

**NIHR Innovation Observatory  
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**Pentosan polysulfate sodium (Elmiron) for bladder  
pain syndrome (interstitial cystitis)**

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**LAY SUMMARY**

Bladder pain syndrome (also known as interstitial cystitis) is a chronic inflammation of the bladder lining. The main symptoms are urinary frequency and urgency, and pain in the pelvis. Bladder pain syndrome affects 400,000 people in the UK, 90% of whom are women. The average age of people affected by the condition is 40 years old. Treatments for bladder pain syndrome are generally aimed at controlling the symptoms, as there is no cure for the condition. Lifestyle changes such as avoiding certain foods and drinks, reducing stress and stopping smoking may help to reduce symptoms. Antihistamine tablets may be prescribed to reduce the inflammation, and painkillers can also be taken. Some medicines can be passed directly into the bladder through a catheter to relieve symptoms.

Pentosan polysulfate sodium is the only oral medication that has been developed for bladder pain syndrome. As well as relieving pain and urgency, it is also thought to help to repair the bladder lining. The drug is taken as oral capsules three times a day. If this medicine is launched in the UK, it will offer an additional treatment option for patients with painful bladder syndrome.

*This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.*

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## TARGET GROUP

Bladder pain syndrome characterised by either glomerulations or Hunner's lesions in adults with moderate to severe pain, urgency and frequency of micturition<sup>1</sup> – first line

## TECHNOLOGY

### DESCRIPTION

Pentosan polysulfate sodium (Elmiron) is a low molecular weight heparin-like compound. It has anticoagulant and fibrinolytic effects.<sup>2</sup> The cause of bladder pain syndrome is not known and may be multifactorial, but one theory is that patients have a defect in the glycosaminoglycan component of the lining of the bladder epithelium, leading to urine leaking through, activation of mast cells, and bladder inflammation. Pentosan is thought to replace a damaged glycosaminoglycan layer in the bladder<sup>3</sup> and to show an anti-inflammatory activity by having an inhibitory effect on mast cell release of histamine.<sup>4</sup>

Pentosan polysulfate sodium is available as 100mg capsules, and the recommended dose is one capsule taken three times a day. Patients should be assessed every six months and treatment should be stopped if no improvement is seen. In responders treatment should be continued chronically as long as the response is maintained.<sup>1</sup>

Pentosan polysulfate sodium is currently unlicensed in the UK but is licensed in USA and other countries in capsule form for treatment of bladder pain syndrome.<sup>5</sup>

Pentosan polysulfate sodium is licensed in the EU in gel form for treatment of thrombophlebitis, contusions and varicose veins.<sup>6</sup>

## INNOVATION and/or ADVANTAGES

Many medicines have been tried in bladder pain syndrome to reduce symptoms and improve quality of life (e.g. hydroxyzine, amitriptyline), but pentosan polysulfate sodium is the only oral treatment licensed for this condition (although not in the UK).<sup>3</sup> The benefits of pentosan polysulfate sodium are its ability to relieve pain and urgency as well as to improve overall symptoms of the disease.<sup>1</sup>

If licensed in the UK, pentosan polysulfate sodium will offer an additional treatment option for patients with bladder pain syndrome.

## DEVELOPER

bene-Arzneimittel GmbH

## AVAILABILITY, LAUNCH or MARKETING

Pentosan polysulfate sodium was designated an orphan drug in USA in August 1985, and was approved for bladder pain syndrome in October 1996.<sup>5</sup>

Pentosan polysulfate sodium was designated an orphan drug in the EU in January 2015. It was withdrawn from the Community register of orphan medicinal products in May 2017 upon request of the marketing authorisation holder at the time of the granting of a marketing authorisation.<sup>1</sup>

The European Medicines Agency (EMA) granted a Marketing Authorisation to the company for pentosan polysulfate sodium to be used in the treatment of bladder pain syndrome in June 2017.<sup>1</sup> The company has not yet indicated a date for UK launch.

