

PRODUCT MONOGRAPH

Pr **ELMIRON**^{®*}

pentosan polysulfate sodium

Capsules 100 mg

Glycosaminoglycan Substitute

Janssen Inc.
19 Green Belt Drive
Toronto, Ontario
M3C 1L9

Date of Preparation:
September 28, 1998

Date of Revision:
October 1, 2020

www.janssen.com/canada

Submission Control No: 239842

*Registered trademark of IVAX Research, LLC. Used under license.

©2020 JANSSEN Inc.

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION.....	3
SUMMARY PRODUCT INFORMATION	3
INDICATIONS AND CLINICAL USE.....	3
CONTRAINDICATIONS	3
WARNINGS AND PRECAUTIONS.....	4
ADVERSE REACTIONS.....	6
DRUG INTERACTIONS	8
DOSAGE AND ADMINISTRATION.....	8
OVERDOSAGE	8
ACTION AND CLINICAL PHARMACOLOGY	10
STORAGE AND STABILITY.....	11
DOSAGE FORMS, COMPOSITION AND PACKAGING	11
PART II: SCIENTIFIC INFORMATION	12
PHARMACEUTICAL INFORMATION.....	12
CLINICAL TRIALS.....	12
DETAILED PHARMACOLOGY	13
TOXICOLOGY	14
REFERENCES	16
PART III: CONSUMER INFORMATION.....	19

Pr **ELMIRON®***

pentosan polysulfate sodium

Capsules 100 mg

Glycosaminoglycan Substitute

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	capsules 100 mg	<i>For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i>

INDICATIONS AND CLINICAL USE

ELMIRON® (pentosan polysulfate sodium) is indicated for the initial and maintenance treatment of interstitial cystitis.

Pediatrics (< 18 years of age):

Safety and effectiveness in children and adolescents below the age of 18 years have not been established.

CONTRAINDICATIONS

ELMIRON® is contraindicated in patients with a personal history of any macular pathology (see **WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions** and **Ophthalmologic**).

Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

ELMIRON[®] is contraindicated in patients with a personal history of any macular pathology. Cases of pigmentary maculopathy have been reported with long-term use of ELMIRON[®]. Baseline and regular retinal examinations are recommended for early detection of pigmentary maculopathy. The benefits and risks of treatment with ELMIRON[®] should be assessed periodically for each patient (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS, Ophthalmologic**).

General

ELMIRON[®] is a weak anticoagulant (only 1/15 the activity of heparin) and has been used in prevention of thrombotic disease.

Carcinogenesis and Mutagenesis

Long-term carcinogenicity studies in rats showed no evidence of carcinogenic potential at exposures up to 60 times the maximum recommended human dose (MRHD) on a mg/kg basis. In a 2-year carcinogenicity study in mice, there was an increase in hemangiosarcomas in male mice and hepatocellular neoplasms in male and female mice at a dose approximately 117 times the MRHD on a mg/kg basis. No mutagenic activity has been observed. See **TOXICOLOGY, Mutagenesis** and **Carcinogenesis** sections for discussion on animal data.

Hematologic

A small number of bleeding complications of ecchymosis, epistaxis, and gum hemorrhage have been reported (see **ADVERSE REACTIONS**). At a daily dose of 300 mg (n = 128), rectal hemorrhage was reported as an adverse event in 6.3% of patients.

Patients at increased hemorrhagic risk due to diseases such as ulcerative GI lesions, aneurysms, internal or external hemorrhoids, thrombocytopenia, hemophilia, polyps or diverticulae should also be evaluated carefully if they are to receive ELMIRON[®].

Hepatic

Pentosan polysulfate sodium is desulfated by both the liver and the spleen. The extent to which hepatic insufficiency or splenic disorders may increase the bioavailability of the parent or active metabolites of pentosan polysulfate sodium is not known. Caution should be exercised when using ELMIRON[®] in these patients.

Mildly (<2.5 x normal) elevated transaminase, alkaline phosphatase, γ -glutamyl transpeptidase, and lactic dehydrogenase occurred in 1.2% of patients. The increases usually appeared 3 to 12 months after the start of ELMIRON[®] therapy, and were not associated with jaundice or other clinical signs or symptoms. These abnormalities are usually transient, may remain essentially unchanged, or may rarely progress with continued use.

