Evidence Review for Prescribing Clinical Network

Treatment: Pentosan polysulfate sodium (or pentosan)

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Topic Submitted by: Linda Honey

Date: 7.6.13

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Summary page

- How strong is the evidence for claimed efficacy?
  Grade A

- Potential advantages in terms of: efficacy, compliance, pharmacokinetics, drug interactions and adverse effects?
  It is unlikely that any single treatment will improve symptoms in all patients with interstitial cystitis and they may have to try several options or combinations before benefit is seen. Pentosan offers another option.

- Is there a clear place in therapy / treatment pathway?
  (E.g. patient type / characteristics, and relationship to other therapies)
  Yes, recommended in European Association of Urology Guidelines 2012.

- Is monitoring for efficacy required?
  Yes - it may take several months for full benefits to be seen, so patients taking pentosan need to persevere with treatment. In addition, the clinical value and risks of continued treatment in patients whose pain has not improved by 6 months is not known.

- Is monitoring for toxicity required?
  No

- Is dose titration required?
  No

- Traffic light status (i.e. who will prescribe the drug and any restrictions required)?
  Red or Amber*
• **Role of the specialist (if applicable)?**
  If Red - initiating and continued clinical responsibility.
  If Amber* - initiating, stabilising patient and handing over to primary care.

• **Role of GP (if applicable)?**
  If Amber* - accepting clinical responsibility, prescribing, monitoring effect and stopping if not effective.

• **Financial implications:**

  **Estimated cost or saving per 100,000 population:**
  There are an estimated 400,000 people in the UK with IC but the proportion of patients prescribed pentosan or the length of treatment is not known. The cost of Elmiron® 100mg capsules from Australia is currently £2,439.66 per patient per year.

  If an arbitrary assumption is made that 1% of patients with IC are prescribed pentosan, then the cost per 100,000 population per year is £15,467.

• **Other issues:**
  Pentosan is not licensed in the UK and is available from specialist importers from countries such as US, Australia and Canada on a named-patient basis.

• **National Guidance available:**
  The European Association of Urology (EAU) prepared the Guidelines for Chronic Pelvic Pain 2012.

  **Recommendations:**
  Studies of pentosan included in the meta-analysis and systematic review showed clear benefit against placebo.

  The EAU Guidelines for Chronic Pelvic Pain awarded oral pentosan a Grade A recommendation in the standard treatment of BPS.

  **Options for PCN consideration:**
  1. **Red: not routinely recommended for prescribing in primary care - unlicensed.**
  2. **Amber*: for initiation by specialist and subsequent transfer to primary care when the patient is stable.
  3. **Black: not supported.**

• **Questions:**

  **Urologists:**
  1. How many patients would require treatment with pentosan each year?
  2. Describe the current treatment pathway and where pentosan is used.
**Trust Pharmacy:**

1. What is the price of pentosan in secondary care?

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**VERSION CONTROL SHEET**

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1. Purpose of the Review

Pentosan polysulfate sodium (pentosan) is a semi-synthetically produced heparin-like macro molecular carbohydrate derivative. It is available under the brand name of Elmiron® in the USA by Ortho-McNeil-Janssen Pharmaceuticals Inc and in other countries such as Australia and Canada. Elmiron® is the only oral medication that is FDA approved for the relief of bladder pain or discomfort associated with interstitial cystitis.2

Elmiron® does not have a marketing authorisation in the UK.3 It is only available in the UK on a named-patient basis through specialist importers.

Local decision makers must consider the appropriate prescribing status for pentosan.

2. Appropriateness

2.1 The patient:

Elmiron® is indicated for the relief of bladder pain or discomfort associated with interstitial cystitis in adult patients. Safety and effectiveness in paediatric patients below the age of 16 years have not been established.1

2.2 The problem:

Definition:
Interstitial cystitis (IC) is a chronic bladder condition characterised by urinary urgency, urinary frequency, dysuria, pelvic pain and pressure in the bladder and pelvis, in the absence of bacterial infection or other definable pathologies.2,4

Synonyms: interstitial cystitis/painful bladder syndrome (IC/PBS), painful bladder syndrome (PBS), bladder pain syndrome (BPS), hypersensitive bladder syndrome.4

Effects and prognosis:
The prognosis is very variable and ranges from complete resolution of symptoms within months, a waxing and waning course, completely asymptomatic with intermittent flares or a chronically progressive course of increasing symptoms over several years.

Some patients do recover spontaneously and some may have the condition for many years and there may be spontaneous resolution only to return days or months later.4

IC can have a significant and even profound effect on quality of life. The initial symptoms of urinary urgency, urinary frequency and mild pain are common to other disease states which may lead to numerous consultations and misdiagnosis. Over time, IC can become debilitating as the patient is voiding up to several times an hour
in order to relieve the pain. This can have severe limitations on the patient’s lifestyle, professional life and self-esteem.

