NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Pentosan polysulfate sodium for treating bladder pain syndrome

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using pentosan polysulfate sodium in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- 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?

Issue date: July 2019

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using pentosan polysulfate sodium in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 1 August 2019

Second appraisal committee meeting: 21 August 2019

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 Pentosan polysulfate sodium is not recommended, within its marketing authorisation, for treating bladder pain syndrome with glomerulations or Hunner's lesions in adults with moderate to severe pain, urgency and frequency of urination.

1.2 This recommendation is not intended to affect treatment with pentosan polysulfate sodium that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Bladder pain syndrome is managed with oral treatments, then bladder instillations if symptoms don't improve. Pentosan polysulfate sodium is an oral treatment.

Clinical trials suggest that pentosan polysulfate sodium may be more effective at relieving pain than placebo. A comparison of clinical trials that includes best supportive care and bladder instillations suggests that pentosan polysulfate sodium may have a moderate benefit over these alternatives. But how much benefit it provides is unclear because these treatments haven't been compared directly. Also, the available evidence is not of high quality.

The most plausible cost-effectiveness estimates for pentosan polysulfate sodium are likely to be much higher than what NICE usually considers to be a cost-effective use of NHS resources. So, it cannot be recommended.

2 Information about pentosan polysulfate sodium

Marketing authorisation indication	Pentosan polysulfate sodium (Elmiron, Consilient Health) has a marketing authorisation for treating 'bladder pain syndrome characterised by either glomerulations or Hunner's lesions in adults with moderate to severe pain, urgency and frequency of micturition'.
Dosage in the marketing authorisation	300 mg/day taken as 1×100 mg capsule orally 3 times daily. Treatment is stopped if no improvement is reached 6 months after starting treatment. In people whose condition responds, treatment should be continued as long as the response is maintained.
Price	A pack of 90 capsules (100 mg each) costs £450. The company has a commercial arrangement, which would have applied if the technology had been recommended.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Consilient Health, a review of this submission by the evidence review group (ERG), and the technical report developed through engagement with stakeholders. See the committee papers for full details of the evidence.

The appraisal committee was aware that several issues were resolved during the technical engagement stage, and agreed that these were acceptable:

- using a lifetime time horizon in the economic model (issue 2, see technical report page 21)
- assuming response rates to best supportive care do not recede over time in the model (issue 3, see technical report pages 7 to 10)
- using the ERG's updated survival analysis that censors those who died and uses a log-normal extrapolation (issue 4, see technical report page 21)
- assuming utility scores and costs return to baseline in the model for people whose condition does not respond to treatment who move on to best supportive care (issue 6, see technical report pages 21 to 22).

It recognised that there were remaining areas of uncertainty associated with the analyses presented (see technical report, table 2, pages 19 to 20), and took these

into account in its decision making. It discussed the following issues (issues 1, 3, 5 and 7), which were outstanding after the technical engagement stage.

The condition

Bladder pain syndrome is challenging to manage and disrupts normal living

3.1 The clinical experts explained that bladder pain syndrome is a chronic bladder condition characterised by pain, urinary urgency, frequency and getting up at night to pass urine. The patient expert explained that bladder pain syndrome can lead to people needing the toilet up to 60 times a day and that some people had considered suicide because of the pain. Treatments generally aim to control the symptoms because there is no cure for the condition. The committee concluded that bladder pain syndrome is incurable, very challenging to manage and causes extreme pain, which disrupts normal living.

Clinical management

The relevant population is people with bladder pain syndrome and either glomerulations or Hunner's lesions

3.2 The clinical experts explained that bladder pain syndrome may affect approximately 400,000 people in the UK but only around 10% of these will present for treatment. The committee acknowledged that within the broader bladder pain syndrome population are people who also have glomerulations or Hunner's lesions. The marketing authorisation for pentosan polysulfate sodium is for treating bladder pain syndrome characterised by either glomerulations or Hunner's lesions in adults with moderate to severe pain, urgency and frequency of micturition. The committee considered that this was the relevant population for the appraisal.