Ophthalmologic

Cases of pigmentary maculopathy have been reported with long-term use of ELMIRON[®] (see **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**). Although most of these cases occurred after 3 years of use or longer, cases have been seen with a shorter duration of use. While the etiology is unclear, cumulative dose appears to be a risk factor. Visual symptoms in these cases included difficulty reading, slow adjustment to low or reduced light environments, and blurred vision. The benefits and risks of treatment with ELMIRON[®] should be considered for all patients, may change over time, and should be assessed periodically for each patient. Detailed ophthalmologic history should be obtained in all patients prior to starting treatment with ELMIRON[®]. If there is a family history of hereditary macular pathology, genetic testing should be considered. For patients with pre-existing ophthalmologic conditions, a comprehensive baseline retinal exam (including color fundoscopic photography, ocular coherence tomography (OCT), and auto-fluorescence imaging) is recommended prior to starting therapy. For patients continuing with ELMIRON[®] therapy, it is recommended to perform baseline and periodic comprehensive retinal examinations (see above) and detailed ophthalmologic histories for early detection of pigmentary maculopathy. Patients should be informed that changes in vision should be reported and evaluated. If pigmentary maculopathy or other retinal changes are confirmed, risks and benefits of continuing treatment should be discussed including discontinuation of treatment, since these changes may be irreversible. Follow-up retinal examinations should be continued given that retinal and vision changes may progress even after cessation of treatment.

The benefit-risk profile of continued treatment with ELMIRON[®] in patients whose pain has not improved by 6 months is not known.

Peri-Operative Considerations

Patients undergoing invasive procedures, having signs or symptoms of underlying coagulopathy or who are otherwise at increased risk of bleeding (due to other therapies such as coumarin anticoagulants e.g. warfarin, heparin, tPA, streptokinase, high-dose aspirin, or nonsteroidal anti-inflammatories) should be evaluated for hemorrhagic risk.

Reproduction

Reproductive studies performed in the rat had no effect on fertility. The effect of pentosan polysulfate sodium on spermatogenesis has not been investigated. See **TOXICOLOGY, Teratology** section for discussion on animal data.

Laboratory Tests Findings

Pentosan polysulfate sodium inhibits the generation of factor Xa in plasma and inhibits thrombin-induced platelet aggregation in human platelet rich plasma ex-vivo.

Special Populations

Pregnant Women: There are no adequate and well-controlled studies in pregnant women. Therefore, this drug should be used during pregnancy only if the potential benefit clearly exceeds the potential risk.

Nursing Women: It is not known if ELMIRON[®] is excreted in human milk. Many drugs are excreted in human milk; therefore, caution should be exercised when ELMIRON[®] is administered to a nursing mother.

Pediatrics (< 18 years of age): Safety and effectiveness in children and adolescents below the age of 18 years have not been established. This drug should be kept out of the reach of children.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

ELMIRON® is usually well tolerated. Reported adverse reactions are infrequent and usually do not require discontinuation of treatment. The most common reactions are gastrointestinal, hematologic or dermatologic (see **WARNINGS AND PRECAUTIONS**). Adverse events reported are summarized in Table 1.1 and 1.2.

Table 1.1 Low Frequency (≤3%) Adverse Events Reported in Patients Treated with ELMIRON®

BODY SYSTEM	ADVERSE EVENT
Body as a Whole	Headache
Digestive	GI discomfort Diarrhea Nausea
Skin and Appendages	Alopecia Rash

Table 1.2 Uncommon (≤1%) Adverse Events Reported in Patients Treated with ELMIRON®

BODY SYSTEM	ADVERSE EVENT
Body as a Whole	Malaise Pelvic pain
Digestive	Liver function abnormalities Vomiting Mouth ulcer Colitis Esophagitis Gastritis
Hematologic	Anemia Ecchymosis Prothrombin decrease Thrombocytopenia Retinal hemorrhage
Hypersensitive Reactions	Allergic reaction Photosensitivity
Metabolic	Weight gain Weight loss Edema
Musculoskeletal	Myalgia Arthralgia
Neurologic	Dizziness Paresthesia Insomnia
Respiratory	Sinusitis
Skin and Appendages	Sweating
Urogenital	Urgency Urinary tract infection Urethritis

Rare events (single occurrence only in over 1,000 patients with interstitial cystitis): gastritis, leukopenia, depression, rhinitis, lacrimation, angina pectoris, chronic myelogenous leukemia, prostate cancer, loss of appetite, subarachnoid hemorrhage, epistaxis, gum hemorrhage, menorrhagia and hematuria.

Post-Market Adverse Drug Reactions

In post-market safety reports, adverse events of dyspnea, pruritus, urticaria and pigmentary maculopathy (see **WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions and Ophthalmologic**) have been reported with ELMIRON® use. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Rectal hemorrhage: ELMIRON[®] was evaluated in a randomized, double-blind, parallel-group, Phase 4 study conducted in 380 patients with interstitial cystitis dosed for 32 weeks. At a daily dose of 300 mg (n = 128), rectal hemorrhage was reported as an adverse event in 6.3% of patients. The severity of the events was described as “mild” in most patients. Patients in that study who were administered ELMIRON[®] 900 mg daily, a dose higher than the approved dose, experienced a higher incidence of rectal hemorrhage, 15%.

