Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2194

pentosan polysulfate sodium 100mg hard capsules (Elmiron®)

Consilient Health Ltd

04 October 2019

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission considered under the orphan equivalent process

pentosan polysulfate sodium (Elmiron®) is accepted for use within NHSScotland.

Indication under review: for the treatment of bladder pain syndrome characterised by either glomerulations or Hunner's lesions in adults with moderate to severe pain, urgency and frequency of micturition.

In patients with bladder pain syndrome and glomerulations or Hunner's lesions, pentosan polysulfate sodium was associated with significantly more patients achieving at least moderate improvement in overall symptoms of bladder pain syndrome compared with placebo.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of pentosan polysulfate sodium. This advice is contingent upon the continuing availability of the PAS in NHSScotland or a list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chairman
Scottish Medicines Consortium

Indication

For the treatment of bladder pain syndrome characterised by either glomerulations or Hunner's lesions in adults with moderate to severe pain, urgency and frequency of micturition.[1]

Dosing Information

The recommended dose is 300mg/day taken as one 100mg capsule orally three times daily. The capsules should be taken with water at least 1 hour before meals or 2 hours after meals. Response to treatment with pentosan polysulfate sodium should be reassessed every 6 months. In case no improvement is reached 6 months after treatment initiation, treatment with pentosan polysulfate sodium should be stopped. In responders pentosan polysulfate sodium treatment should be continued chronically as long as the response is maintained.[1]

Product availability date

September 2018

Pentosan polysulfate sodium meets SMC orphan equivalent criteria.

Summary of evidence on comparative efficacy

Pentosan polysulfate sodium is a semi-synthetic low molecular weight heparin-like compound, which chemically and structurally resembles glycosaminoglycans. The exact mechanism of action of pentosan polysulfate sodium in the treatment of bladder pain syndrome is unknown but it has anticoagulant, fibrinolytic, and anti-inflammatory effects. It is thought to have a local effect following excretion in the urine by binding of glycosaminoglycans to the deficient mucous of the bladder reducing bacterial adherence to the inner surface of the bladder and in consequence the incidence of infections is reduced as well. It is hypothesised that a potential barrier function of pentosan polysulfate sodium instead of the damaged urothelial mucus might play a role as well as the anti-inflammatory activity of pentosan polysulfate sodium.[1, 2]

The key evidence to support the use of pentosan polysulfate sodium for patients with bladder pain syndrome characterised by either glomerulations or Hunner's lesions comes from four randomised, double-blind studies. Eligible patients had symptoms of pain, frequency, urgency and/or nocturia and evidence of bladder pain syndrome with inflammation from cystoscopic examination with or without bladder hydrodistention. Other inclusion criteria varied between the studies.[2-6]

In two similar studies, eligible patients were randomised equally to pentosan polysulfate sodium 100mg orally three times daily or placebo for 3 months. The primary outcome was a patient-reported questionnaire based on a 6-point global response assessment (GRA). Patients reporting ≥50% improvement (where 50%=moderate; 75% great; 100%=complete cure) were responders. At 3 months, a GRA was achieved by significantly more pentosan polysulfate sodium patients than

placebo patients: 32% (24/74) versus 16% (12/74) respectively, p=0.01, in one study and by 28% (15/54) versus 13% (7/56) respectively, p=0.04, in the other study.[2, 5, 6]

The third pilot study used a 2 x 2 factorial design to assess the initial efficacy of pentosan polysulfate sodium and hydroxyzine in eligible patients with bladder pain syndrome. Eligible patients were randomised to 24 weeks treatment with pentosan polysulfate sodium (100mg three times daily), hydroxyzine (10mg daily for one week, 25mg daily for one week then 50mg daily thereafter), pentosan polysulfate sodium plus hydroxyzine or placebo. The primary outcome was based on a patient-reported 7-point GRA after 24 weeks. Patients who assessed themselves as moderately improved or markedly improved were defined as responders. At 24 weeks, this was achieved by 34% (20/59) in the pentosan polysulfate sodium +/- hydroxyzine group compared with 18% (11/62) in the placebo +/- hydroxyzine group; the treatment difference was not significant. In the individual randomised groups, GRA was achieved by 40% (12/30) of pentosan polysulfate sodium plus hydroxyzine patients, 28% (8/29) of pentosan polysulfate sodium alone patients, 23% (7/31) of hydroxyzine alone patients and 13% (4/31) of placebo patients.[2, 3]

