

Evidence on Therapeutic Uses of Pentosan Polysulfate Sodium

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FDA Labelled Indication: **Interstitial cystitis, chronic, relief of bladder pain or discomfort**

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1) Overview

FDA Approval: Adult, yes; Pediatric, yes (16 yr and older)

Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIa; Pediatric, Class IIa

Strength of Evidence: Adult, Category B; Pediatric, Category B

2) Summary

Indicated for symptomatic relief of interstitial cystitis (Prod Info ELMIRON(R) oral capsules, 2006).

Treatment with oral **pentosan** polysulfate sodium at daily doses of 300, 600, and 900 milligrams led to similar clinical responses in the symptomatic treatment of chronic interstitial cystitis in a randomized, double-blind, parallel-group, multicenter, dose-ranging study (n=380); notably, the study was underpowered due to high discontinuation rates (Nickel et al, 2005). Combination therapy with subcutaneous low-dose heparin and oral **pentosan** polysulfate sodium (PPS) was safe and led to a significant improvement in overall patient well-being compared to PPS therapy alone in patients with interstitial cystitis in an open-label, prospective, controlled study (n=58) (vanOphoven et al, 2005)

3) Effectiveness

a) In a randomized, double-blind, parallel-group, multicenter, dose-ranging study (n=380), treatment with oral **pentosan** polysulfate sodium (PPS) at daily doses of 300, 600, and 900 milligrams (mg) led to similar clinical responses in the symptomatic treatment of chronic interstitial cystitis; however, the study was underpowered due to high discontinuation rates.

The study included adults (mean age, 44.2 years; 90% female) diagnosed with IC for 6 months or longer and randomized them to receive, in a double-

dummy fashion, either 100 mg, 200 mg, or 300 mg of PPS orally three times daily for 32 weeks. Patients using antihistamines and antidepressants at baseline were allowed to continue them during the study; however, initiation of these agents during the study was not allowed. The primary endpoint measure was the O'Leary-Sant IC Symptoms Index (ICSI), which is a four-item, validated questionnaire yielding scores ranging from 0-6 (mild symptoms), 7-14 (moderate symptoms), and 15-20 (severe symptoms). The secondary endpoint measure was the Patient's Overall Rating of Symptoms Index (PORIS), which assessed the overall change in IC, pain, and urgency with treatment and rated it as worse, no better (0% improvement), slightly improved (25%), moderately improved (50%), greatly improved (75%), or symptoms gone (100%). Patients achieving 50% to 100% improvement were considered to be responders.

At baseline, the mean duration of IC since diagnosis was 11 months, and mild, moderate, and severe symptoms were reported by 3.2%, 34.6%, and 62.2% of patients, respectively. With only 230 patients completing the 32-week study (39.5% attrition rate), the study was underpowered for clinical outcomes. While the overall rate of treatment discontinuation was not dose-related, the 900-mg dose group had the highest proportion of patients (30.7%) discontinuing due to adverse events (versus 18% and 16.8% for the 300 and 600 mg/day groups, respectively; p less than 0.05).

An intent-to-treat analysis revealed a significant improvement of mean ICSI scores from baseline (11.2, 11.9, and 11.9) to endpoint (8.2, 8.1, and 8.6) for all dosages (300-, 600-, and 900-mg, respectively), with improvements occurring as early as 4 weeks after therapy initiation. However, the difference between the groups was not statistically significant for ICSI scores as well as time to response. At study end, the proportion of patients reporting severe symptoms had decreased to 15.7%, with 27.5% and 56.9% of patients reporting mild and moderate symptoms, respectively. At week 32, 49.6%, 49.6%, and 45.2% of patients in the 300, 600, and 900 mg/day groups, respectively, were classified as responders based on PORIS scores, and the ICSI results correlated well with the PORIS scores.

Adverse events were mostly mild and transient, with diarrhea (25.3%), headache (18.2%), nausea (15%), pelvic pain (12.9%), and abdominal pain (12.6%) being the most common. Diarrhea as well as rectal bleeding (4% to 14%; mostly mild) were dose-related (p less than 0.001 and $p=0.02$, respectively). Mild alopecia occurred in 5.5% of patients, with 3 patients discontinuing treatment due to alopecia. There were no serious treatment-emergent adverse events during the study (Nickel et al, 2005).