**Epidemiology:**
The exact prevalence is unknown because of misdiagnosis but there is an estimated 400,000 people in the UK with IC of whom 80% are female and 10% are male.

**Etiology:**
The cause of the condition is unknown and there is no one treatment that helps everybody.

**Diagnosis:**
The diagnosis of IC is usually based on typical symptoms and the exclusion of other causes such as overactive bladder, endometriosis, urinary tract infection and prostatitis which complicate the differential diagnosis.

**Tests:**
- Urinalysis and midstream urine for urine cultures to rule out urinary tract infection, including tuberculosis.
- Cervical swabs for herpes and chlamydia.
- Urodynamic studies: there are no specific findings but pain with bladder filling that reproduces the symptoms is very supportive of a diagnosis of IC.
- Most cases need cystoscopy to exclude bladder cancer. Hunner's ulcers (large areas of mucosal inflammation and damage) may be seen but are uncommon.
- Biopsies of the bladder wall do not show signs of infection.
- Men should have urethral swabs and prostatic secretion cultures (for chronic prostatitis).

**Assessment Tools**
Clinicians and researchers use a variety of questionnaires to evaluate the severity of patients’ symptoms and assess their progress. Some are also used to help screen patients for possible IC, although none is appropriate for diagnosis.

These tools include:

- Global Response Assessment (GRA)
- O'Leary-Sant Symptom and Problem Indexes
- Pelvic Pain and Urgency/Frequency Patient Symptom Scale (PUF questionnaire)
- NIH-Chronic Prostatitis Symptom Index (NIH-CPSI)

**2.3 The intervention:**
Pentosan is a semi-synthetically produced heparin-like macromolecular carbohydrate derivative, which chemically and structurally resembles glycosaminoglycans.

**How does it work:**
Pentosan is a low molecular weight heparin-like compound. It has anticoagulant and fibrinolytic effects with 1/15 the activity of heparin. The mechanism of action in IC is
unknown. In preliminary clinical models, pentosan adhered to the bladder wall mucosal membrane. The drug may act as a buffer to control cell permeability preventing irritating solutes in the urine from reaching the cells.¹,²

**Care setting:**
Primary and/or secondary care.

**Frequency:**
The recommended oral dose of pentosan is 300mg/day, taken as one 100 mg capsule three times daily. The capsules should be taken with water at least 1 hour before meals or 2 hours after meals.¹

Patients should be reassessed after 3 months. If improvement has not occurred and if limiting adverse events are not present, it may be continued for another 3 months.¹

Pentosan may take up to 6 months to be fully effective.

The clinical value and risks of continued treatment in patients whose pain has not improved by 6 months is not known.¹

**2.4 Alternative treatments:**

**Nondrug:**
- Behavioural therapy: biofeedback, pelvic floor exercises and bladder training programmes may be effective.
- Diet: there is no evidence for specific dietary measures but alcohol, tomatoes, spices, chocolate, caffeinated and citrus drinks and acidic foods may contribute to bladder irritation and inflammation.
- Some people report a reduction in symptoms following distension of the bladder during diagnostic cystoscopy. There is belief that distending the bladder causes the nerve cells to be stretched and thus less sensitive for a time.
- Transcutaneous electrical nerve stimulation (TENS) helps in conjunction with other therapies.

**Drugs:**
- Ibuprofen and tricyclic antidepressants may be beneficial for pain relief.
- The anti-histamine, hydroxyzine can improve nocturia.
- In highly motivated chronic sufferers, self-catheterisation and therapeutic dimethyl sulfoxide (DMSO) is instilled into the bladder, retained for fifteen minutes and then voided. Treatments are repeated every two weeks for 8-week cycles and may help to reduce frequency and urgency.
- H2-receptor antagonists such as cimetidine have been found to help in some 60-70% of cases but the mechanism of action remains uncertain.
- In the severest of cases, strong opiates are needed for pain relief. Again, because of the chronic nature of the problem, the lowest dose possible in conjunction with other therapies is advisable.
- Anticholinergic agents (e.g. oxybutynin, tolterodine) reduce urinary frequency but can impair bladder emptying and so exacerbate pelvic pain. They should therefore be used with caution in patients with interstitial cystitis.
- Some women improve on the oral contraceptive pill.

**Surgical:**
- Sacral nerve stimulation (neuromodulation) has been shown to be effective in patients with refractory IC.
- Urinary diversion may be resorted to in refractory cases but results are poor.

