosan polysuphate is the only oral agent approved by the FDA specifically for the management of bladder pain syndrome. Many women do not respond adequately to other analgesics or to bladder instillations and many do not wish to consider instillation or are unable to hold them in for the required length of time.*

*BPS can be highly distressing and severely impair quality of life and is often difficult or even impossible to manage adequately. without the ability to prescribe elmiron even 3rd or 4th line therapy, management strategies will be even more limited.*

*This guidelines does not make it clear if it we can still use this treatment in newly diagnosed patients with mild to mod or mod to severe pain without Hunner's lesions or glomerulations. It also is not clear that it can be used in those in line with its marketing authorization that are intolerant of other oral agents and refuse / or cannot have instillations.*

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| **Name** | [redacted] |
| **Organisation** | York Teaching Hospital |
| **Comments on the ACD:** | |

**Has all of the relevant evidence been taken into account?**
*European Urology Guidelines Chronic Pelvic pain*
*Pentosane polysulphate improves global assessment and QoL score in PPS. - level 1b evidence*
*https://uroweb.org/guideline/chronic-pelvic-pain/#5*

**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**
*Burden of bladder pain;*
*The Burden of Bladder Pain in Five European Countries: A Cross-sectional Study Urology. Volume 99, January 2017, Pages 84-91*

**Are the recommendations sound and a suitable basis for guidance to the NHS?**
*It would be useful to keep this option.*

***Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?***

*Painful bladder / IC is not fully understood disease / syndrome, with a range of symptoms and suggestive theories.*

*A number of these patient when the disease is controlled and no effect on QOL are managed at the community by primary care. However, majority have significant symptoms which impacted on QOL. There are no treatment pathways, but suggestions. However, most of these patient end up with a urologist or urogynecologist who has a specific interest is such complex patient, with link to pain team and psychologist. We have a close link with York University and involved in painful bladder /Interstitial cystitis research.*

*In our trust in York Teaching Hospital, we use Pentosane polysulphate as a treatment option, as well as bladder instillation. The choice tend to be a discussion between the consultant and the patient (risk, side effect, convenience, and duration of treatment). Patients given written information for both options (mostly from FDA approval application) and bladder instillation, with link to main charities. These two option are for potential treatment, rather than best supportive care.*

*As there are limited treatment options (for patients without Hunner's Ulcer), Pentosane polysulphate is effected in some patient and bladder instillation in others. In addition, there are other group that all options are not effective and considered surgery.*

**ERG critique of Consilient Health's response to the ACD for pentosane polysulfate for treating bladder pain syndrome [ID1364]**

| Comment number | Comment from Consilient Health | ERG critique |
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| 1 | Section 3.5 – "It recognised that pentosan polysulfate sodium could be given at different points in the treatment pathway but it would tend to be used before bladder instillations."<br><br>We agree that pentosan polysulfate sodium (PPS) and bladder instillations are all part of the treatment pathway for patients with IC/BPS; however the ACD does not fully recognise the positioning of PPS within that pathway. PPS would only be considered as an option for the treatment of patients when 'best supportive care' (BSC), which is typically started in primary care, has failed; PPS is not as an alternative to BSC. In addition, the ACD does not recognise that PPS can only be given once the patient has been referred to secondary care. In this case, patients can be offered either PPS or bladder instillations as second-line treatment, as PPS has been shown to be an effective and cost-effective alternative to bladder instillations.<br><br>The ACD states that some patients would refuse bladder instillations because of their invasive nature and would instead choose best supportive care. Whilst we agree with this statement, it should be recognised that this would apply to a very small number of patients. As stated in our submission, consensus among clinical experts at an advisory board was that <5% BPS patients are contraindicated to or refuse bladder instillations. This was accepted by the ERG and its clinical expert. | Consilient Health (referred to hereafter as 'the company') argues that pentosan polysulfate sodium (PPS) will only be used after best supportive care (BSC) has failed and therefore BSC is not an appropriate comparator.<br><br>The ERG notes that best supportive care (BSC) is defined as an appropriate comparator, "for people for whom bladder instillations are inappropriate, cannot be tolerated or are unsuccessful" in the NICE final scope for this appraisal.<br><br>In this group of patients who are unable to receive bladder instillations (BIs), BSC remains the only treatment option even if patients have had an inadequate response to BSC, and therefore it is an appropriate comparator for PPS in this group.<br><br>The ERG notes that surgery is a last resort option for patients who do not respond to any available treatment but the proportion of patients receiving surgery in the UK is very low (2-5%, see page 19 of the ERG report) and therefore patients who cannot receive BIs are likely to remain on BSC even if the response has been inadequate. |