There is an unmet need for effective treatment options

3.3 Treatment options for people with bladder pain syndrome and either glomerulations or Hunner's lesions include:

- oral treatments (such as amitriptyline, gabapentin, pregabalin, paracetamol, non-steroidal anti-inflammatory drugs, hydroxyzine, cimetidine and ranitidine) and
- bladder instillations (a plastic tube inserted into the bladder to administer liquid medication).

The patient expert stated that there are few treatment options and people often need multiple treatments to manage the symptoms. The clinical experts explained that bladder instillations are invasive and can cause adverse effects. The committee concluded that there is an unmet need for effective treatment options that can be used instead of invasive bladder instillations.

There is substantial variability in the treatment pathway

3.4 The clinical experts explained that the treatment pathway for bladder pain syndrome can vary substantially between services across the country. They explained that the condition is difficult to diagnose and that the presence of glomerulations is not specific to bladder pain syndrome. The clinical guideline recommendations for treating the condition vary and services use a variety of international guidelines to guide clinical management. The company noted that bladder pain syndrome is initially treated with oral medication (see section 3.3). If glomerulations or Hunner's lesions are found, then people can continue to have oral treatments, or be offered bladder instillations. The patient experts explained that not all treatments are available in all areas of the country; treatments depend on where a person lives and what is offered at their local hospital rather than what is suitable for their condition. The committee recognised that there is substantial variability in the clinical management of bladder pain syndrome and the treatment pathway is poorly defined.

The comparisons with bladder instillations and best supportive care are relevant for decision making

3.5 The company submitted analyses comparing pentosan polysulfate sodium with bladder instillations and with best supportive care. Bladder instillations are offered to people who can tolerate them. Best supportive care continues to be offered to people who can't tolerate bladder instillations, or if bladder instillations are unsuitable for them. The clinical experts highlighted that some people would choose not to have bladder instillations because of their invasive nature and would instead choose best supportive care. The company noted that best supportive care is the continuation of oral treatments (see section 3.3). The clinical experts explained that, if available, pentosan polysulfate sodium would be tried before bladder instillations. The clinical experts explained that other treatment options for the condition are available. But they noted that laser surgery for Hunner's lesions can be considered at any point in the treatment pathway and that botulinum toxin type A and sacral neuromodulation are generally used in research and not routine clinical practice. The committee acknowledged the variation in clinical practice. 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. However, considering the information from clinical experts, the committee agreed that bladder instillations and best supportive care were the standard clinical management options for this condition and were the most relevant comparators.

Clinical effectiveness

There is substantial uncertainty in the pentosan polysulfate sodium evidence

3.6 The company's clinical effectiveness evidence came from 4 randomised controlled trials comparing pentosan polysulfate sodium with placebo in people with bladder pain syndrome and either glomerulations or Hunner's lesions. The trials were published between 1987 and 2003. The ERG noted that:

- 3 of the trials were of good methodological quality but the other trial should be interpreted with caution because of uncertainty about allocation concealment and numbers of patients withdrawing from treatment
- sample sizes were not calculated for 3 of the trials and the target sample size for the other trial was not met
- the author was common to all 4 trials and there were no independent studies validating the results
- the definition of the primary outcome used in the company's model varied and
- follow-up times varied between all trials.

The committee concluded that the company's evidence for pentosan polysulfate sodium was relevant for decision making but acknowledged the limitations of the trials. It considered that there was substantial uncertainty in the evidence.

There are substantial uncertainties in determining the relative treatment effect using an indirect treatment comparison

3.7 To compare pentosan polysulfate sodium with bladder instillations, the company used an indirect treatment comparison. Both the company and the ERG acknowledged that this was necessary, but agreed it was challenging because of:

- Differences in trial populations: Uracyst was the only bladder instillation suitable for indirect comparison with pentosan polysulfate sodium via placebo. The pentosan polysulfate sodium trials were in people with interstitial cystitis or bladder pain syndrome who have Hunner's lesions or glomerulations or both. But the Uracyst trials were in people with the broader bladder pain syndrome.
- Differences in placebos: Pentosan polysulfate sodium was compared with an oral placebo, whereas Uracyst was compared with a placebo instillation.