### 3. Effectiveness

#### 3.1 Expected benefits
An improvement or resolution of the symptoms of IC and enhanced quality of life.

#### 3.2 Is there a plausible biological basis for effectiveness?
Most literature supports the belief that the symptoms of IC are associated with abnormal permeability of the epithelium in the lower urinary tract. Normally, the bladder epithelium is coated with a protective mucin layer that contains glycosaminoglycan (GAG). Disruption of this normally impermeable structure allows penetration of the underlying urothelium by potentially caustic agents in the urine, thereby affecting nerves and muscles in the bladder wall. This process of nerve and muscle irritation will lead to the IC symptoms of urgency, frequency and pain. The cause of initial injury to the GAG layer is unknown.\(^5\)

Although the mechanism of action is unknown, pentosan is believed to facilitate the restoration of the defective layer, thereby preventing further injury.\(^5\)

#### 3.3 Side-effects/complications:
The most common side effects are hair loss, diarrhoea, nausea, blood in the stool, headache, rash, upset stomach, abnormal liver function tests, dizziness and bruising.\(^1\)

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.

Patients on concomitant anticoagulants, heparin, fibrinolytic drugs such as streptokinase, aspirin, or non-steroidal anti-inflammatory drugs should be assessed for bleeding.

Pentosan should be used with caution in patients with hepatic insufficiency, aneurysms, thrombocytopenia, haemophilia, gastro-intestinal ulceration, polyps or diverticula.\(^8\)

#### 3.4 Review of evidence
(See Appendix 1. for Search Strategy and Summary of Results)
(See Appendix 2. for hierarchy of evidence quality)

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.\(^8\)

**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). 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/PBS included 1,470 patients from 21 trials (papers up to 2007). 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. 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. 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. 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. 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.

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. 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. The validated O’Leary-Sant IC Symptom Index, one of the tools used in trials, assesses patients’ perceptions of frequency, urge, pain and nocturia.

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. 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. 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.

In the pilot study with hydroxyzine, the power calculation estimated that 136 patients would be necessary to show a difference in response rates. 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.

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. The study was underpowered because only 60.5% of patients completed it. 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.

4. Summary of Key Points for Consideration

4.1 National guidance:
The European Association of Urology (EAU) prepared the Guidelines for Chronic Pelvic Pain 2012 in which they stated that the EAU, the International Society for the study of BPS (ESSIC), the International Association for the Study of Pain (IASP) and several other groups now prefer the term bladder pain syndrome (BPS) to embrace all patients suffering from bladder pain while assuming IC with Hunner’s lesion, as a specific type of chronic inflammation of the bladder.9

Their conclusions and recommendations for the treatment of BPS in relation to pentosan are:

<table>
<thead>
<tr>
<th>Conclusions: treatment of BPS</th>
<th>LE</th>
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<tbody>
<tr>
<td>Oral pentosanpolysulphate sodium is effective in pain and related symptoms of BPS.</td>
<td>1a</td>
</tr>
<tr>
<td>Oral pentosanpolysulphate sodium plus subcutaneous heparin is effective in pain and related symptoms of BPS especially in patients initially low responders to pentosanpolysulphate sodium alone.</td>
<td>1b</td>
</tr>
<tr>
<td>Global response on cyclosporin A was superior to pentosanpolysulphate sodium, but associated with more adverse effects.</td>
<td>1b</td>
</tr>
<tr>
<td>Intravesical pentosanpolysulphate sodium is effective based on limited data and may enhance effect of oral treatment.</td>
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### Recommendations

<table>
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<th>Recommendations</th>
<th>Grade</th>
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<tbody>
<tr>
<td>Multimodal behavioural, physical and psychological techniques should always be considered alongside oral or invasive treatments for BPS.</td>
<td>A</td>
</tr>
<tr>
<td>Oral pentosanpolysulphate sodium is recommended for use in BPS.</td>
<td>A</td>
</tr>
<tr>
<td>Treatment with oral pentosanpolysulphate sodium plus subcutaneous heparin is recommended especially in low responders to pentosanpolysulphate sodium alone.</td>
<td>A</td>
</tr>
<tr>
<td>Consider intravesical pentosanpolysulphate sodium before more invasive treatment alone or combined with oral pentosanpolysulphate sodium.</td>
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</table>

### 4.2 Efficacy
Studies of pentosan included in the meta-analysis and systematic review showed clear benefit against placebo. However, studies with active comparators have shown less benefit.⁸

### 4.3 Potential Benefits over existing therapy
Patients often require different options and combinations for effective treatment.

### 4.4 Potential disadvantages
Pentosan is not licensed in the UK and is available from specialist importers from countries such as US, Australia and Canada on a named-patient basis. Prices fluctuate: the price from Australia is currently £222.80 excluding VAT for 100 capsules of Elmiron® 100mg but due to recent supply problems in Australia, the specialist importer obtained stocks from the US at a price of £422.90 excluding VAT for the same product.