Liver Function Abnormality: A randomized, double-blind, parallel-group, Phase 2 study was conducted in 100 men (51 ELMIRON[®] and 49 placebo) dosed for 16 weeks. At a daily dose of 900 mg, a dose higher than the approved dose, elevated liver function tests were reported as an adverse event in 11.8% (n = 6) of ELMIRON[®] treated patients and 2% (n = 1) of placebo-treated patients.

DRUG INTERACTIONS

Drug-Drug Interactions

In a study in which healthy subjects (24 completed) received pentosan polysulfate sodium 100 mg or placebo every 8 hours for 7 days, and were titrated with warfarin to an INR of 1.4 to 1.8, the pharmacokinetic parameters of R-warfarin and S-warfarin were similar in the absence or presence of pentosan polysulfate sodium. Prothrombin time, partial thromboplastin time and INR for warfarin + placebo and warfarin + pentosan polysulfate sodium were comparable. See also **WARNINGS AND PRECAUTIONS, Peri-Operative Considerations**.

Drug interactions with other anticoagulant drugs have not been studied.

Care should be taken when administering ELMIRON[®] to patients receiving anticoagulant drugs such as warfarin, heparin, tPA, streptokinase, high-dose aspirin, and nonsteroidal anti-inflammatory drugs.

DOSAGE AND ADMINISTRATION

Dosing Considerations

The capsules should be taken with water at least 1 hour before meals or 2 hours after meals.

Recommended Dose

The recommended dose of ELMIRON[®] is 300 mg/day taken as one 100 mg capsule orally three times daily.

Some patients with interstitial cystitis may require 6 to 8 weeks of therapy with ELMIRON[®] to achieve relief of symptoms. Long-term continuation of ELMIRON[®] therapy is necessary for persistent therapeutic effect.

OVERDOSAGE

Overdose has not been reported. Based upon the pharmacodynamics of the drug, toxicity is likely to be reflected as anticoagulation, bleeding, thrombocytopenia, liver function abnormalities, and gastric distress. (See **ACTION AND CLINICAL PHARMACOLOGY** and

WARNINGS AND PRECAUTIONS sections). At a daily dose of 900 mg for 32 weeks (n = 127) in a clinical trial, rectal hemorrhage was reported as an adverse event in 15% of patients. At a daily dose of ELMIRON[®] 900 mg for 16 weeks in a clinical trial that enrolled 51 patients in the ELMIRON[®] group and 49 in the placebo group, elevated liver function tests were reported as an adverse event in 11.8% of patients in the ELMIRON[®] group and 2% of patients in the placebo group. In the event of acute overdose, the patient should be given gastric lavage if possible, carefully observed and given symptomatic and supportive treatment.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

ELMIRON[®] is orally bioavailable pentosan polysulfate sodium. Its mechanism of action is thought to be adherence to the bladder surface supplementing the defective natural glycosaminoglycan layer. It is hypothesized that this action ameliorates the symptoms of interstitial cystitis.

Pharmacodynamics

ELMIRON[®] is intended for the treatment of interstitial cystitis. In interstitial cystitis patients, a deficient or defective bladder protective glycosaminoglycan layer allows diffusion of irritating components in urine through to the underlying bladder wall. The resultant inflammatory response in the bladder wall produces the symptoms of interstitial cystitis. Definitive proof for this is not available.

In addition to its action as a glycosaminoglycan replacement in the bladder, pentosan polysulfate sodium has weak anticoagulant effect, fibrinolytic effect, a lipolytic effect and anti-inflammatory actions.

Absorption

In a clinical pharmacology study in which healthy female volunteers received a single oral 300 mg or 450 mg dose of pentosan polysulfate sodium containing radiolabeled drug under fasted conditions, mean maximal levels of plasma radioactivity were seen approximately 2 hours after dosing. Based on urinary excretion of radioactivity, a mean of approximately 6% of a radiolabeled oral dose of pentosan polysulfate sodium is absorbed and reaches the systemic circulation. In clinical trials, ELMIRON[®] was administered with water 1 hour before or 2 hours after meals; the effect of food on absorption of pentosan polysulfate sodium is not known.

Distribution

Parenteral radiolabelled studies in animals indicate significant distribution to the uroepithelium of the genitourinary tract with lesser amounts found in the liver, spleen, lung, skin, periosteum and bone marrow. Erythrocyte penetration is very low.