- Differences in the timings of outcome measurement.
- Differences in the definition of the main outcome (global response assessment).

The company compared meta-analysed data from 2 Uracyst trials with meta-analysed data from 4 pentosan polysulfate sodium trials using the Bucher method of indirect treatment comparison (an adjusted method that retains patients' original randomisation). Response rates to treatment were 33% for pentosan polysulfate sodium compared with 22% for bladder instillations.

The ERG considered that the Bucher method did not adequately acknowledge the heterogeneity in treatment effect between the studies. Instead, it proposed using a Bayesian network meta-analysis, which provides a more flexible framework for incorporating and exploring the uncertainties in the evidence. The committee acknowledged that both the Bucher method and Bayesian approach are valid methods of analysis in this setting, but the company's application of the Bucher method did not account for heterogeneity. The committee agreed that there was significant heterogeneity in the treatment effect and therefore concluded that it would prefer a Bayesian network meta-analysis.

The ERG's Bayesian network meta-analysis is an acceptable method for an indirect treatment comparison

3.8 The ERG did a Bayesian network meta-analysis, which showed response rates of 33% for pentosan polysulfate sodium compared with 24% for bladder instillations. After the technical engagement stage, the company also did a Bayesian network meta-analysis comparing pentosan polysulfate sodium with bladder instillations as a scenario analysis. This showed response rates of 38% for pentosan polysulfate sodium compared with 28% for bladder instillations. The ERG advised that the company's network meta-analysis had methodological limitations because it did not use separate baseline and treatment effects models to estimate absolute

response rates. The committee understood that although both the company's and the ERG's approaches had their limitations, the best possible methods for an indirect treatment comparison should be used. The committee concluded that the ERG's Bayesian network meta-analysis was acceptable because it better characterised the uncertainty in comparing active treatments.

It is acceptable to use the 16% response rate to placebo from the pentosan polysulfate sodium trials in the cost-effectiveness analysis

3.9 The company noted that the high response rates (16%) in the placebo arms of the pentosan polysulfate sodium trials did not reflect clinical practice. It considered these high response rates would underestimate the effectiveness of pentosan polysulfate sodium. The ERG noted that the high response rates could be explained by regression to the mean, which would also be present in the intervention arms. The ERG also noted that in the company's model, the absolute difference in treatment effect becomes greater with increasing best supportive care response. This would result in the high response rate in the placebo arm favouring pentosan polysulfate sodium because the company's analysis used relative risks. In the company's updated analysis, it included the placebo arms of the bladder instillation trials which gave an 18.9% estimated response rate. The clinical experts explained that real world evidence may suggest even higher placebo response rates. This is expected because patients with the condition initially derive benefit but this is not sustained beyond 3 months. The committee acknowledged that the clinical experts' views and the ERG's analysis results (15.5%) were broadly in line with the placebo response rates from the pentosan polysulfate sodium trials (16%). The committee concluded that a 16% response rate to placebo was acceptable to use in the cost-effectiveness analysis.

Utilities

Missing data on utility values are not adequately accounted for in the company's model

3.10 In its base-case model, the company applied a utility decrement associated with bladder instillations. The company mapped patient survey data collected in the Sant et al. (2003) trial to EQ-5D data. The company used responses to a question in the survey on the use of bladder instillations in the previous 6 months. The ERG noted that the wording of the question in the survey about previous bladder instillation use was vague. This could have meant that patients who never used bladder instillation did not answer the question and this was recorded incorrectly as missing data. The ERG's preferred method to account for the missing data was to use multiple imputation (a statistical method used to reduce bias arising from missing data). It also highlighted that the patient survey did not collect data on utilities associated with pentosan polysulfate treatment. The committee concluded that missing data from the patient survey was not adequately accounted for in the company's model.