b) A meta-analysis of 4 clinical studies reported that **pentosan**, in a minimum dose of 300 milligrams/day, is significantly more effective than placebo for relieving the following symptoms of interstitial cystitis: pain ($p=0.507$), urgency ($p=0.799$), and frequency ($p=0.680$). Results for nocturia were not significant. The overall success rates for **pentosan** for the relief of pain, urgency, and frequency were 37%, 28%, and 54%, respectively. Only 2 of the studies included in the meta-analysis specified the severity of disease in the subjects and the authors of the meta-analysis suggested that future studies stratify results by disease severity (Hwang et al, 1997).

c) Available studies were unable to clearly identify which patients, regardless of method of diagnosis, were most likely to respond to **pentosan** polysulfate. Stratification of patients based on initial cystoscopic findings has suggested that a decrease in micturition frequency and possibly an increase in the mean volume per void per 24 hours can be expected in patients without bladder ulceration, but not in those with ulceration (who also had smaller bladder volumes). Improvements in pain were similar in each group (Fritjofsson et al, 1987a). Further studies employing this type of stratification are needed to confirm these findings. With regard to symptoms, pain appears to respond best to **pentosan** polysulfate, whereas daytime urinary frequency is affected least (Parsons et al, 1983; Mulholland et al, 1990b; Parsons & Mulholland, 1987b).

d) Early conflicting results regarding clinical improvement with **pentosan** polysulfate (or inconsistent improvement among various parameters) were undoubtedly related to lack of a uniform definition for the disease, and resultant inconsistent diagnostic criteria for patient inclusion. Varying criteria for the diagnosis of interstitial cystitis have been employed in available studies, based on pathologic and/or clinical findings (Hanno & Wein, 1987). In one study reporting no improvement of clinical symptoms (Holm-Bentzen et al, 1987b), the pathological anatomical criterion for interstitial cystitis was the presence of more than 28 mast cells/millimeter². However, a significant improvement in cystoscopic bladder appearance and bladder capacity during anesthesia was reported in **pentosan** polysulfate-treated patients with verified disease after 4 months of treatment. In other investigations, patients were considered to have interstitial cystitis based on a variety of criteria, including clinical symptoms (eg, pain, nocturia, frequency) with or without the presence of petechial hemorrhages or ulcers or gross blood in the fluid return on cystoscopic examination (Fritjofsson et al, 1987a; Mulholland et al, 1990b). Without a clear definition for patient selection, differing results of therapy can be expected. Other factors may also explain inconsistent responses, including the dose of the drug, the significant placebo effect observed in some studies, differing methods of response evaluation, and the spontaneously fluctuating nature of the disease. Up to 11% of patients may experience a spontaneous remission of up to 6 months (Hanno & Wein, 1987).

e) In several studies, some degree of clinical benefit was maintained with continuous **pentosan** polysulfate therapy for up to 2 years (Parsons et al, 1983; Parsons & Mulholland, 1987b; Mulholland et al, 1990b). Lowering of the dose by less than 50% (to less than 100 or 150 milligrams daily) in responding patients was associated with recurrent symptoms in 1 study (Parsons et al, 1983), suggesting the need for continuous therapy to sustain improvement. However, another study reported stable improvement for 3 months after discontinuation of **pentosan** polysulfate (Fritjofsson et al, 1987a). Additional studies are necessary to determine if stabilization can be maintained after therapy is completed.

4) Adverse Reactions

Oedema

a) PERIPHERAL OEDEMA, occasionally requiring discontinuation of therapy, has been reported during oral **pentosan** polysulfate therapy (Fritjofsson et al, 1987; Holm-Bentzen et al, 1987a). This complication was observed in approximately 5% of interstitial cystitis patients in 1 study (Holm-Bentzen et al, 1987a).

Dermatologic Effects

a) SKIN RASHES have occurred in some patients treated with oral **pentosan** polysulfate (Parsons & Mulholland, 1987a; Holm-Bentzen et al, 1987a).

b) ALOPECIA has been reported at an incidence of 4%; the vast majority of cases were limited to just a single area on the scalp. Loss of hair may be noticed as soon as 4 weeks after the initiation of therapy (Prod Info Elmiron(R), 1996).