## PATIENT GROUP

### BACKGROUND

Bladder pain syndrome (also known as interstitial cystitis) is a chronic inflammation of the bladder wall,<sup>7</sup> characterised by symptoms of urinary urgency and frequency with pelvic pain but in the absence of infection or other obvious pathology. The exact cause of the condition is not known but diagnosis is made by exclusion of other causes of bladder pain.<sup>8</sup> Bladder pain syndrome can have a significant impact on quality of life, affecting the ability to work, exercise and have a social life. Severe sufferers can find themselves virtually housebound, which can lead to other problems such as social isolation and depression. Severe tiredness can also occur if the sufferer has to get up repeatedly during the night.<sup>7</sup>

## CLINICAL NEED and BURDEN OF DISEASE

Bladder pain syndrome affects 400,000 people in the UK, 90% of whom are women. The average age of people affected by bladder pain syndrome is 40 years old.<sup>9</sup>

In England in 2015/16 there were 8,542 hospital admissions with primary diagnosis ICD-10 code N30.1 (chronic interstitial cystitis), and 905 finished consultant episode bed days. Most admissions were day cases.<sup>10</sup>

The population likely to be eligible to receive pentosan polysulfate sodium could not be estimated from available published sources.

## PATIENT PATHWAY

### RELEVANT GUIDANCE

#### NICE GUIDANCE

- NICE evidence summary. Interstitial cystitis: oral pentosan polysulfate sodium (ESUOM43). April 2015.

- NICE evidence summary. Interstitial cystitis: dimethyl sulfoxide bladder instillation (ESUOM26). February 2014.

## NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Specialised Pain (Adult). D08/S/a.

## OTHER GUIDANCE

- European Association of Urology. Chronic Pelvic Pain Guideline. 2017.<sup>11</sup>
- Royal College of Obstetricians and Gynaecologists. Management of Bladder Pain Syndrome (Green-top Guideline No. 70). December 2016.
- UK Medicines Information. Oral Pentosan for Painful Bladder Syndrome/Interstitial Cystitis: Unlicensed and Off-label Medicines Reports Number 2. February 2011.

## CURRENT TREATMENT OPTIONS

Initial management of bladder pain syndrome is conservative, including dietary modification, stress management, stopping smoking and analgesia. UK guidelines recommend that oral amitriptyline or cimetidine may be considered when first-line conservative treatments have failed. Compliance with amitriptyline is often affected by the adverse effects, which include dry mouth, constipation, sedation, weight gain and blurred vision. Cimetidine is not licensed to treat bladder pain syndrome, but may be commenced by a clinician specialised in treating the condition.<sup>8</sup>

If conservative and oral treatments are unsuccessful, other therapies may be added or substituted using an individualised approach. These will depend on the experience and expertise of the clinical team involved, and access to chronic pain management specialists may be appropriate. Options include:

- Intravesical lidocaine
- Intravesical hyaluronic acid
- Intravesical injection of botulinum toxin A (Botox)
- Intravesical dimethyl sulfoxide (DMSO)
- Intravesical heparin
- Intravesical chondroitin sulfate<sup>8</sup>

Further options, which should only be considered after referral to a pain clinic and discussion with a multidisciplinary team meeting, include:

- Cystoscopic fulguration and laser treatment, and transurethral resection of lesions
- Posterior tibial or sacral neuromodulation
- Oral cyclosporin A
- Cystoscopy with or without hydrodistension
- Major surgery<sup>8</sup>