There is insufficient evidence of a direct link between bladder instillations and urinary tract infections

3.11 After the technical engagement stage, the company provided clinical expert evidence and a systematic review to support their assumption that bladder instillations are associated with an increase in urinary tract infections (UTIs). The company explained that the evidence showed that people with UTIs have substantially lower quality of life than those without UTIs. It also proposed that UTIs in people with bladder pain syndrome have a bigger impact on quality of life than UTIs in the general population. The ERG noted that the company's model assumed that everyone having bladder instillations would have a UTI and that the associated decrement was modelled for a lifetime. The clinical experts explained that not all people having bladder instillations would get a UTI and although the symptoms may last longer than for the general population these would not

continue indefinitely. They also noted that people would be given the choice of continuing bladder instillation treatment if they did get a UTI. The company noted that UTIs are only 1 aspect of the decrement associated with bladder instillations. It provided an alternative sensitivity analysis based on a paper by Cervigni et al. (2017). The committee noted that this analysis did not include a utility decrement for UTIs and resulted in incremental cost-effectiveness ratios (ICERs) that are similar to the company's base case. However, the committee also noted that this analysis included a trial population who were not covered by the marketing authorisation, which introduced some uncertainty into the analyses. The committee 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.

It is not appropriate to include a utility decrement for bladder instillations

3.12 The company justified modelling a utility decrement for bladder instillations because it considered bladder instillations to be invasive and associated with adverse effects. The committee noted that the utility decrement was applied for all patients who had bladder instillations for the lifetime of the company's model. It also 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. This was unlikely to be the case. The ERG noted that the difference in utility in the patient survey between people who had and people who had not recently used bladder instillations may reflect baseline patient characteristics rather than being treatment specific. The patient and clinical experts explained that both bladder instillations and pentosan polysulfate sodium may be associated with decrements. The clinical experts also added that any decrement associated with bladder instillations was likely to be short-lived because the treatment would be stopped if there were any adverse events. The committee concluded that applying a utility decrement for bladder instillations was not appropriate.

Resource use

It is acceptable to assume 6-weekly administration of subsequent bladder instillations and first-time bladder instillations after the first year

3.13 The company modelled weekly administration of first-time bladder instillations for the first 4 weeks, and 4-weekly administration after this point. This frequency also applied to all subsequent bladder instillations. The clinical experts explained that initial treatment with bladder instillations would be weekly for 4 weeks followed by maintenance treatment once monthly for 4 to 6 months, and continuation would be based on response to treatment. They also noted that it is reasonable to administer maintenance treatment at 6-weekly intervals for subsequent bladder instillations if this achieved the same response in patients as a 4-weekly administration. The patient expert explained that maintenance treatment intervals vary according to the person and can be either monthly or when symptoms return. If maintenance treatment is led by the patient based on their symptoms, this would lengthen the interval between instillations beyond 4 weeks. The ERG's model accounted for this variation. It included 6-weekly maintenance intervals for subsequent bladder instillations and for first-time bladder instillations after a year of treatment. The committee acknowledged the variation in clinical practice and recognised that administration would be different for first-time and subsequent bladder instillations. The committee concluded that it was acceptable to assume 6-weekly administration for subsequent bladder instillations and for first-time bladder instillations after the first year (in line with the ERG's model).

Most people on bladder instillations would not stay on treatment indefinitely

3.14 The company's model assumed that bladder instillations are administered indefinitely. The clinical experts explained that bladder instillations would not continue for a lifetime and estimated that only 5% of patients would continue with them after 5 years. The committee acknowledged that in clinical practice bladder instillations would not continue indefinitely and

most patients would stop within 5 years. It also recognised that best supportive care becomes a more relevant comparator if more patients stop treatment with bladder instillations.

Inpatient resource use is overestimated in the company's model

3.15 The company's model included a proportion of patients who would have inpatient care for bladder instillations. The ERG noted that the disease-related costs in the company's model had been overestimated because not all of the resource use is a result of bladder pain syndrome with glomerulations or Hunner's lesions. The clinical experts explained that most people having bladder instillation are seen in outpatient care; the number having inpatient care is negligible. The committee considered that the company had overestimated the disease-related costs by modelling a proportion of patients to have inpatient care. The committee concluded that inpatient resource use would be minimal in a population having bladder instillations.