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| | If patients discontinue bladder instillations because of apparent symptom resolution, they will not receive PPS as further treatment would not be required. If their symptoms recur, patients would be offered either a bladder instillation or PPS. As described by our advisory board (Appendix M of the company submission), patients that fail on one type of bladder instillation would typically be offered alternative bladder instillations in an attempt to find one that works for the patient. Given the lack of treatment options for this condition, if both PPS and the various bladder installations ultimately fail in secondary care, patients may be tried again on best supportive care/palliative care as a last resort prior to surgery.<br><br>In summary, PPS can be used as an alternative to bladder instillations as second-line therapy after BSC has failed, but is not an alternative to BSC. | |
| 2 | Sections 3.7-3.8<br><br>The company base case uses the Bucher method to source treatment response rates, recognising that there was considerable heterogeneity in the trials to allow for a robust indirect comparison. As highlighted by the ERG, neither the Bucher method nor a Bayesian network meta-analysis (NMA) are ideal for comparing PPS and bladder instillations due to challenges with both approaches. The ERG expressed a preference for a Bayesian NMA. Both the ERG and Consilient Health conducted a Bayesian NMA using the same clinical data included in the original submission. We consider that all methods have limitations and that any differences in the methods are mainly centred around the handling of | The company has presented no new information and therefore the ERG maintains its position that the Bayesian network meta-analysis is preferable to the Bucher method despite both having limitations. |

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| | heterogeneity. Therefore, there was no ideal method to be used in this particular case. | |
| 3 | Section 3.9 – "In the company's updated analysis, it included the placebo arms of the bladder instillation trials which gave an 18.9% estimated response rate".<br><br>This statement is inaccurate. The company base case analysis uses a 15.8% placebo response rate which is in line with the 16% recognised as reasonable by the committee. The quoted 18.9% was used in a scenario analysis submitted by the company using a Bayesian NMA approach. | The ERG agrees that the company's base-case which used the Bucher method had a placebo response rate of 15.8% which was based on the response rate in the trials which compared PPS to placebo in patients with IC/ BPS.<br><br>The figure of 18.9% was for the company's scenario analysis using the company's Bayesian NMA in which the placebo response was estimated using the 4 studies comparing PPS to placebo in the IC/BPS population and the 2 studies comparing BIs to placebo studies in the broader BPS population. |
| 4 | Section 3.10 – Missing data on utility values<br><br>The ACD states that the ERG's preferred method to account for the missing data relating to recent treatment with bladder instillation is multiple imputation. As previously stated, the missing data for the variable 'received bladder instillations in the previous 6 months' are not missing at random. There were statistically significant differences in the EQ-5D scores and ages of those who responded to this question. No other variables, with a clinically plausible explanation, were found to explain the missingness for this variable.<br><br>A multiple imputation analysis would therefore use EQ-5D score and age to predict the response to 'received bladder instillations in the previous 6 months'. However, the imputed bladder instillation variable would then be used in the analysis to predict the EQ-5D score (with ICSI score and age), i.e. the EQ-5D value and bladder instillation variable would be | The ERG maintains their position that alternative assumptions for missing data on the previous use of BIs have not been adequately explored in the analysis of the patient survey data. For this reason, the utility regression including the term for 'received bladder instillations in the previous 6 months' is subject to considerable uncertainty and the ERG still prefers to use the regression excluding this term.<br><br>The information on the number receiving oral PPS reported in the patient survey is helpful. However, the company is not able to give any information on whether oral PPS would be associated with a utility decrement similar to that observed for patients who have 'received bladder instillations in the previous 6 months' based on the patient survey and this remains a limitation of the evidence provided. |