The fourth study used a crossover design and randomised eligible patients to treatment A for 3 months: pentosan polysulfate sodium (100mg three times daily or 200mg twice daily depending on study centre) or placebo. After 3 months, patients who failed to respond to treatment A were crossed over to treatment B (from pentosan polysulfate sodium to placebo or from placebo to pentosan polysulfate sodium). Patients responding to treatment A at 3 months continued for a further 3 months at which point if still responding they were crossed over to treatment B. There was no specified primary outcome and overall improvement was not assessed. Instead this study, patients assessed improvements in individual symptoms (urgency, frequency, nocturia and pain) as 0%, 25%, 50%, 75% or 100%. Patients with ≥50% improvement from baseline to 3 months were considered responders. Analyses based on completer data, not ITT, after crossover found that significantly more pentosan polysulfate sodium than placebo patients were considered responders. An improvement of ≥50% in pain was reported by 45% (19/42) and 18% (7/38) of patients respectively; in urgency by 50% (21/42) and 19% (9/48) respectively and in frequency 63% (33/52) and 39% (16/41) respectively. Nocturia was reduced by 1.5 episodes in pentosan polysulfate sodium patients and by 0.5 episodes in placebo patients.[2, 4]

Two additional studies (Nickel 2015 and Holm-Bentzen 1987) were performed in a broader population of patients; they had bladder pain syndrome but were not required to have glomerulations or Hunner's lesions.[7, 8] One of these, the Nickel 2015 study, was a more recent and larger study of double-blind, placebo-controlled design. It recruited patients aged ≥18 years with interstitial cystitis or bladder pain with an O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI) total score of ≥8 and a score >0 for each component (bladder pain, urinary urgency, frequency and nocturia) for ≥6 months before screening and ≥10 voids per day. Eligible patients were randomised equally to receive pentosan polysulfate sodium 100mg three times daily, 100mg daily or placebo for 24 weeks. The study enrolled 369 of a planned 645 patients and was stopped early despite numerous efforts to promote recruitment. Interim analysis indicated that study continuation was futile. The primary outcome was a responder analysis based on ≥30% improvement from baseline in the ICSI total score at week 24 which was achieved by 43% (52/122), 40% (51/128) and 41% (48/118) of pentosan 100mg three times daily, 100mg daily and placebo patients respectively. A

post hoc analysis was performed in a subgroup of 94 patients who had objective findings on cystoscopy consistent with National Institute of Diabetes and Kidney Disease criteria for interstitial cystitis ≥30 days before enrolment; these patients more closely reflect the indication under review. In this post hoc subgroup ≥30% improvement in ICSI total score was achieved by 34% (10/29), 30% (10/33) and 50% (16/32) of pentosan 100mg three times daily, 100mg daily and placebo patients respectively.[8]

A meta-analysis of the four key studies using a primary outcome of response rate (based on patient's GRA as defined in the individual studies or calculated afterwards if not directly reported) found a difference between pentosan polysulfate sodium and placebo of 17% (95% CI: 9.3 to 25).[2]

There are no direct comparative data with alternative treatment options and the company presented an indirect comparison with Uracyst®, a bladder instillation of chondroitin, using placebo as a common comparator. Although it is not commonly used, it was selected due to a lack of studies comparing other bladder instillations with placebo. The submitting company assumed that the efficacy of Uracyst® versus placebo would be similar to the efficacy of all bladder instillations. This assumption was supported by an advisory panel. The submitting company stated that an indirect comparison using Bucher methods compared the results from the meta-analysis of the four key studies for pentosan polysulfate versus placebo with results from a meta-analysis of two studies for Uracyst® versus placebo.[2, 9, 10] However, the treatment difference versus placebo from each meta-analysis was recalculated as a risk ratio (2.09 [95% CI: 1.47 to 2.97] for pentosan polysulfate sodium and 1.39 [95% CI: 0.89 to 2.17] for Uracyst®). These were applied to the placebo response rate from the pentosan polysulfate sodium studies (16% [95% CI: 12% to 21]) to give response rates of 33% for pentosan polysulfate sodium and 22% for Uracyst® which were used in the economic case. The submitting company performed a sensitivity analysis using a Bayesian network meta-analysis (NMA) with random effects model of the same data which gave response rates of 38% for pentosan polysulfate sodium and 28% for Uracyst® and 19% for placebo and a relative treatment effect of 0.73 (95% credible interval: 0.38 to 1.30).

