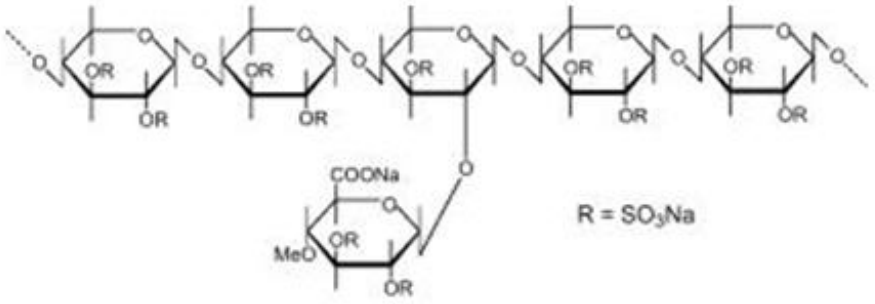
ELMIRON- pentosan polysulfate sodium capsule, gelatin coated
Janssen Pharmaceuticals, Inc.

ELMIRON®-100 mg
(pentosan polysulfate sodium)
Capsules

PRESCRIBING INFORMATION

DESCRIPTION

Pentosan polysulfate sodium is a semi-synthetically produced heparin-like macromolecular carbohydrate derivative, which chemically and structurally resembles glycosaminoglycans. It is a white odorless powder, slightly hygroscopic and soluble in water to 50% at pH 6. It has a molecular weight of 4000 to 6000 Dalton with the following structural formula:



ELMIRON® is supplied in white opaque hard gelatin capsules containing 100 mg pentosan polysulfate sodium, microcrystalline cellulose, and magnesium stearate. It also contains pharmaceutical glaze (modified) in SD-45, synthetic black iron oxide, FD&C Blue No. 2 aluminum lake, FD&C Red No. 40 aluminum lake, FD&C Blue No. 1 aluminum lake, D&C Yellow No. 10 aluminum lake, n-butyl alcohol, propylene glycol, SDA-3A alcohol, and titanium dioxide. It is formulated for oral use.

CLINICAL PHARMACOLOGY

General

Pentosan polysulfate sodium is a low molecular weight heparin-like compound. It has anticoagulant and fibrinolytic effects. The mechanism of action of pentosan polysulfate sodium in interstitial cystitis is not known.

Pharmacokinetics

Absorption

In a clinical pharmacology study in which healthy female volunteers received a single oral 300 or 450 mg dose of pentosan polysulfate sodium containing radiolabeled drug as a solution under fasted conditions, maximal levels of plasma radioactivity were seen approximately at a median of 2 hours (range 0.6-120 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.

Food Effects

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

Preclinical studies with parenterally administered radiolabeled pentosan polysulfate sodium showed 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 low in animals.

Metabolism

The fraction of pentosan polysulfate sodium that is absorbed 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 administration of an oral solution 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. A large proportion of the orally administered dose of pentosan polysulfate sodium (mean 84% in the 300 mg group and 58% in the 450 mg group) 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 in urine.

Special Populations

The pharmacokinetics of pentosan polysulfate sodium has not been studied in geriatric patients or in patients with hepatic or renal impairment. See also *PRECAUTIONS-Hepatic Insufficiency*.

Drug-Drug Interactions

In a study in which healthy subjects received pentosan polysulfate sodium 100 mg capsule 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 and presence of pentosan polysulfate sodium. INR for warfarin + placebo and warfarin + pentosan polysulfate sodium were comparable. See also *PRECAUTIONS* on the use of ELMIRON® in patients receiving other therapies with anticoagulant effects.

Pharmacodynamics

The mechanism by which pentosan polysulfate sodium achieves its effects in patients is unknown. In preliminary clinical models, pentosan polysulfate sodium 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.

CLINICAL TRIALS

ELMIRON® was evaluated in two clinical trials for the relief of pain in patients with chronic interstitial cystitis (IC). All patients met the NIH definition of IC based upon the results of cystoscopy, cytology, and biopsy. One blinded, randomized, placebo-controlled study evaluated 151 patients (145 women, 5 men, 1 unknown) with a mean age of 44 years (range 18 to 81). Approximately equal numbers of patients received either placebo or ELMIRON® 100 mg three times a day for 3 months. Clinical improvement in bladder pain was based upon the patient's own assessment. In this study, 28/74 (38%) of patients who received ELMIRON® and 13/74 (18%) of patients who received placebo showed greater than 50% improvement in bladder pain ($p = 0.005$).

A second clinical trial, the physician's usage study, was a prospectively designed retrospective analysis

of 2499 patients who received ELMIRON® 300 mg a day without blinding. Of the 2499 patients, 2220 were women, 254 were men, and 25 were of unknown sex. The patients had a mean age of 47 years and 23% were over 60 years of age. By 3 months, 1307 (52%) of the patients had dropped out or were ineligible for analysis, overall, 1192 (48%) received ELMIRON® for 3 months; 892 (36%) received ELMIRON® for 6 months; and 598 (24%) received ELMIRON® for one year.

Patients had unblinded evaluations every 3 months for the patient's rating of overall change in pain in comparison to baseline and for the difference calculated in "pain/discomfort" scores. At baseline, pain/discomfort scores for the original 2499 patients were severe or unbearable in 60%, moderate in 33% and mild or none in 7% of patients. The extent of the patients' pain improvement is shown in Table 1.