Cost-effectiveness estimate

There are uncertainties in the cost-effectiveness estimates that are unlikely to be resolved

3.16 The committee noted the substantial uncertainty in the model inputs, specifically:

- the considerable variability in the treatment pathway (see section 3.4)
- the significant uncertainty in the pentosan polysulfate sodium evidence (see section 3.6)
- the methodological limitations with all approaches to indirect treatment comparisons (see section 3.7)
- the challenges with the missing data on utility values (see section 3.10).

The committee concluded that these uncertainties are unlikely to be resolved in the cost-effectiveness modelling.

Pentosan polysulfate sodium is unlikely to be cost effective for bladder pain syndrome compared with bladder instillations

3.17 The company's updated base case included the following committee-preferred assumptions:

- incorporated a lifetime time horizon in the model (issue 2 of the technical report)
- time to discontinuation was based on the ERG's time-to-discontinuation data set (which included deaths as discontinuations, whereas the technical team would have preferred deaths to have been censored) and a log-normal extrapolation (issue 4 of the technical report).

The company's base-case ICER for pentosan polysulfate sodium compared with bladder instillations (using the Bucher method for the indirect treatment comparison and a confidential commercial arrangement) was £9,952 per quality-adjusted life year (QALY) gained. The committee's preferred modelling assumptions were reflected in the ERG's analyses:

- a Bayesian network meta-analysis using the ERG's preferred approach (see section 3.8)
- assumption of no utility decrement associated with bladder instillation use in the previous 6 months (see sections 3.10 to 3.12)
- 6-weekly administration of bladder instillations (see section 3.13).

The ERG's revised ICER using the committee's preferred assumptions and applying the confidential commercial arrangement was £86,502 per QALY gained when compared with bladder instillations. The committee concluded that the most plausible cost-effectiveness estimate for pentosan polysulfate sodium compared with bladder instillations was above the range usually considered a cost-effective use of NHS resources (see NICE's guide to the methods of technology appraisal).

Pentosan polysulfate sodium is unlikely to be cost effective for bladder pain syndrome compared with best supportive care

3.18 The company's updated base case included the following committee-preferred assumptions:

- incorporated a lifetime time horizon in the model (issue 2 of the technical report)
- best supportive care response rates do not recede over time (issue 3 of the technical report)
- deaths censored from treatment discontinuation in line with the ERG's censoring rules, and extrapolated using a log-normal distribution (issue 4 of the technical report)
- utility scores and costs return to baseline for people whose condition does not respond to treatment who move on to best supportive care (issue 6 of the technical report).

3.19 The company's base-case ICER compared with best supportive care (including a confidential commercial arrangement) was £76,213 per QALY gained. The committee's preferred modelling assumptions were reflected in the ERG's analyses:

- a Bayesian network meta-analysis using the ERG's preferred approach (see section 3.8)
- 16% placebo response rate from the pentosan polysulfate sodium trials (see section 3.9).

The ERG's revised ICER using the committee's preferred assumptions and applying the confidential commercial arrangement was £72,355 per QALY gained when compared with best supportive care. The committee concluded that the most plausible cost-effectiveness estimate for pentosan polysulfate sodium compared with best supportive care was above the range usually considered a cost-effective use of NHS resources (see NICE's guide to the methods of technology appraisal).

Other factors

There are no equalities issues that can be addressed in the guidance

3.20 The company and a clinical expert highlighted that bladder pain syndrome affects more women than men. However, issues related to differences in prevalence or incidence of a disease cannot be addressed in a technology appraisal.

Conclusion

Pentosan polysulfate sodium is not recommended

3.21 Pentosan polysulfate sodium is not recommended for use in the NHS, within its marketing authorisation, for treating bladder pain syndrome. Despite taking into account the unmet need for effective treatment options for this population and the committee's most plausible assumptions, the ICERs for the comparisons with bladder instillations and with best supportive care were much higher than what is considered to be a cost-effective use of NHS resources. Therefore, the committee could not recommend pentosan polysulfate sodium for treating bladder pain syndrome with glomerulations or Hunner's lesions in adults with moderate to severe pain, urgency and frequency of urination.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Gary McVeigh

Chair, appraisal committee

July 2019

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5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Omar Moreea
Technical lead

Lucy Beggs
Technical adviser

Gemma Barnacle
Project manager

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