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| | dependent on each other. Therefore, we consider it inappropriate to conduct multiple imputation for this variable.<br><br>In addition, the ACD states that "It also highlighted that the patient survey did not collect data on utilities associated with pentosan polysulfate treatment."<br><br>As PPS was previously only available through unlicensed import in the UK, it was anticipated that very few patients would be receiving treatment with PPS in current clinical practice. Therefore, the survey did not ask a specific question about treatment with PPS. Conversely, bladder instillations are part of standard care of IC/BPS and a specific question was therefore included. However, a free text field was included in the survey which asked patients to report oral medications that they were currently receiving. Only [redacted] of the [redacted] patients in the survey who stated that they were on any oral medication for their BPS reported treatment with PPS in this time period. With so few patients reporting treatment with PPS it would not have been possible to robustly include a covariate for PPS treatment in the mapping model. | |
| 5 | Sections 3.11-3.12 – Bladder instillations utility decrement<br><br>Bladder instillations are an invasive and uncomfortable procedure, and have been associated with adverse effects (as also portrayed in the patient cases studies we submitted in the original company submission, Appendix N). This was noted by the NICE clinical experts as stated in the ACD. Clinical experts confirmed the likelihood of reduced quality of life with bladder instillations, highlighting in particular the | No new evidence is provided by the company in response to this section of the ACD. The comments made by the company all relate to evidence previously submitted or discussed at the committee meeting.<br><br>However, the ERG wishes to make the following comments on the sensitivity analysis using data from Cervigni which was discussed briefly during the committee meeting but wasn't commented on in the ERG report. |

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| | potential for an increase in urinary tract infections (UTIs) as well as the fact that the efficacy following an instillation wanes over time, which can leave the patient in increasing pain prior to each treatment. This is summarised in Appendix M of the company submission and was also mentioned by the clinical expert participating in this appraisal process. UTIs are known to be associated to bladder instillations and are considered the commonest side effect (alongside bladder pain) by the British Association of Urological Surgeons (BAUS 2017). As noted by the patient and clinical experts in the committee meeting, UTIs in patients with IC/BPS are significantly different from those experienced by the general population both in duration and severity.<br><br>The ACD underappreciates the potential for a negative impact on patients' quality of life associated with the use of bladder instillations, arising from the: inconvenience and lifestyle disruption of attending regular hospital outpatient clinics; discomfort of administration; and waning efficacy between doses. Of note, these features of treatment are not short-lived but are ongoing. Therefore, considering that UTIs are not the only potential negative effects associated with bladder instillations, we consider the decrement of [redacted] found in the survey to be reflective of this fact.<br><br>Evidence from Cervigni et al. (2017) does not include a utility decrement for bladder instillations; nonetheless, they indicate that the quality of life (QoL) difference between patients at baseline and after 6 months of treatment may be greater than what is currently modelled in the company cost-effectiveness model for patients pre-response assessment/non-responders and responders. Using QoL evidence from this paper in the | The ERG notes that the sensitivity analysis using utility data from Cervigni applied utility values of 0.25 pre-assessment, 0.25 for non-responders and 0.65 for responders. These were based on EQ-5D scores at base-line (0.25) and the change in EQ-5D scores from base-line to 6 months (+0.39) reported by Cervigni et al. (2017), giving an estimate of the absolute EQ-5D score at 6 months of 0.65.<br><br>There are several issues with the applicability of this study to the decision problem and its use within the cost-effectiveness sensitivity analysis. Firstly, the population is adult women (aged >18 years) with BPS (diagnosed according to ESSIC criteria) refractory to first-line non-invasive treatment (including oral PPS) or at first observation. Approximately one third was refractory to first line non-invasive treatments with the remainder enrolled at first observation. Therefore patients were not required to have either glomerulations or Hunner's lesions and the population was broader than that indicated for PPS. The population may also have included some patients refractory to PPS, and it included a large proportion who had not previously tried non-invasive treatments which is inconsistent with the position of PPS and BIs in Figure 2 of the company's submission where they are positioned after first-line oral treatments. Secondly, the tariff is based on the Italian valuation of the EQ-5D. Finally, the values applied in the model represent the change in utility from before treatment to 3 months after the end of treatment for patients completing 13 weeks of weekly bladder instillations with hyaluronic acid (1.6%) and chondroitin sulfate (2.0%) (IAluril®; IBSA) as part of a clinical trial. [The comparator was 13 weeks of weekly instillations with a 50% |