Summary of evidence on comparative safety

No comparative safety data are available. The four key studies compared pentosan polysulfate sodium with placebo. The reporting of safety was limited in key study publications but pentosan polysulfate sodium was generally considered to be well tolerated. Due to its weak anticoagulant effect, the SPC recommends that patients undergoing invasive procedures or having signs or symptoms of underlying coagulopathy or other increased risk of bleeding should be evaluated for haemorrhagic events. Rare cases of pigmentary maculopathy have been reported with use of pentosan polysulfate sodium, especially after long term use and the SPC recommends that patients should have regular ophthalmic examinations for early detection.[1, 2]

Summary of clinical effectiveness issues

Bladder pain syndrome is a chronic bladder condition which is characterised by pain associated with bladder filling, urinary urgency, frequency and nocturia and in some patients it is associated with inflammation, with Hunner's lesions and/or glomerulations present on cystoscopic examination or biopsy. The condition can undergo periods of exacerbation and remission and the severity of symptoms varies. In up to 50% of patients the symptoms of bladder pain syndrome will resolve themselves over time. There is no consensus on optimal treatment. Treatment aims to relieve symptoms and includes lifestyle changes, simple analgesia, the use of off-label medicines including medicines for neuropathic pain (amitriptyline, gabapentin, pregabalin), antihistamines (hydroxyzine) and immunosuppressants (azathioprine) and bladder instillations. Other invasive procedures, including major surgery are reserved for refractory patients. Pentosan polysulfate sodium was available as an unlicensed special for a number of years before it received marketing authorisation and is currently the only medicine specifically licensed for bladder pain syndrome.[2, 11, 12] Clinical experts consulted by SMC considered that pentosan polysulfate sodium fills an unmet need in this therapeutic area by providing a licensed treatment. Pentosan polysulfate sodium meets SMC orphan equivalent criteria.

There are no standardised outcomes for evaluating efficacy in patients with bladder pain syndrome and the EMA considered that the patient's global assessment or any impact of the disease are most relevant. Three of the four key studies used a primary outcome of overall global improvement (GRA) assessed by self-evaluation on reporting at least moderate improvement on individually defined, numerical rating scales. In two of these three studies, the proportions of patients who considered themselves to be GRA responders were significantly higher with pentosan polysulfate sodium compared with placebo.[2, 5, 6] A third study failed to meet its primary outcome but was a small and underpowered pilot study possibly confounded by concomitant anti-histamine use. A fourth key study only assessed symptoms individually and did not measure overall improvement, although this was later calculated to use in the meta-analysis.[3 4]

The results of the meta-analysis of the four pivotal studies found a treatment benefit in GRA response of 17% compared with the placebo groups. The EMA notes that in the context of unmet need, with no medicine licensed for this indication, this response rate is clinically relevant in the target population in which efficacy was significantly demonstrated.[2]

There are a number of limitations with the available evidence, including the age of the four key studies which were performed >10 years ago and are based on relatively old methodological standard requirements and small patient numbers. There were also recruitment problems since pentosan polysulfate sodium was available for use outwith the clinical trial setting. These factors limit the robustness of the evidence. In addition the inclusion criteria of the studies varied and efficacy was assessed by individually defined methods at different time-points. The study results were inconsistent and this may limit the appropriateness of the meta-analysis.[2] However an assessment of heterogeneity between studies indicated that this was low.

The four key studies ranged in duration from 3 to 6 months and this is relatively short for treatment of a chronic condition. There was a notable GRA response to placebo in each of the key studies (13% to 18%) which may be higher than expected in clinical practice. This may be a result of the subjective nature of the assessment of efficacy.

The results of this meta-analysis may limit the validity of the indirect comparison with chondroitin bladder instillation (Uracyst®). There were also differences between the two studies which were included in the Uracyst® meta-analysis and its results may be limited.[9, 10] There were notable differences between the control groups (oral placebo in the pentosan polysulfate sodium studies and placebo bladder instillation in the Uracyst® studies) and the response rates for placebo bladder instillation were higher than for oral placebo. There were also differences between the patients enrolled in the pentosan polysulfate sodium studies and the Uracyst® studies, the latter enrolling a broader patient population without the need for presence of glomerulations or Hunner's lesions. There were also differences between the durations of the pentosan polysulfate sodium and Uracyst® studies and outcomes were assessed at different time-points. The submitting company stated that the indirect comparison used Bucher methods in the base case but do not provide any relative risks for pentosan polysulfate sodium compared with Uracyst®. Results of response rates from a Bayesian NMA were used in a sensitivity analysis as part of the economic analysis. However a relative treatment effect for pentosan polysulfate sodium versus Uracyst® of 0.73 (95% credible interval: 0.38 to 1.30) was estimated from the NMA, suggesting no evidence of a difference.