Metabolism

The absorbed fraction of a dose of pentosan polysulfate sodium is metabolized by partial desulfation in the liver and spleen, and by partial depolymerization in the kidney to a large number of metabolites. Both the desulfation and depolymerization can be saturated with continued dosing.

Excretion

Following oral administration of a 300 or 450 mg dose of pentosan polysulfate sodium containing radiolabeled drug to groups of healthy subjects, plasma radioactivity declined with mean half-lives of 27 and 20 hours, respectively. Most of an orally administered dose of pentosan polysulfate sodium (mean 84%) is excreted in feces as unchanged drug. A mean of 6% of an oral dose is excreted in the urine, mostly as desulfated and depolymerized metabolites. Only a small fraction of the administered dose (mean 0.14%) is recovered as intact drug.

Special Populations

No data are available in geriatric patients or in patients with hepatic or renal impairment. See also **WARNINGS AND PRECAUTIONS**.

STORAGE AND STABILITY

Store at controlled room temperature (15°C to 30 °C).

DOSAGE FORMS, COMPOSITION AND PACKAGING

ELMIRON[®] is supplied in white opaque hard gelatin capsules imprinted “BNP7600” containing 100 mg pentosan polysulfate sodium.

Each capsule of ELMIRON[®] contains 100 mg pentosan polysulfate sodium and the following inactive ingredients: gelatin, magnesium stearate, microcrystalline cellulose, and titanium dioxide.

Available in bottles of 100 capsules.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

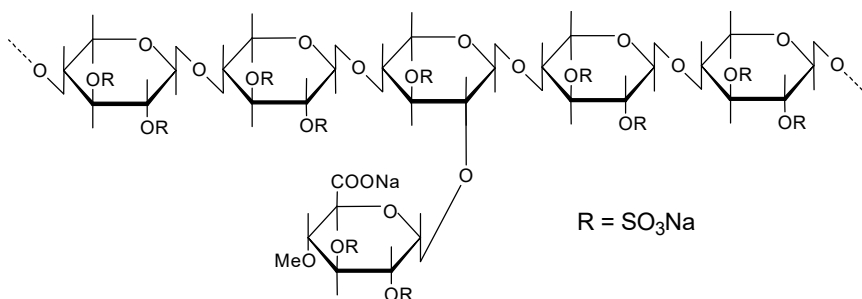
Drug Substance

Proper name: pentosan polysulfate sodium

Chemical name: β -D-Xylan, (1 \rightarrow 4), 2,3-bis (hydrogen sulfate), sodium salt

Molecular formula and molecular mass: $[\text{C}_5\text{H}_6\text{Na}_2\text{O}_{10}\text{S}_2]_n$ where $n = 6$ to 12
4,000-6,000 Dalton

Structural formula:



Physicochemical properties: Pentosan polysulfate sodium is a semi-synthetically produced heparin-like macromolecular carbohydrate derivative which chemically and structurally resembles glycosaminoglycans. It is a white odourless powder, slightly hygroscopic and soluble in water to 50% at pH 6.

CLINICAL TRIALS

ELMIRON[®] was evaluated for the treatment of interstitial cystitis in two placebo-controlled, randomized clinical trials. Approximately equal numbers of patients received either placebo or ELMIRON[®] 100 mg three times a day over a three-month double-blind period. Overall clinical evaluation was based on the patients' overall evaluation of their improvement, the investigators' evaluation of improvement, and pain and urgency scales. In these studies (N=258 combined), twice as many ELMIRON[®] patients as placebo patients saw a > 25% improvement in overall condition in both patient and investigator based evaluations (~30% versus ~ 15%, $p < 0.05$). In the 5-point pain scale evaluation, ~50% of patients on ELMIRON[®] reported a one point or greater reduction in pain score from baseline. Reduction in urgency was seen in 62% of ELMIRON[®] patients compared to 43% of placebo patients in the second study.

During these studies, four ELMIRON[®] patients and 8 placebo patients were withdrawn due to an adverse event. Five per cent and nine per cent of ELMIRON[®] patients in the first and second studies, respectively, reported an adverse event (placebo patients: 14% and 13%). During an

open study (N=1274), which included 246 long-term ELMIRON[®] patients, 137 patients reported adverse events. The most commonly reported adverse events include nausea, diarrhea, rash, hair loss, headache and dizziness.

DETAILED PHARMACOLOGY

Animal Pharmacology

Studies have demonstrated that the transitional cells of the bladder secrete and bind to their surface a glycosaminoglycan (GAG) substance. It has been shown that this GAG layer may be replaced by exogenous GAGs such as heparin or pentosan polysulfate sodium (PPS). In two studies, it was found that bacterial adherence to acid-treated rabbit bladders was brought back to control levels by treatment of the bladder with these compounds. Pretreating bacteria with either compound had no effect on the bacteria's ability to adhere to the acid-treated bladder indicating that the effect was due to an interaction of the compounds with the injured bladder wall rather than an interaction with the bacteria.