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| | cost-effectiveness model resulted in incremental quality-adjusted life-year (QALY) differences that are similar to those in the company base-case (which includes a bladder instillation utility decrement). | dimethyl sulfoxide (DMSO) solution (RIMSO®; Bioniche) which had an EQ-5D change of 0.31 at 6 months)] Therefore the utility values included in the model do not represent the difference in utility values for responders to treatment versus non-responders to treatment. It is likely that there will be some degree of placebo response associated with being enrolled in a trial and started on a new treatment. Particularly as the trial was an open-label study without a placebo comparator and therefore patients would be likely to expect some improvement. Also, patients had to withdraw from any previous therapy for 3 months prior to enrolment which may be detrimental if the response to first-line treatment had been marginal but not adequate. |
| 6 | Section 3.12 – "The committee noted that the utility score for patients having subsequent bladder instillations was counter-intuitive when compared against the utility score for people whose condition did not respond to treatment having best supportive care."<br><br>The utility of subsequent treatments used in the economic model is a weighted average of the utility of responders and non-responders to bladder instillations. Since the treatment response rate to bladder instillations is 20-30%, the weighted average is mainly driven by the utility score of non-responders. | As the company points out, some of the patients having second line bladder instillations respond to treatment and some do not. Logically therefore, the average utility should be somewhere between that expected for a responder and a non-responder. The reason that the utility score for second line bladder instillations is counterintuitive is that it is lower than the utility score for those who do not respond to BSC. This would suggest that, on average, patients would accrue more QALYs by not receiving bladder installations even though they are effective for a proportion of patients. The ERG maintains its position that the utility decrement attributed to receiving bladder instillations in the model produces utility values that lack face validity. |
| 7 | Section 3.12 – "The patient and clinical experts explained that both bladder instillations and pentosan polysulfate sodium may be associated with decrements"<br><br>Unlike bladder instillations which are invasive, PPS is an oral treatment and its administration would not be expected to be | The ERG notes that in the committee papers (page 357 of 441) there is a comment from a clinical expert (Jonathan Goddard (Consultant urological surgeon) – TC 12/04/2019) on the issue of utility values which says "PPS is also very inconvenient to administer because patients must take it 3 times a day and coordinate this with meal times". |

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| | associated with a disutility. Furthermore, the adverse effects of bladder instillations are acknowledged by clinical experts and the NICE committee. No specific adverse effects of PPS have been suggested by the clinical or patient experts, or the committee. Therefore, it is unclear what evidence supports this statement in the ACD. | Although the ERG cannot be sure if this was the issue that this statement refers to. |
| 8 | Section 3.13 – Frequency of bladder instillation administration<br><br>The manufacturers' recommendations for administration of bladder instillations is typically weekly for 4 weeks then increased to once every 4 weeks. This was also discussed at an advisory board in September 2018 with 9 urology/urogynaecology consultants or specialist nurses. The advisory board agreed that treatment should be tailored to the individual patient's needs, and frequency of bladder instillations was typically guided by when the patient experienced a return of painful symptoms. This leads to a degree of variability in the dosing frequency of bladder instillations in clinical practice; while some patients are able to tolerate a longer interval than 4 weeks, others unfortunately require even more frequent instillations.<br><br>Feedback from 11 UK experts was obtained and has previously been presented. The feedback from these 11 respondents again shows that there is a degree of variability in clinical practice and while intervals of longer than 4 weeks are used in some patients, there is a not insignificant minority (10-30%) that require more frequent instillations. | No new information has been provided in the company's response to section 3.13.<br><br>The ERG previously reviewed the feedback from the 11 UK experts and this was taken into account when deciding upon the appropriate dosing frequency for long-term use in their preferred analysis which was 6 weekly. The ERG previously stated that they accepted that "there is significant variation in practice with a proportion of clinicians appearing to adhere to the four-weekly treatment regimen in the majority of their patient cohort, and a proportion appearing to favour less frequent administrations in the majority of their patient cohort". However, the ERG felt on balance that the evidence provided was consistent with 6 weekly administration and noted in particular the HES data showing an average of 7.2 weeks between instillations. |

