Oral Pentosan for Painful Bladder Syndrome/Interstitial Cystitis

*Unlicensed and Off-label Medicines Report Number 2. February 2011*
1.0 Summary for Patients

- Pentosan polysulfate sodium (or pentosan) is a medicine used to treat painful bladder syndrome/interstitial cystitis (known as PBS/IC). If successful, it reduces the pain and stops people wanting to pass water so often.

- Before taking medicines for IC, patients can try changes to their diet, pelvic floor relaxation exercises, or regular painkillers.

- No single treatment helps everyone with IC. To find relief, people may need to try several options. Sometimes combinations of treatments may be needed.

- Some studies of patients taking pentosan have shown it works in some people. It can cause mild side effects such as stomach upsets and headaches.

- It can take several months for pentosan to work fully, so it is important to keep taking the capsules even if they don't work straight away.

- Pentosan capsules should be swallowed with a glass of water at least one hour before a meal, or two hours afterwards.

- Patients with IC may find joining a support group helpful. One to try is The Cystitis and Overactive Bladder Foundation (http://www.cobfoundation.org/).

1.1 Summary for Healthcare Professionals

- Painful bladder syndrome/interstitial cystitis (PBS/IC) is characterised by remissions and exacerbations, which makes it difficult to assess the real impact of any treatment. There is also a lack of consensus on diagnosis.

- It has been suggested that oral medicines, such as pentosan, should be second line options for the management of this condition, after interventions such as dietary manipulation, non-prescription analgesics and pelvic floor relaxation exercises [1].

- Although older studies of pentosan, mainly from the 1980s, showed clear benefit against placebo, newer studies with active comparators have shown less benefit. It is difficult to quantify these benefits because the studies are small and have used different endpoints and methodologies. However, the overall trend in results is for some symptomatic improvement. It may take several months for full benefits to be seen, so patients taking pentosan need to persevere with treatment.

- Common adverse events seen in trials have included gastro-intestinal disturbances, headache and rash.

- Although severity of disease is ill-defined, there is little published information on the management of mild disease. It is unlikely that any single treatment will improve symptoms in all patients and they may have to try several options or combinations before benefit is seen [2].

- Oral pentosan at a dose of 100mg three times a day costs £1,800 per patient per year (excluding VAT).
The figure below highlights the balance of risks, benefits, evidence, costs and regulatory position for this intervention:

The data in the diagram above is taken from assessment against the standard options below:

<table>
<thead>
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<tbody>
<tr>
<td><strong>Health benefits</strong></td>
<td>Minor symptom control, or potential but unproven patient benefit</td>
<td>Symptom control, improved health related quality of life (HRQoL)</td>
<td>Major HRQoL gain e.g. months of life gained</td>
<td>Transforming HRQoL e.g. years of life gained</td>
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<tr>
<td><strong>Safety</strong></td>
<td>Early death or substantial morbidity</td>
<td>Severe side effects affecting HRQoL</td>
<td>Moderate side effects</td>
<td>Minor side effects</td>
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<tr>
<td><strong>Strength of evidence</strong></td>
<td>Speculative approach</td>
<td>Single case or small case series, uncontrolled studies</td>
<td>Small controlled studies</td>
<td>At least one large RCT</td>
</tr>
<tr>
<td><strong>Regulatory status</strong></td>
<td>No UK licensed product. No licence globally</td>
<td>No UK licensed product. Licensed products exist in USA/Europe but not necessarily for this intervention</td>
<td>UK licensed product. Intervention off-label in UK, and in USA/Europe</td>
<td>UK licensed product. Intervention off-label in UK but licensed in USA/Europe</td>
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<tr>
<td><strong>Affordability</strong></td>
<td>Very significant costs above current best care option</td>
<td>Increased costs above current best care option</td>
<td>Modest increased costs or cost neutral</td>
<td>Cost saving compared with current best option</td>
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2.0 Intervention

Pentosan polysulfate sodium (referred to as pentosan) is a carbohydrate derivative with some heparin-like effects [3]. For the treatment of interstitial cystitis (IC) pentosan is taken as 100mg capsules three times a day, one hour before or two hours after meals.

IC is a chronic condition, characterised by symptoms of urinary urgency and frequency with pelvic pain but in the absence of infection or other obvious pathology [1]. It is more common in women. Estimates of incidence vary between different surveys, for example between 1.6 and 158 per 100,000 women [4].

The cause of IC 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 [1,5]. Pentosan is thought to replace the glycosaminoglycan.

It has been suggested that oral medicines, such as pentosan, should be second line options for the management of this condition, after interventions such as dietary manipulation, non-prescription analgesics and pelvic floor relaxation exercises [1]. Many medicines have been tried in IC to reduce symptoms and improve quality of life (e.g. hydroxyzine, amitriptyline), but pentosan is the only oral treatment licensed for this condition, although not in the UK. Patients with IC may find joining a support group helpful.

3.0 Review of Data Available

Most trials of oral pentosan have included adult patients, mainly women, which corresponds to the population affected by IC. Trials of pentosan as single therapy have not produced consistent results. Further details are shown below.