Urinary tract infection was significantly higher in rabbits with acid-treated bladders than in rabbits with intact bladders or whose acid-treated bladders were treated with PPS prior to instillation of pathogenic bacteria. These data indicate that bacterial adherence is an essential factor in pathogenesis that can be prevented by GAGs in the injured bladder. It has also been shown that PPS reduced the adherence of calcium and protein to the urinary bladder of the rabbit suggesting that the antiadherence activity extends to the molecular and ionic level.

Human Pharmacology

Pentosan polysulfate sodium (PPS) levels in plasma and urine were measured in eight volunteers after intravenous and oral doses of PPS. At steady state with oral administration, plasma levels of PPS ranged from 0.02 to 0.05 mcg/mL. Using either the plasma or urine values of the oral and the IV studies, the bioavailability of PPS was estimated to be 0.5 to 1%.

The absorption and elimination of radioactive PPS was measured in 3 male volunteers after a single oral dose of tritiated PPS. Approximately 84% and 11.6% of the radioactive PPS was recovered in the urine and feces within 120 hours. About 3.5% of the recovered radioactivity was recovered within 24 hours in the urine, and within 72 hours in the feces.

Tritiated PPS was administered to 8 male volunteers in a two-way crossover study. About 27% of the parenteral dose and 11% of the oral dose of tritiated PPS were excreted in the urine up to 144 hours post dosing. This study indicates that PPS reaches the urine unmetabolized in sufficient amounts to be effective in interstitial cystitis.

The metabolism of an iodinated derivative of PPS as well as unlabelled PPS was studied by IV and SC injection in 5 healthy volunteers. Radioactivity was detectable in the urine within 1 hour of IV injection. The imaging data indicated that the major portion of the labelled PPS was localized in the liver and spleen. Only depolymerised labelled PPS was found in the urine after injection of labelled PPS alone while after injection of labelled PPS with 50 mg of unlabelled PPS, both macromolecular label (some with affinity for polybrene) and depolymerised label were detected. This study provides evidence that the desulphation and depolymerisation mechanisms of PPS can become saturated at pharmacologically relevant doses.

In a single-dose, sequential group study, the time course of radioactivity following oral administration of ^3H -pentosan polysulfate sodium (PPS) was evaluated in healthy women. Group 1 (7 subjects completed) received a single dose of ^3H -PPS (200 μCi , ~15 mg PPS) supplemented with 300 mg unlabeled PPS, and Group 2 (8 subjects completed) received a single dose of ^3H -PPS (300 μCi , ~15 mg PPS) supplemented with 450 mg unlabeled PPS. Radioactivity measurements were made in both groups from blood, urine, and feces samples collected for up to 5 days post dose. Median (CV%) peak plasma PPS concentrations [250 (25) and 358 (9.3) ng-equiv/mL for Groups 1 and 2, respectively] were noted 2.08 and 1.83 hours, respectively, after dosing. Most of the radioactivity was recovered in the feces (84.1% and 57.8% in Groups 1 and 2, respectively), primarily as intact PPS. Radioactivity levels in the plasma and urine were low, consistent with the poor oral bioavailability of PPS. Most of the PPS in the circulation was characterized as partially desulfated with a molecular size smaller than intact PPS. The ratios of the log-transformed, dose-normalized C_{max} and AUC values for the 200 μCi ^3H -PPS treatment (Group 1) to those of the 300 μCi ^3H -PPS treatment (Group 2) were 100.65% and 106.26%, respectively, and the 90% confidence intervals for both pharmacokinetic variables fell within 80% to 125%, indicating dose-proportional pharmacokinetics.

TOXICOLOGY

The oral LD_{50} of pentosan polysulfate sodium (PPS) in the rat or mouse is 36 - 56 g/kg. In six-month and one-year oral toxicology studies at doses of 5, 25, 50, 100 mg/kg/day PPS in rats, there were no drug-related deaths or abnormal clotting studies at any dose. Above 25 mg/kg/day orally, mild leukopenia was noted in one study. The gross and microscopic necropsy evaluations were normal in all groups. Twelve monkeys were exposed to oral doses of PPS at 2, 50, 200 mg/kg/day over six months. There was no detectable toxic effect at 2 or 50 mg/kg. The 200 mg/kg dose level (fifty times the intended human dose) caused gastrointestinal hemorrhaging and death in three of the four animals after the fourth month. Eighteen baboons were injected subcutaneously with PPS for a period of four weeks at doses of 4.5, 6.7 or 10 mg/kg/day. At three weeks, elevated PTT levels were noted in the 6.7 and 10 mg/kg groups.