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| | The effect of a bladder instillation wanes over time following the dose and, increasingly, the pain returns before the patient receives their next dose. Therefore, extending the interval between instillations is not without adverse consequences for patients and their quality of life.<br><br>Overall, there is variability in clinical practice with regard to frequency of bladder instillations, with some patients requiring instillations more often than 4 weekly and some less often. Applying an administration frequency of 6 weeks for bladder instillations is likely to be inaccurate and not representative of a substantial proportion of the BPS patient population. Furthermore, a 4-week administration frequency is in line with manufacturer recommendations. | |
| 9 | Section 3.14 – Long-term use of bladder instillations<br><br>Evidence from an advisory board included in our evidence submission indicates that current clinical practice for patients whose symptoms cannot be handled by best supportive care is to cycle through multiple bladder instillation cycles. As stated in section 3.1 of the ACD, BPS is incurable and as a result many patients will require long-term treatment. There is insufficient evidence to support a specific symptom resolution/condition relapse pattern that would enable us to model the long-term treatment pathway more granularly. In addition, any modelling scenarios would need to consider assumptions about intermittent use of either bladder instillations or PPS.<br><br>Recognising the aforementioned uncertainty, we believe our updated PAS discount, which offers an ICER below the lower | The ERG notes that no evidence was presented by the company on the long-term treatment persistence with bladder instillations. The evidence on treatment persistence with PPS is based on the Hanno (1997) study which was poorly reported making the correct interpretation of the data unclear. In the absence of any better source of data, this was used to extrapolate long-term persistence for both PPS and bladder instillations. In addition, the studies for both PPS versus placebo and BIs versus placebo are short-term and do not provide any evidence on whether the treatment effect is maintained with long-term use.<br><br>Despite this lack of information on long-term use of BIs, the model assumes that patients discontinuing either first-line BIs or PPS, switch to alternative BIs and that they cycle through the alternative BIs for the rest of their life. |

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| | end of the NICE threshold band, is accounting for this fact, making PPS a cost-effective use of NHS resources.<br><br>Section 3.14 of the ACD states that '…best supportive care becomes a more relevant comparator if more patients stop treatment with bladder instillations.' We disagree with this statement as PPS is positioned as an alternative to bladder instillations in secondary care for patients who have already failed best supportive care, i.e. as second-line therapy.<br><br>For patients who receive bladder instillations and then discontinue due to apparent symptom resolution, continued treatment with bladder instillations or PPS would not be appropriate. At such a time that symptoms return, patients could then be considered for active treatment again with PPS (or bladder instillations) as PPS is an effective and cost-effective alternative to bladder instillations.<br><br>As reported by the company's advisory board and accepted by the ERG, the number of patients for whom bladder instillations are contraindicated or not tolerated is a very small (<5%) proportion of the already small IC/BPS population. If patients fail treatment with bladder instillations and/or PPS, best supportive care may be tried again as palliative therapy prior to last-resort surgery. Therefore, PPS is positioned only when best supportive care has failed and cannot be considered an alternative to best supportive care. | The ERG would agree with the committee that BSC is a relevant comparator if patients stop treatment with bladder instillations due to either contraindications or being unable to tolerate bladder instillations. However, if patients stop bladder instillations because their symptoms have relapsed then they would be able to restart bladder instillations if symptoms returned. However, the company's model does not allow the cost-effectiveness of intermittent use in response to relapsing and remitting symptoms to be evaluated.<br><br>The ERG report states that the ERG's clinical advisors believed the estimate of <5% for the number of BPS patients for whom BIs are contraindicated or who refuse bladder instillations was reasonable.<br><br>As stated above (see comment 1), the ERG would consider BSC to be a comparator in those unable to receive bladder instillations, even when patients have had an inadequate response to BSC, as surgical treatment is used only as a last resort in a very small minatory of patients. |
| 10 | Section 3.15 – Inpatient resource use<br><br>Disease-related costs in the cost-effectiveness model were sourced from the survey of 252 patients included in our | Whilst inpatient visits account for a low proportion of resource use, they account for a much higher proportion of cost due to the high unit cost for an inpatient stay relative to outpatient or primary care activity. The ERG estimate, from |