3.1 Benefits

Meta-Analysis and Systematic Review
A meta-analysis of older studies included four prospective, randomised, placebo-controlled trials of pentosan used for 3 to 4 months in a total of 448 patients with IC (searches performed up to June 1994) [6]. Pentosan was found to be more effective than placebo for pain, frequency and urgency. The effect on nocturia was not statistically significant, but only one small study assessed this outcome. A Number Needed to Treat (NNT) of 7 was calculated in the paper for pentosan for treating bladder pain, and an NNT of 6 for frequency.

A systematic review of randomised, double-blind, controlled trials of pharmacological treatments for IC/painful bladder syndrome included 1,470 patients from 21 trials (papers up to 2007) [4]. There were sufficient data from trials of oral pentosan to pool results. Combining the results from five trials (the four included in the meta-analysis above, plus one further study of 6 months duration) gave a relative risk of 1.78 for overall patient-rated improvement compared with placebo (95% confidence interval [CI] 1.34 to 2.35).
Randomised, controlled studies
Oral plus intravesical pentosan was compared to oral pentosan plus intravesical placebo in a randomised, double-blind trial lasting 18 weeks [7]. Twenty women were allocated to combination treatment and 20 to oral plus intravesical placebo, but it is not clear whether there was concealed allocation to treatment. One patient discontinued therapy in the combination group for a reason unrelated to treatment. She was replaced in the trial, so the combination group included 21 patients in the intention-to-treat (ITT) analysis. Patients had been diagnosed with IC within a year of the start of the trial, had moderate to severe IC and had not been previously treated with pentosan. Patients in the combination group had a median age of 36.9 years and those in the oral pentosan group 38.7 years. The primary endpoint was change from baseline to weeks 6, 12 and 18 in the O’Leary-Sant IC Symptom and Problem Index, which is a 36-point scale. Last observation carried forward (LOCF) was used to impute missing data. Improvements in median O’Leary-Sant scores in the combination group were -7, -12 and -12 at weeks 6, 12 and 18 respectively. In the oral pentosan group the scores were -4, -5.5 and -8, respectively. The authors concluded that combination therapy was more effective than oral pentosan (P =0.04 at week 18), but also noted that oral pentosan alone led to significant improvement over baseline (P <0.05).

A double-blind, randomised, pilot trial compared pentosan alone, hydroxyzine plus pentosan, hydroxyzine alone, and placebo over 24 weeks [8]. Patients (mean age 45 years) had moderate symptoms of urinary frequency with pain and discomfort. The primary outcome was change in participant-reported global response assessment from baseline to week 24 using ITT analysis. A total of 20/59 (34%) of patients who received pentosan were reported to be responders compared to 18% (11/62) of patients who did not receive pentosan, but this was not statistically significant (P =0.064). The combined treatment of pentosan plus hydroxyzine gave the highest response rates: 40% compared to 28% on pentosan alone or 23% on hydroxyzine alone.

Randomised, uncontrolled study
A dose-ranging trial of the currently recommended dose and two higher doses was carried out to study the onset of effect and dose-response of oral pentosan [9]. The trial was randomised and double-blind but, if they concealed allocation the method was not stated in the paper. A total of 128 patients received pentosan 100mg three times a day, 125 took 200mg three times a day, and 127 received 300mg three times a day for 32 weeks. Patients (mean age 44 years) mainly had moderate to severe symptoms and about 70% had received at least one other medication before the trial. The primary endpoint was improvement in O’Leary-Sant IC Symptom Index. LOCF was used to deal with missing data and a modified ITT analysis was used (all patients who received at least one dose of study medication). Only 60.5% of patients completed the study. All doses of pentosan improved mean O’Leary-Sant scores from baseline to week 32 by around 3 points. This was a statistically significant improvement compared to baseline (P <0.001), but increasing the dose did not produce greater or faster improvement. Patients’ ratings of symptoms improved from about 18% of patients reporting a 50 to 100% improvement at week 4 to 48% of patients at week 32.

Open-label study
Pentosan was compared to ciclosporin in a randomised, open-label trial with concealed allocation [10]. 64 patients were treated with pentosan 100mg three times a day or ciclosporin 3mg/kg in two divided doses for six months. Patients had previously been treated with other options and had a mean age of 58 years. Patients in the ciclosporin group were voiding urine on average 16.7 times in 24 hours at baseline (standard deviation [SD] 4.4) and the pentosan patients 19.1 times (SD 8.4). The primary outcome was reduction by half in micturition frequency per 24 hours. This was achieved by 34% of patients on ciclosporin but no patients on pentosan (P <0.001), analysed using ITT.
Summary

Studies of pentosan included in the meta-analysis and systematic review showed clear benefit against placebo [4,6]. However, studies with active comparators have shown less benefit [7-10].

3.2 Strength of Evidence

Few medicines for IC have been tested in randomised, double-blind, controlled trials of sufficient duration and numbers of patients. Generally IC is a condition characterised by remissions and exacerbations, which make assessment of therapeutic impact difficult [11]. In addition, a lack of consensus with regard to diagnosis of IC and the use of several different endpoints, make it difficult to compare treatments across studies [12]. The validated O’Leary-Sant IC Symptom Index [13], one of the tools used in trials, assesses patients’ perceptions of frequency, urge, pain and nocturia [14].