Teratology

Reproduction studies in the rat given PPS intramuscularly or intraperitoneally at doses up to five times the recommended human oral dose had no effect on fertility and produced no malformations in the offspring. Pregnant mice and rabbits were given subcutaneous PPS injections two to four times the human oral dose at the time of fetal organogenesis without effect on fetal development. There was no teratogenic effect. No adverse effect has been noted on peri- or post-natal development in the offspring of rats exposed to parenteral PPS. The effect of pentosan polysulfate sodium on spermatogenesis has not been investigated. Studies in pregnant women undergoing abortion have indicated that pentosan polysulfate sodium does not cross the placental barrier although direct in vitro bathing of cultured embryos may cause limb bud abnormalities.

Mutagenesis

PPS has no mutagenic action in the bacterial Ames test. Likewise, in the in vivo mammalian mouse micronucleus assay, PPS did not produce any mutagenic effect. On the basis of PPS's chemical structure and lack of mutagenic activity, PPS is unlikely to be carcinogenic. PPS

substance is closely related to the naturally occurring glycosaminoglycans found in many vertebrate connective tissues and fluids, such as skin, bone, cartilage, arterial walls, umbilical cord, vitreous humor, cornea and synovial fluid.

Carcinogenesis

Long-term carcinogenicity studies with ELMIRON[®] in rats showed no evidence of carcinogenic potential at exposures up to 60 times the maximum recommended human dose (MRHD) on a mg/kg basis.

Male and female mice were administered ELMIRON[®] for two years at 56, 168 and 504 mg/kg. There was a statistically significant increase in hemangiosarcomas in male mice and hepatocellular neoplasms (adenoma and/or carcinoma) in male and female mice exposed to the highest dose, which is approximately 117 times the MRHD on a mg/kg basis. There was also a significant increase in malignant lymphomas in the female mice at this dose. There was no statistically significant increase in the incidence of any neoplasm in either male or female mice at the middle dose or at the lowest dose. The lowest dose is approximately 13 times the MRHD on a mg/kg basis.

REFERENCES

1. Parsons CL, Schmidt JD, Pollen JJ. Successful treatment of interstitial cystitis with sodium pentosan polysulfate. *J Urol* 1983;130:51-53.
2. Hurst RE, et al. Functional and structural characteristics of the glycosaminoglycans of the bladder luminal surface. *J Urol* 1987;138:433-437.
3. Parsons CL. Sodium Pentosanpolysulfate Treatment of Interstitial Cystitis: An Update Supplement. *Urology* 1987;29:14-16.
4. Mulholland SG, et al. Pentosan polysulfate sodium for therapy of interstitial cystitis. *Urology* 1990;35:552-558.
5. Fischer AM, et al. A comparison of pentosan polysulphate and heparin II: Effects of subcutaneous injection. *Thromb Haemost* 1982;47:109-113.
6. Schneider J, Bierbaum D, Mross F, Kapp-Schwoerer H: Medikamentöse thrombose und embolieprophylaxe mit SP-54 bei der therapie gynakologischer karzinome mit radium und telekobaltsbestrahlung. *Med Welt* 18:1446, 1967.
7. Fellstrom B, et al. Pentosan polysulphate (ELMIRON®): pharmacokinetics and effects on the urinary inhibition of crystal growth. In: Vahlensieck W, Gasser G, eds. *Pathogenese und Klinij der Harnsteine*. Darmstadt: Steinkopff-Verlag, 1987.
8. Grigsby PW, Pilepich MV, Parsons CL. Preliminary results of a phase I/II study of sodium pentosanpolysulphate in the treatment of chronic radiation-induced proctitis. *Am J Clin Oncol* 1990;13:28-31.
9. Vinazzer H, et al. Influence of heparin, of different heparin fractions, and of a low molecular weight heparin-like substance on the mechanism of fibrinolysis. *Thromb Res* 1982;27:341-352.
10. Frandoli G and Spreafico PL. Lipoprotein-lipase modifications in subjects treated with a synthetic, heparin-like polyanion (SP-54). *Il Farmaco* 1972;27:514-519.
11. Kalben DA. Pharmacological studies on the anti-inflammatory effect of a semisynthetic polysaccharide (pentosan polysulphate). *Pharmacology* 1973;9:74-78.
12. Greenslade D, Vickers J, Hopkins R. 3H-sodium polysulphate: A pharmacokinetic study in man after oral administration. Hazleton Laboratories Europe Ltd., Harrogate, North Yorkshire, England. Report No. 33350-021/2, July 1983.
13. Losonczy H, Naggy I, David M. Effects of various doses of SP54 on fibrinolytic activity in patients with thrombotic diseases. *Folia Haematol Int Mag Klin Morphol* 1988;115:388-393.