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| | evidence submission. Prior use of bladder instillations was not a coefficient in the regression used to relate ICSI values to costs; therefore, background disease-related costs did not vary per treatment. Questions directed to patients inquiring about their healthcare visits were strictly phrased in relation to their interstitial cystitis/bladder pain syndrome. The total number of visits (in the previous 6 months) per type and as a percentage of total healthcare visits are reported below.<br><br>Inpatient visits = 67 (3% of total healthcare visits)<br>Outpatient visits = 796 (39% of total healthcare visits)<br>GP visits = 840 (42% of total healthcare visits)<br>Nurse visits = 318 (16% of total healthcare visits)<br><br>Therefore, we consider that a 3% inpatient visits figure is in line with the committee expectations. | Appendix 1 of the ERG report, that inpatient visits account for [redacted] of the total cost.<br><br>However, the ERG does not believe that the cost-effectiveness estimates are particularly sensitive to the disease-related costs because they apply equally to both treatment arms. For example, halving the disease-related costs increases the deterministic ICER for PPS versus BI from [redacted] and doubling the disease related costs reduces the ICER to [redacted]. For PPS versus BSC halving the disease-related costs would reduce the ICER from [redacted] to [redacted] whilst doubling them would reduce the ICER to [redacted]. Insufficient information is provided in the company submission for the ERG to estimate what the relationship between costs and response to treatment (as determined by ICSI score) would be without the inclusion of inpatient costs. However, removing any relationship between cost and disease control, by setting the coefficient for ICSI score in the cost regression to zero, increases the deterministic ICER for PPS versus BI from [redacted] and increases the deterministic ICER for PPS versus BSC from [redacted] to [redacted]. |

# Pentosan polysulfate sodium for treating bladder pain syndrome: A Single Technology Appraisal: third addendum


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None of the authors have any conflicts of interest to declare.

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**Contributions of authors**

Sarah Davis and Kate Ennis extracted and presented the results incorporating the PAS described in this addendum.

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**Abbreviations**

| | |
|---|---|
| BI | Bladder instillations |
| BSC | Best supportive care |
| ICER | Incremental Cost Effectiveness Ratio |
| NMA | Network meta-analysis |
| PAS | Patient Access Scheme |
| PPS | Pentosan polysulfate sodium |
| PSA | Probabilistic sensitivity analysis |
| QALY | Quality-Adjusted Life Year |

# 1 ERG additional analyses incorporating revised PAS

This addendum provides the results for the ERG's preferred base-case following technical engagement as presented in section 3 of the first addendum to the ERG report, but with the application of the revised patient access scheme (PAS) discount provided to the ERG on the 15th of July 2019. The PAS is a simple discount to the list price of [redacted].

See section 3.1 of the first addendum to the ERG report for a description of the ERG's preferred base-case following technical engagement. Results when including the revised PAS are provided in

Table **1**.

The ICER for the ERG's preferred base-case for PPS versus BI when using the revised PAS is £14,418. The deterministic ICER using the mean of the CODA samples for the absolute response rate is £18,321 for the ERG's preferred scenario using the revised PAS. The mean QALYs gained for PPS vs BI in the deterministic model, which used mean NMA outputs was [redacted], whereas the mean QALY gain from the probabilistic model which used the CODA samples was [redacted]. This is why the probabilistic ICER is lower than the deterministic ICER. The probability that PPS has an ICER under £20,000 when compared to BIs is [redacted] and the probability that PPS has an ICER under £30,000 when compared to BIs is [redacted].

The ICER for the ERG's preferred base-case for PPS versus BSC when using the revised PAS is £50,740. The deterministic ICER using the mean of the CODA samples for the absolute response rate is £51,450 for the ERG's preferred scenario using the revised PAS. The probability that PPS has an ICER under £20,000 when compared to BSC is [redacted] and the probability that PPS has an ICER under £30,000 when compared to BSC is [redacted].

**Table 1: Results for ERG's preferred base-case (including revised PAS)**

| Option | Costs | QALYs | Inc. costs | Inc. QALYs | ICER (per QALY gained) |
|---|---|---|---|---|---|
| **PPS vs BI** | | | | | |
| PPS | [redacted] | [redacted] | [redacted] | [redacted] | **£14,418** |
| BI | [redacted] | [redacted] | [redacted] | [redacted] | - |
| **PPS vs BSC** | | | | | |
| PPS | [redacted] | [redacted] | [redacted] | [redacted] | **£50,740** |
| BSC | [redacted] | [redacted] | [redacted] | [redacted] | - |