The introduction of pentosan polysulfate sodium would offer patients the first licensed medicine for the treatment of bladder pain syndrome with glomerulations and/or Hunner's lesions. Since it is administered orally, pentosan polysulfate sodium may offer an advantage in convenience over intravesical treatment with bladder instillations.

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of pentosan polysulfate sodium, as an orphan-equivalent medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Bladder pain syndrome with glomerulations or Hunner's lesions is an incurable condition resulting in severe pain and urinary frequency. These symptoms affect all aspects of a patient's life and may have a significant impact of their physical and mental health.

- There are currently limited options for this difficult to treat condition and response to treatments is very variable in this heterogeneous patient population.

- Pentosan polysulfate sodium is the only oral medicine licensed for this condition which acts to repair the inflamed bladder lining. It offers an alternative treatment for patients for whom catheterisation and bladder instillations is not possible.

- Pentosan polysulfate sodium increases the treatment choice for patients and its oral administration offers convenience and reduces the risks and costs associated with bladder instillations.

- A patient responding to pentosan polysulfate sodium could have a significant improvement in quality of life by returning to normal daily activities and work, family and personal relationships, and improving sleep.

Additional Patient and Carer Involvement

We received patient group submission from Bladder Health UK, which is a registered charity. Bladder Health UK has received 30% pharmaceutical company funding in the past two years, including from the submitting company. A representative from Bladder Health UK participated in the PACE meeting. The key points of their submission has been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis comparing pentosan polysulfate sodium to bladder instillations for the treatment of adult patients with interstitial cystitis/bladder pain syndrome with glomerulations and/or Hunner's lesions. The company also provided a comparison with best supportive care (BSC) in those patients considered inappropriate for, or who cannot tolerate, bladder instillations and this was presented as a scenario analysis. SMC clinical expert feedback stated that a range of treatments including oral agents, bladder instillations, and surgery are used, but expects pentosan polysulfate sodium to be used following failure to oral agents, suggesting bladder instillations is likely to be an appropriate comparator.

The economic analysis used a discrete event simulation model with four key events: first-line treatment response, treatment discontinuation, subsequent lines of therapies, death. Response was based on the GRA at 6 months, with treatment discontinued if a non-responder with use of subsequent therapies. The average age of the patients in the model was 45.6 years based on one of the pentosan polysulfate sodium clinical studies, and a 20 year time horizon was adopted in the base case.[3]

The clinical evidence is based on an indirect comparison of GRA defined response outcomes from a meta-analysis of four clinical studies for pentosan polysulfate sodium versus placebo, and two clinical studies for Uracyst® (considered a representative bladder instillation for efficacy) versus placebo. The estimated response rates from these meta-analyses of 33% and 22% for pentosan polysulfate sodium and bladder instillations respectively, representing risk ratios of 2.09 (95% CI:

1.47-2.97) and 1.39 (95% CI: 0.89-2.17) respectively, were applied in the model to represent response rates for each treatment at 6 months. For the comparison with BSC the placebo arms from the meta-analysis of the four pentosan polysulfate sodium studies were used as a proxy for the response rates of BSC, estimated as 15.8%. A scenario analysis was also provided using the Bayesian NMA as described above.

Beyond 6 months for patients who respond to initial treatment time to treatment discontinuation for pentosan polysulfate sodium patients was estimated by fitting a parametric function to patient data from a US observational study on long run pentosan polysulfate sodium use.[13] The exponential function was selected for the base case based on clinical plausibility, which produced an estimated mean treatment duration of 11.25 years. It was assumed bladder instillations would have the same discontinuation rate as pentosan polysulfate sodium. After discontinuation of pentosan polysulfate sodium or the initial bladder instillation, patients were assumed to receive further bladder instillations as subsequent therapies for the duration of the model time horizon. Mortality in the economic analysis was based on general Scottish population life expectancy tables.