## EFFICACY and SAFETY

<b>Trial</b>	NCT00086684; pentosan polysulfate sodium vs placebo; phase IV trial
<b>Sponsor</b>	Johnson & Johnson Pharmaceutical Research & Development
<b>Status</b>	Published
<b>Source of Information</b>	Publication <sup>12</sup> , trial registry <sup>13</sup>
<b>Location</b>	USA, Canada
<b>Design</b>	Randomised, placebo-controlled
<b>Participants</b>	n=369; aged 18yrs and older; interstitial cystitis
<b>Schedule</b>	Randomised into three arms: Arm I: one 100mg pentosan polysulfate sodium capsule in the morning, and one matching placebo capsule in the afternoon and evening for 24 wks. Arm II: one 100mg pentosan polysulfate sodium capsule three times a day for 24 wks. Arm III: one placebo capsule three times a day for 24 wks.
<b>Follow-up</b>	Active treatment for 24 wks. Follow-up not stated.
<b>Primary Outcomes</b>	Number of responders defined as having at least a 30% reduction in the O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI) from baseline to study endpoint (Wk 24).
<b>Secondary Outcomes</b>	Number of responders defined as having at least a four point reduction in ICSI from baseline to study endpoint (Wk 24).
<b>Key Results</b>	No statistically significant difference between the pentosan polysulfate sodium group and the placebo group or between the two pentosan polysulfate sodium groups for the primary endpoint.
<b>Adverse effects (AEs)</b>	The most common treatment emergent adverse events were bladder pain, nausea, headache and exacerbation of interstitial cystitis symptoms. Most adverse events were rated as moderate in intensity.
<b>Expected reporting date</b>	—

## ESTIMATED COST and IMPACT

### COST

The cost of pentosan polysulfate sodium is not yet known. However, a NICE evidence summary presented the following table of estimated costs of alternative oral treatment options for treating interstitial cystitis.<sup>2</sup>

	Usual dose	Estimated cost for 30 days treatment (excluding VAT)
Pentosan polysulfate sodium	100mg 3 times daily	£374.40
Amitriptyline	10mg to 150mg once a day	£1.13 to £3.70
Cimetidine	400mg twice a day	£1.82
Ciclosporin	100mg twice a day	£145.14

A report by UK Medicines Information stated that oral pentosan at a dose of 100mg three times a day would cost £1,800 per patient per year (excluding VAT).<sup>3</sup>

### IMPACT – SPECULATIVE

#### IMPACT ON PATIENTS AND CARERS

- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- Other
- No impact identified

#### IMPACT ON HEALTH and SOCIAL CARE SERVICES

- Increased use of existing services
- Decreased use of existing services
- Re-organisation of existing services
- Need for new services
- Other
- None identified

#### IMPACT ON COSTS and OTHER RESOURCE USE

- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs
- Other reduction in costs

Other

None identified

## OTHER ISSUES

Clinical uncertainty or other research question identified

None identified

## REFERENCES

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- <sup>2</sup> National Institute for Health and Care Excellence. *Interstitial cystitis: oral pentosan polysulfate sodium (ESUOM43)*. April 2015. Available from: <https://www.nice.org.uk/advice/esuom43/chapter/Key-points-from-the-evidence> [Accessed 29 August 2017]
- <sup>3</sup> UK Medicines Information. *Oral Pentosan for Painful Bladder Syndrome/Interstitial Cystitis. Unlicensed and Off-label Medicines Report Number 2*. February 2011. Available from: [http://www.medicinesresources.nhs.uk/upload/pentosan%20review\\_final.pdf](http://www.medicinesresources.nhs.uk/upload/pentosan%20review_final.pdf) [Accessed 29 August 2017]
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- <sup>10</sup> NHS Digital. *Hospital Admitted Patient Care Activity, 2015-16*. Available from: <http://www.content.digital.nhs.uk/catalogue/PUB22378> [Accessed 29 August 2017]

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<sup>11</sup> European Association of Urology. *Chronic Pelvic Pain*. Available from: <http://uroweb.org/guideline/chronic-pelvic-pain/> [Accessed 29 August 2017]

<sup>12</sup> Nickel JC, Herschorn S, Whitmore KE et al. Pentosan Polysulfate Sodium for Treatment of Interstitial Cystitis/Bladder Pain Syndrome: Insights from a Randomized, Double-Blind, Placebo Controlled Study. *The Journal of Urology*. 2015; 193(3): 857-862

<sup>13</sup> Clinical Trials.gov. *Effectiveness and Safety Study of Pentosan Polysulfate Sodium for the Treatment of Interstitial Cystitis: NCT00086684*. Available from: <https://clinicaltrials.gov/ct2/show/results/NCT00086684> [Accessed 29 August 2017]