14. Taugner R and Karsunky K-P. Resorption, Verteilung und Ausscheidung von S35 markierten SP-54 an Ratten. Report from I. Physiol. Institut der Universität Heidelberg. Report on file.
15. MacGregor IR, et al. Metabolism of sodium pentosan polysulphate in man – catabolism of iodinated derivatives. *Thromb Haemost* 1984;51:321-325.
16. MacGregor IR, et al. Metabolism of sodium pentosan polysulphate in man measured by a new competitive binding assay for sulphated polysaccharides – comparison with effects upon anticoagulant activity: lipolysis and platelet α -granule proteins. *Thromb Haemost* 1985;53:411-414.
17. Kummer M, Krinz K, Bauer R. Absorption distribution and excretion of 3H SP54 after parenteral and oral application in eight healthy male volunteers. Final Report SP54, MK/a-37. Labor für Pharmakokinetik und Biopharmazie, Paschelanger 11, 8000 Munich 83, West Germany.
18. Raasch E: Acute oral toxicity of Na-pentosan polysulphate in rats and mice. *Battelle, BlV*, V.63, 592.
19. Klocking HP, Markwardt F. Report on toxicological trials with sodium pentosan polysulphate (6 months) in rats after oral uptake. Institute for Pharmacology and Toxicology. January 1987. Report on file.
20. Toxicité Chronique du 8061 CB (SP 54) Oct. 1963. French translation.
21. Ginocchio AV. Compound SP 54 six month toxicity study in Rhesus monkeys, Consultax Labs, Ltd., April, 1972. Report on file.
22. Virgo DM, et al: Four week subcutaneous toxicity study in baboons. *Life Science Research*, 3, March, 1980. Report on file.
23. Schafer H. Toxicity examination in rats II. Fecundity disturbances and teratogenous effects during intramuscular application. Physiological Institute, University Heidelberg, 23 January 1963. Report on file.
24. Schafer H. Toxicity examination in rats II. Fecundity disturbances and teratogenous effects during intraperitoneal application. Physiological Institute, University Heidelberg, 17 September 1963. Report on file.
25. Palmer AK, et al. Effect of SP54 on pregnancy of the mouse. Huntingdon Research Centre, 20 February 1967. Report on file.
26. Palmer AK, et al. Effect of SP54 on pregnancy of the New Zealand White Rabbit. Huntingdon Research Centre, 11 February 1969. Report on file.
27. Morriss GM, et al. Effect of SP54 on peri and postnatal development of the rat. Huntingdon Research Centre, 8 August 1969. Report on file.

28. Forestier F, et al. Absence of transplacental passage of pentosan polysulfate during mid trimester of pregnancy. *Thromb Haemost* 1986;56: 247-249.
29. Schonforn, W. Investigation on the mutagenicity of pentosan polysulfate using the reserve mutation assay with Salmonella Typhimurium according to Ames, Battelle Institute e.v., 2 September, 1982. Report on file.
30. Raasch E. Investigation of pentosan polysulfate for mutagenicity in the Micronucleus Test, Battelle Institute e.v., August 1982. Report on file.
31. Abdo KM, Johnson JD, Nyska A. Toxicity and carcinogenicity of Elmiron in F344/N rats and B6C3F1 mice following 2 years of gavage administration. *Arch Toxicol* 2003; 77(12):702-711.
32. NTP technical report on the toxicology and carcinogenesis studies of Elmiron (Cas. No. 37319-17-8) in F344/N rats and B6C3F1 mice (Gavage Studies). *Natl Toxicol Program Tech Rep Ser* May 2004;(512):7-289.
33. Goad KE, Horne MK 3rd, Gralnick HR. Pentosan-induced thrombocytopenia: support for an immune complex mechanism. *Br J Haematol* 1994;88(4):803-808.
34. Sandhu SS, Goldstraw M, Woodhouse CR. The management of haemorrhagic cystitis with sodium pentosan polysulphate. *Br J Urol Int* 2004;94(6):845-847.
35. van Ophoven A, Heinecke A, Hertle L. Safety and efficacy of concurrent application of oral pentosan polysulfate and subcutaneous low-dose heparin for patients with interstitial cystitis. *Urology* 2005;66(4):707-711.
36. Nickel JC, Barkin J, Forrest J, Mosbaugh PG, et al. Randomized double-blind, dose-ranging study of pentosan polysulfate sodium for interstitial cystitis. *Urology* 2005; 65(4):654-658.