Utilities were estimated for pre-response baseline, response and non-response based on a UK study of bladder pain syndrome patients with or without bladder instillations in the previous 6 months which provided data in order to map the IC symptom Index (ICSI) score to the EQ- 5D-5L. ICSI scores for responders and non-responders were estimated from one of the pentosan polysulfate sodium clinical studies, but as the ICSI score was not available by response status in this study, the categorisation of response was derived by assuming a statistical relationship between GRA and ICSI. This mapping exercise resulted in utility values which were higher for patients treated with pentosan polysulfate sodium. Following the New Drugs Committee (NDC) meeting, the company provided a revised base case in which no difference in responder utilities for pentosan polysulfate sodium and bladder installations was assumed and this is reflected in the base case results below. Disutilities and costs for adverse events were not included in the economic analysis.

Medicine acquisition costs, costs associated with bladder administration, treatment-specific event costs, subsequent treatment, and surgery costs (in a scenario analysis) have been included in the model. The cost associated with sodium hyaluronate (Cystistat®, Hyacyst®) have been included in the base case, which seems reasonable as representative of the cost of bladder instillation. Costs by ICSI score for each of the events (pre-response assessment, responders, non-responders, subsequent treatments) stratified by treatment, were estimated using resource use data from the survey of UK BPS patients.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland.

With the PAS, pentosan polysulfate sodium was the dominant treatment compared to bladder instillation (cheaper, more effective).

In one-way sensitivity analysis the incremental cost-effectiveness ratio (ICER) was most sensitive to variation in responder utility (Table 1). In addition, there was some sensitivity to the cost of bladder instillation administration, the frequency of bladder instillation application, the response rate for pentosan polysulfate sodium, and the inclusion of two further pentosan polysulfate sodium studies in the meta-analysis conducted in a wider bladder pain syndrome patient population than the licensed indication. The results were not highly sensitive to varying the time horizon, applying response check at 3 months, use of Interstitial Cystitis Problem Index estimated utilities, the use of alternative extrapolated estimates of time to treatment discontinuation, or the inclusion of surgery in 2% of patients as part of subsequent therapies.

Table 1: Selected sensitivity and scenario analysis results at PAS price

	Scenario analysis	**ICER**
1	PPS versus BSC	£24,082
2	Incorporating Bayesian NMA	Dominant
3	Responder utility [PPS, BI, BSC] (+/-10% from base)	Dominant
4	PPS response reduced to 0.25	Dominant
5	Response rate for PPS including 2 wider population clinical trials	Dominant
6	Frequency BI administrations (post first month) set to 6 weeks (base-case is 4 weeks)	£22,849
7	Using least expensive product for BI (subsequent treatment)	Dominant
8	Increasing/reducing BI administration cost by +/-25%	Dominant - £5,278
9	20% shorter time to bladder instillation discontinuation	Dominant
10	20% shorter time to bladder instillation discontinuation followed by BSC	£82,717

BI = bladder instillations, BSC = best supportive care, ICER = incremental cost-effectiveness ratio, ICPI = Interstitial Cystitis Problem Index, PPS = pentosan polysulfate sodium, QALY = quality adjusted life year

The economic analysis was associated with several limitations and uncertainties:

- There are weaknesses in the pentosan polysulfate sodium and bladder instillation meta-analyses as described in the summary of clinical effectiveness issues section. There was a lack of formal indirect treatment comparison in the original submission, but the company helpfully used the results of the Bayesian NMA in the economic analysis (Table 1 scenario 2). However, the relative treatment effect of pentosan polysulfate sodium versus bladder instillation from the NMA is 0.73 but with credible intervals that cross one (of 0.38 – 1.30). As such, there is some uncertainty with the predicted benefits of treatment.
- There are concerns over the long-run extrapolation of treatment benefit for pentosan polysulfate sodium and bladder instillations which is based on a pentosan polysulfate sodium usage study conducted in the USA over 20 years ago, so relevance to Scottish practice isuncertain.[13] Also, an assumption of same time to discontinuation for bladder instillations as pentosan polysulfate sodium with subsequent therapies seems implausible. This consisted of a continual cycling through further bladder instillations, incurring a relatively low utility and the cost of bladder instillations, when the alternative in the model could be a switch to best supportive care with no additional cost, The company was requested to provide a scenario analysis assuming a 20% shorter time to bladder instillation

discontinuation than pentosan polysulfate sodium followed by BSC, resulting in an increased ICER (see table 1 scenario 10), although this scenario is uncertain as this does not account for potential use of BSC in the pentosan polysulfate sodium treatment pathway. SMC clinical experts gave mixed views on the treatment pathway post bladder instillations and thus the likely impact on cost-effectiveness is not clear.