### 4.5 Budgetary Impact

#### 4.5.1 Cost:
At the time of writing this review, the cost of oral pentosan is £2,439.66 per patient per year excluding VAT in community pharmacy.¹⁰

#### 4.5.2 Precedent setting:
The exact prevalence is unknown but there is an estimated 400,000 people in the UK with IC/PBS of whom 80% are female and 10% are male.⁶
Patients often try several different options and combinations before benefit is seen so it is difficult to establish the exact number of patients on pentosan.

5. **Conclusions and Recommendations**

Studies of pentosan included in the meta-analysis and systematic review showed clear benefit against placebo. The EAU Guidelines for Chronic Pelvic Pain awarded oral pentosan a Grade A recommendation in the standard treatment of BPS.

Options for PCN consideration:

1. **Red**: not routinely recommended for prescribing in primary care - unlicensed.
2. **Amber**: for initiation by specialist and subsequent transfer to primary care when the patient is stable.
3. **Black**: not supported.
Appendix 1: Evidence search

Search terms used:

<table>
<thead>
<tr>
<th>Resource</th>
<th>Used in this review?</th>
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<td>National Library for Health (NLH) NHS Evidence</td>
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<td><a href="https://www.evidence.nhs.uk/nhs-evidence-content/journals-and-databases">https://www.evidence.nhs.uk/nhs-evidence-content/journals-and-databases</a></td>
<td></td>
</tr>
<tr>
<td>A gateway site with access to other resources such as Reviews (Bandolier, Cochrane, CRD etc), Guidelines (e.g. NICE), Clinical Knowledge Summaries (CKS) and Journals including AMED, British Nursing Index, CINAHL, E-books, EMBASE, HMIC, MEDLINE, My Journals, PsycINFO, PubMed, Databases from Dialog.</td>
<td>✓</td>
</tr>
<tr>
<td>National Institute of Health and Clinical Excellence (NICE)</td>
<td>✓</td>
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<tr>
<td><a href="http://www.nice.org.uk/">http://www.nice.org.uk/</a></td>
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<tr>
<td>NICE produces national guidance in three areas of health:</td>
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<tr>
<td>1. Public health - guidance on the promotion of good health and the prevention of ill health</td>
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<tr>
<td>2. Health technologies - guidance on the use of new and existing medicines, treatments and procedures within the NHS</td>
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<tr>
<td>3. Clinical practice - guidance on the appropriate treatment and care of people with specific diseases and conditions within the NHS.</td>
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<tr>
<td>Bandolier</td>
<td>✓</td>
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<tr>
<td><a href="http://www.medicine.ox.ac.uk/bandolier/index.html">http://www.medicine.ox.ac.uk/bandolier/index.html</a></td>
<td></td>
</tr>
<tr>
<td>Bandolier is a website about the use of evidence in health, healthcare, and medicine. Information comes from systematic reviews, meta-analyses, randomised trials, and from high quality observational studies.</td>
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<tr>
<td>Centre for Reviews and Dissemination</td>
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<tr>
<td><a href="http://www.york.ac.uk/inst/crd/">http://www.york.ac.uk/inst/crd/</a></td>
<td></td>
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<tr>
<td>CRD undertakes high quality systematic reviews that evaluate the effects of health and social care interventions and the delivery and organisation of health care. Databases maintained by CRD include Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED), Health Technology Assessment (HTA) Database</td>
<td>✓</td>
</tr>
<tr>
<td>Scottish Intercollegiate Guidelines Network (SIGN)</td>
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</table>
The principal role of the Medical Services Advisory Committee (MSAC) is to advise the Australian Minister for Health and Ageing on evidence relating to the safety, effectiveness and cost-effectiveness of new medical technologies and procedures.

The Canadian Agency for Drugs and Technologies in Health (CADTH) is a national body that provides Canada’s federal, provincial and territorial health care decision makers with credible, impartial advice and evidence-based information about the effectiveness and efficiency of drugs and other health technologies.

Evidence retrieved

Guidelines:
The European Association of Urology (EAU) prepared the Guidelines for Chronic Pelvic Pain 2012.

Appendix 2: Grading of evidence

- Ia: systematic review or meta-analysis of randomised controlled trials

Appendix 3: References


4. Patient.co.uk [Internet]. UK: Egton Medical Information Systems Limited; [updated 20.4.10, cited 5.6.13]. Available at: http://www.patient.co.uk/doctor/Interstitial-Cystitis.htm


8 NHS Evidence [Internet]. UK: UKMi; Oral Pentosan for Painful Bladder Syndrome/Interstitial Cystitis; 2011 February [cited 6.6.13]. Available at: https://www.evidence.nhs.uk/search?q=pentosan

9 NHS Evidence [Internet]. UK: European Association of Urology; Guidelines on Chronic Pelvic Pain; 2012 [cited 6.6.13]. Available at: https://www.evidence.nhs.uk/search?q=pentosan

10 Personal communication IDIS 6.6.13