PART III: CONSUMER INFORMATION

^{Pr}ELMIRON®*
pentosan polysulfate sodium capsules

This leaflet is Part III of a three-part "Product Monograph" published when ELMIRON® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ELMIRON®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

The treatment of inflammation and irritation of the bladder wall (interstitial cystitis).

What it does:

ELMIRON® is thought to adhere to the bladder surface supplementing the defective bladder layer. It is hypothesized that this action improves the symptoms of interstitial cystitis.

When it should not be used:

- Do not use ELMIRON® if you are allergic to pentosan polysulfate sodium, related compounds or any of the other ingredients.
- Do not use ELMIRON® if you have a personal history of eye disease that affects the retina.

What the medicinal ingredient is:

pentosan polysulfate sodium

What the nonmedicinal ingredients are:

gelatin capsule, magnesium stearate, microcrystalline cellulose, and titanium dioxide.

What dosage forms it comes in:

Capsules: 100 mg

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Do not use ELMIRON® if you have a personal history of eye disease that affects the retina.

Cases of retinal changes (pigmentary maculopathy) have been reported with long-term use of ELMIRON®. This eye disease changes the centre of the retina (called the 'macula'). This may harm your vision and may lead to a permanent decrease or loss of central vision. Tell your doctor and eye doctor right away if you notice any changes in your vision.

While taking ELMIRON®, regular eye exams that include checking your retina are recommended for detection of pigmentary maculopathy. Your doctor will decide when these eye exams are needed, and if the treatment should be continued.

BEFORE you use ELMIRON® talk to your doctor or pharmacist if:

- You are taking anticoagulant therapy such as coumarin anticoagulants, heparin, tPA, streptokinase, high-dose ASA (acetylsalicylic acid) or anti-inflammatory drugs such as ibuprofen
- You are at increased risk of bleeding due to diseases such as ulcerative GI lesions (sores inside your digestive tract), aneurysms (balloon-like bulges in a blood vessel), or diverticulae (small protrusions of the lining of the intestine into the surrounding muscle).
- You will be undergoing surgery
- You are pregnant or breastfeeding
- You have liver problems
- You have a personal or family history of eye problems. Tell your doctor if you notice any changes in your vision.

The safety and effectiveness of ELMIRON® in children and adolescents below the age of 18 years have not been established.

INTERACTIONS WITH THIS MEDICATION

Since ELMIRON® is a weak anticoagulant (blood thinner), tell your doctor or pharmacist if you are taking any other anti-coagulant therapy such as warfarin, high-dose ASA (acetylsalicylic acid), and nonsteroidal anti-inflammatory drugs (NSAIDS).

PROPER USE OF THIS MEDICATION

Usual dose:

The recommended dose of ELMIRON® is 300 mg/day taken as one 100 mg capsule orally three times daily. The capsules should be taken with water at least 1 hour before meals or 2 hours after meals.

Overdose:

Call your doctor or go to the nearest hospital emergency department. Take the labelled medicine bottle with you.

Missed dose:

Take the dose as soon as you remember. If it is almost time for your next dose, skip the dose you missed and take your next dose. Do not double doses to make up for the missed dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

ELMIRON® is usually well tolerated. Reported adverse reactions are infrequent and usually do not require discontinuation of treatment. The most common reactions are associated with digestion, blood, and skin. Common reactions you may experience include nausea and hair loss. Other possible side effects include urticaria (hives), itching, and shortness of breath.

This medication can raise your liver enzymes. This can be confirmed by blood tests ordered by your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Headache	✓		
	Abdominal pain	✓		
	Diarrhea	✓		
	Rash		✓	
	Abnormal liver function test		✓	
	Blood in stool		✓	
	Nose bleed		✓	
	Gum bleeding		✓	
Uncommon	Dizziness	✓		✓
	Bruising		✓	
	Allergic reactions			

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Unknown	Pigmentary Maculopathy (Eye disease that affects the retina): difficulty reading; slow adjustment to low or reduced light, blurry vision, blurry or wavy vision near or in the center of your field of vision		✓	

This is not a complete list of side effects. For any unexpected effects while taking ELMIRON®, contact your doctor or pharmacist.

HOW TO STORE IT

Store at controlled room temperature (15°C to 30°C).

Keep out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 1908C
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect® Canada Web site at www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For questions, concerns or full Product Monograph go to:
<http://www.janssen.com/canada>
or contact the manufacturer, Janssen Inc., at:
1-800-567-3331 or 1-800-387-8781

This leaflet was prepared by
Janssen Inc.
Toronto, Ontario M3C 1L9

Last revised: October 1, 2020

*Registered trademark of IVAX Research, LLC. Used under license.