- As noted above, there are potential limitations with the mapping study used to estimate utilities for the model events, and as such the company revised the base case analysis to remove an advantage in utility scores that the mapping had produced for responders to pentosan polysulfate sodium. There could be a patient disutility associated with use of bladder instillations relative to PPS although the level of this disutility is uncertain.
- The ICER versus BSC for patients who are considered inappropriate for bladder instillation is sensitive to the response rate assumed for placebo in the meta-analyses, the utility for BSC and an assumption that the efficacy of BSC wanes after one year (increases the ICER if this assumption is relaxed). However, BSC alone is not considered a major comparator to pentosan polysulfate sodium.

The Committee also considered the benefits of pentosan polysulfate sodium in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for replacing an unlicensed treatment was satisfied. In addition, as pentosan polysulfate sodium is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted pentosan polysulfate sodium for use in NHSScotland.

*Other data were also assessed but remain confidential.**

Additional information: guidelines and protocols

The European Association of Urology (EAU) published guidelines on “Chronic Pelvic Pain” in March 2018. This recommends multimodal behavioural, physical and psychological techniques alongside oral or invasive treatments for bladder pain syndrome. It recommends:

- dietary advice
- oral amitriptyline, or oral pentosan polysulphate and oral pentosane polysulphate plus subcutaneous heparin in low responders to pentosan polysulphate alone
- intravesical lidocaine plus sodium bicarbonate or intravesical pentosane polysulphate alone or combined with oral pentosan polysulphate or intravesical hyaluronic acid, chondroitin sulphate or heparin alone or in combination prior to more invasive methods
- neuromodulation before more invasive interventions
- intravesical bladder wall and trigonal injection of botulinum toxin type A if intravesical instillation therapies have failed

- submucosal injection of botulinum toxin type A (plus hydrodistension if intravesical instillation therapies have failed
- transurethral resection (or coagulation or laser) of bladder lesions, but in bladder pain syndrome type 3 C only
- only undertake ablative organ surgery as the last resort and only by experienced and bladder pain syndrome-knowledgeable surgeons[12]

The Royal College of Obstetricians and Gynaecologists (RCOG) and the British Society of Urogynaecology (BSUG) published guidelines "Management of Bladder Pain Syndrome" in December 2016. This recommends conservative treatments of considering dietary modification and avoidance of caffeine, alcohol, and acidic foods and drinks; stress management and regular exercise; analgesia for the symptom of pelvic or bladder pain. When first-line conservative treatments have failed, oral amitriptyline or cimetidine may be considered (cimetidine is not licensed to treat bladder pain syndrome and should only be commenced by a clinician specialised to treat this condition). Intravesical treatments may be added or substituted using an individualised approach if conservative and oral treatments have been unsuccessful. Intravesical treatment options include lidocaine, hyaluronic acid, botulinum toxin A, dimethyl sulfoxide, heparin, chondroitin sulphate. Nerve stimulation, oral ciclosporin, cystoscopy, laser treatment and transurethral resection of lesions may be considered by multi-disciplinary teams. Major surgery may be considered as a last-line treatment in refractory patients. This guideline does not recommend the use of oral hydroxyzine and oral pentosan polysulfate which do not appear to be effective treatments.[14] This guideline predates the marketing authorisation for pentosan polysulfate sodium but would have had available evidence.

Additional information: comparators

There are no other medicines licensed for the treatment of bladder pain syndrome. Current comparators are off-label use of amitriptyline and anticonvulsants for neuropathic pain and bladder instillation which are classified as medical devices.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
Pentosan polysulfate sodium	**100mg orally three times daily**	**5,460**
Sodium hyaluronate bladder irrigation (Cystistat®)	50ml once weekly for 4 weeks then monthly until symptoms resolve	1,568
Sodium hyaluronate, sodium chondroitin sulfate, calcium	50ml once weekly for 4 weeks, then every 2 weeks for 4 weeks then monthly until symptoms resolve	1,496

chloride bladder irrigation (iAluRil®)		
Sodium hyaluronate bladder irrigation (Hyacyst®)	50ml once weekly for 4 to 6 weeks then monthly until symptoms resolve	1,120
Chondroitin sulfate bladder irrigation (Gepan®)	40ml once weekly for 4 to 6 weeks then monthly until symptoms resolve	1,088

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eMIMS online on 3 June 2019. Other bladder instillations are available but those above are included in eMIMS. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 521 eligible patients for treatment with PPS in year 1, rising to 634 patients treated in year 5 to which confidential estimates of treatment uptake were applied.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 12 July 2019.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for

comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.