Gastrointestinal Effects

a) Incidence: 4%

b) Diarrhea or LOOSE STOOLS have been described during oral **pentosan** polysulfate therapy (Wedren, 1987a; Fritjofsson et al, 1987). In 1 series of 87 patients with interstitial cystitis, diarrhea occurred in 6 (7%) (Fritjofsson et al, 1987). Diarrhea has occasionally resulted in discontinuation of therapy (Wedren, 1987a).

c) Gastrointestinal symptoms associated with oral **pentosan** polysulfate therapy include NAUSEA, INDIGESTION, and nonspecific GASTROINTESTINAL DISTRESS (Mulholland et al, 1990a; Holm-Bentzen et al, 1987a; Fritjofsson et al, 1987). The incidences of these side effects range from 2% to 4% (Prod Info Elmiron(R), 1996).

d) Proctitis, described as RECTAL ULCERATION, was the dose-limiting toxicity in a dose-escalating study (n=21) of oral **pentosan** polysulfate in the treatment of cancer. Doses studied were 180, 270, and 400 milligrams/square meter (mg/m²) three times a day. Development of symptoms was dose-related, ie, symptoms developed more quickly in patients at higher doses than in those taking lower doses. However, clinical or endoscopic examination revealed the condition in all patients. Discontinuation of the drug was the only effective remedy and, in patients rechallenged with **pentosan** polysulfate, symptoms returned within a week. Marginal benefits were achieved with corticosteroid enemas but symptoms were not completely alleviated (Marshall et al, 1997).

Haematologic Effects

a) THROMBOCYTOPENIA (platelet count less than 100,000) and thrombosis have been reported in patients receiving **pentosan** polysulfate (Tardy-Poncet et al, 1994). The association between **pentosan** polysulfate and

thrombocytopenia has been supported by platelet aggregation and serotonin release tests. **Pentosan** polysulfate-induced thrombocytopenia has been reported at prophylactic and therapeutic doses and by intramuscular and subcutaneous routes of administration. Thrombocytopenia can occur between days 5 to 21 after **pentosan** polysulfate administration and platelet counts usually return to baseline within 4 days after discontinuation of the drug. However, the overall frequency of this adverse effect was less than 1% in clinical trials (Prod Info Elmiron(R), 1996). Heparin and low molecular weight heparin should not be used during the acute recovery phase if treating thrombosis, even if platelet aggregation studies do not cross-react, due to the low sensitivity of these tests.

b) THROMBOSIS of the superior sagittal sinus, attributed to HEPARIN-INDUCED THROMBOCYTOPENIA associated with **pentosan** therapy, was reported in a 35-year-old woman treated for interstitial cystitis with **pentosan** 100 mg three times a day. **Pentosan** therapy was discontinued after 3 weeks by a urologist who was sceptical of the initial diagnosis. Two days after discontinuation of **pentosan**, the patient was treated for severe headache, nausea and vomiting and, after a progression of symptoms, was admitted to the hospital 10 days later when the thrombosis was diagnosed with the aid of magnetic resonance imaging. The patient was treated with aspirin, dipyridamole, and slow anticoagulation with warfarin and the symptoms abated. The authors suggest that platelet counts should be monitored at the initiation of **pentosan** therapy and after 7, 10, and 14 days of treatment and that discontinuation of **pentosan** be considered if a 30% decrease occurs (Rice et al, 1998).

c) In clinical trials INCREASED PROTHROMBIN TIME, INCREASED PARTIAL THROMBOPLASTIN TIME, LEUKOPENIA, and ANEMIA have occurred at an incidence of less than 1%. It is unknown if the effects are directly attributable to pentostan polysulfate, or to other factors (Prod Info Elmiron(R), 1996).

Liver effects

a) Liver enzymes (aspartate aminotransferase and alanine aminotransferase) became elevated in 5 of 13 (4 grade II and 1 grade III) patients in a phase I clinical study on the use of continuous intravenous infusions of **pentosan** polysulfate sodium in the treatment of advanced metastatic malignancies (Lush et al, 1996).

b) Elevations in liver enzymes (aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase) have been reported in 1% to 4% of patients treated with oral **pentosan** polysulfate therapy (Prod Info Elmiron(R), 1996; Mulholland et al, 1990a; Fritjofsson et al, 1987).

Neurologic Effects

a) HEADACHE and DIZZINESS have been reported in 2% to 4% of interstitial cystitis patients treated with oral **pentosan** polysulfate (Mulholland et al,

1990a; Holm-Bentzen et al, 1987a). These symptoms have resulted in withdrawal of therapy in some patients (Holm-Bentzen et al, 1987a).

b) Severe MOOD SWINGS and SUICIDAL IDEATION each occurred in 1 of 54 patients (2%) treated with oral **pentosan** polysulfate in 1 study; however, these reactions might not be related to drug therapy. (Mulholland et al, 1990a).

Respiratory Effects

a) Prolongation of respiratory symptoms of influenza or the common cold was described in 4 of 24 patients with nonbacterial prostatitis during therapy with oral **pentosan** polysulfate (Wedren, 1987a).

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