Most of the studies identified for this review have design flaws or have involved only small numbers of patients. Results cannot be extrapolated to the care of patients with mild IC because this population has not generally been studied in trials.

The meta-analysis identified 10 studies of pentosan. Six were rejected, including 4 which were not randomised, placebo-controlled trials [6]. The 4 studies included data from 1987 to 1993. One limitation may be use of older methodology than modern trials. They were also short-term.

The systematic review included the same trials as the meta-analysis but also a 6-month trial from 2003 [4]. Both reviews suggest that oral pentosan is statistically more effective than placebo.

The conclusions that can be drawn from the study involving oral and intravesical pentosan are limited due to the small numbers of patients involved [7].

In the pilot study with hydroxyzine, the power calculation estimated that 136 patients would be necessary to show a difference in response rates [8]. Despite recruitment being extended and relaxing of the exclusion criteria to allow patients who had previously used study medicines, only 121 patients were enrolled. Therefore the trial was underpowered. Including patients part-way through the trial who had prior usage of study medicines may have biased results. A linked editorial contends that the population studied may not be representative of patients seen in usual clinical practice [15].

The results from the dose ranging study are limited by the fact that the trial did not include a placebo arm, although it is known that IC is subject to remissions and exacerbations [11]. The study was underpowered because only 60.5% of patients completed it [9]. Although the results were statistically significant for changes in O’Leary-Sant scores, the mean changes were small.

In the pentosan versus ciclosporin trial, participants, clinicians and assessors were not blind to treatment allocation, which could bias the results of the study [10].

3.3 Risks

US prescribing information describes pentosan as a weak anticoagulant and use may be associated with bleeding from the rectum, nose and gums or under the skin [16]. Patients on concomitant anticoagulants, heparin, fibrinolytic drugs such as streptokinase, aspirin, or non-steroidal anti-inflammatory drugs should be assessed for bleeding [16]. Commonly seen adverse events (with a frequency of about 3 to 4%) include diarrhoea, nausea, headache and rash. Cases of alopecia, limited to a single area of the scalp, have also been reported [16].
Pentosan should be used with caution in patients with hepatic insufficiency, aneurysms, thrombocytopenia, haemophilia, gastro-intestinal ulceration, polyps or diverticula [16].

Adverse events in the dose-ranging study included diarrhoea, headache, nausea and rectal bleeding [9]. Side effects, mainly diarrhoea and abdominal pain, were the commonest reason for patients withdrawing from this study (22.4% of those withdrawing). A dose-response effect was seen for some adverse events, so it is prudent to avoid doses in excess of that recommended since higher doses did not show greater efficacy.

### 3.4 Regulatory Status

Oral pentosan is available as a licensed product to treat IC in some countries including the US, Australia and Canada [17]. It is not licensed for use in the UK, but may be imported.

### 3.5 Affordability

Oral pentosan at a dose of 100mg three times a day costs £1,800 per patient per year (excluding VAT) [18]. There are no other significant costs associated with oral pentosan treatment. No published health economics data were identified during this review.
4.0 References

18. Personal Communication. Idis World Medicines. 22/12/10
5.0 Quality Assurance

5.1 Author
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6.0 Appendix

6.1 Search strategy
The following strategy was used to find the evidence contained in this report:

- Medline (1950 to November 2010): pentosan (exp) and interstitial cystitis (exp); limit to Humans and English language.
- Embase (1980 to November 2010): pentosan (exp) and interstitial cystitis (exp); limit to humans and English language.
- Citations review for all papers retrieved via Embase and Medline.
- CRD Databases: pentosan.
- No UK-based manufacturer/promoter, so not sent to pharmaceutical industry for comment.

6.2 Data selection

Reasons for excluding papers

<table>
<thead>
<tr>
<th>Studies identified through Medline</th>
<th>n=12</th>
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<tr>
<td>Studies identified through Embase</td>
<td>n=18</td>
</tr>
<tr>
<td>Studies identified through other sources</td>
<td>n=1</td>
</tr>
</tbody>
</table>

Studies identified through more than one source removed from count
n=13

Studies screened
n=13

Studies excluded n=7 because:
- not randomised (n=3)
- retrospective analysis of previous study data (n=2)
- retrospective chart review (n=1)
- longitudinal, not parallel-group study (n=1)

Studies included
n=6
6.3 Acknowledgements
None.

6.4 Declarations of Interest
None declared from all those participating in the creation of this review.

6.5 Disclaimer
This review relates solely to the medicine and clinical intervention described within the text and reflects UK practice. Should you have any doubts about whether it is relevant to a specific patient, or are unsure whether you understand it, seek appropriate professional assistance.

The contents were believed to be an accurate reflection of the medical literature at the time of preparation. However, you should always consult the literature and take account of new developments.

The authors are not responsible for the content of external websites and any links are made available solely to indicate their potential usefulness. You must use your judgement to determine the accuracy and relevance of the information they contain.