At 3 months, 722/2499 (29%) of the patients originally in the study had pain scores that improved by one or two categories. By 6 months, in the 892 patients who continued taking ELMIRON®, an additional 116/2499 (5%) of patients had improved pain scores. After 6 months, the percent of patients who reported the first onset of pain relief was less than 1.5% of patients who originally entered in the study (see Table 2).

Table 1: Pain Scores in Reference to Baseline in Open Label Physician's Usage Study (N = 2499)*

Efficacy Parameter	**3 months†**	**6 months†**
Patient Rating of Overall Change in Pain (Recollection of difference between current pain and baseline pain)‡	N = 1161 Median = 3 Mean = 3.44 CI: (3.37, 3.51)	N = 724 Median = 4 Mean = 3.91 CI: (3.83, 3.99)
Change in Pain/Discomfort Score (Calculated difference in scores at the time point and baseline)§	N = 1440 Median = 1 Mean = 0.51 CI: (0.45, 0.57)	N = 904 Median = 1 Mean = 0.66 CI: (0.61, 0.71)

* Trial not designed to detect onset of pain relief

† CI = 95% confidence interval

‡ 6-point scale: 1 = worse, 2 = no better, 3 = slightly improved, 4 = moderately improved, 5 = greatly improved, 6 = symptom gone

§ 3-point scale: 1 = none or mild, 2 = moderate, 3 = severe or unbearable

Table 2: Number (%) of Patients with New Relief of Pain/Discomfort* in the Open-Label Physician's Usage Study (N = 2499)

	at 3 months† (n = 1192)	**at 6 months‡ (n = 892)**
Considering only the patients who continued treatment	722/1192 (61%)	116/892 (13%)
Considering all the patients originally enrolled in the study	722/2499 (29%)	116/2499 (5%)

* First-time Improvement in pain/discomfort score by 1 or 2 categories

† Number (%) of patients with improvement of pain/discomfort score at 3 months when compared to baseline

‡ Number (%) of patients without pain/discomfort improvement at 3 months who had improvement at 6 months

INDICATIONS AND USAGE

ELMIRON® (pentosan polysulfate sodium) is indicated for the relief of bladder pain or discomfort associated with interstitial cystitis.

CONTRAINDICATIONS

ELMIRON® is contraindicated in patients with known hypersensitivity to the drug, structurally related compounds, or excipients.

WARNINGS

None.

PRECAUTIONS

General

ELMIRON® is a weak anticoagulant (1/15 the activity of heparin). At a daily dose of 300 mg (n = 128), rectal hemorrhage was reported as an adverse event in 6.3% of patients. Bleeding complications of ecchymosis, epistaxis, and gum hemorrhage have been reported (see ***ADVERSE REACTIONS***). Patients undergoing invasive procedures or having signs/symptoms of underlying coagulopathy or other increased risk of bleeding (due to other therapies such as coumarin anticoagulants, heparin, t-PA, streptokinase, high dose aspirin, or nonsteroidal anti-inflammatory drugs) should be evaluated for hemorrhage. Patients with diseases such as aneurysms, thrombocytopenia, hemophilia, gastrointestinal ulcerations, polyps, or diverticula should be carefully evaluated before starting ELMIRON®.

A similar product that was given subcutaneously, sublingually, or intramuscularly (and not initially metabolized by the liver) is associated with delayed immunoallergic thrombocytopenia with symptoms of thrombosis and hemorrhage. Caution should be exercised when using ELMIRON® in patients who have a history of heparin induced thrombocytopenia.

Alopecia is associated with pentosan polysulfate and with heparin products. In clinical trials of ELMIRON®, alopecia began within the first 4 weeks of treatment. Ninety-seven percent (97%) of the cases of alopecia reported were alopecia areata, limited to a single area on the scalp.

Hepatic Insufficiency

ELMIRON® has not been studied in patients with hepatic insufficiency. Because there is evidence of hepatic contribution to the elimination of ELMIRON®, hepatic impairment may have an impact on the pharmacokinetics of ELMIRON®. Caution should be exercised when using ELMIRON® in this patient population.

Mildly (< 2.5 × 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. Increases in PTT and PT (< 1% for both) or thrombocytopenia (0.2%) were noted.

Information for Patients

Patients should take the drug as prescribed, in the dosage prescribed, and no more frequently than prescribed. Patients should be reminded that ELMIRON® has a weak anticoagulant effect. This effect may increase bleeding times.

Laboratory Test Findings

Pentosan polysulfate sodium did not affect prothrombin time (PT) or partial thromboplastin time (PTT) up to 1200 mg per day in 24 healthy male subjects treated for 8 days. Pentosan polysulfate sodium also inhibits the generation of factor Xa in plasma and inhibits thrombin-induced platelet aggregation in human platelet rich plasma *ex vivo*. (See ***PRECAUTIONS-Hepatic Insufficiency*** Section for additional information.)

Carcinogenicity, Mutagenesis, Impairment of Fertility

Long term carcinogenicity studies of ELMIRON® in F344/N rats and B6C3F1 mice have been conducted. In these studies, ELMIRON® was orally administered once daily via gavage, 5 days per week, for up to 2 years. The dosages administered to mice were 56, 168 or 504 mg/kg. The dosages administered to rats were 14, 42, or 126 mg/kg for males, and 28, 84, or 252 mg/kg for females. The dosages tested were up to 60 times the maximum recommended human dose (MRHD) in rats, and up to 117 times the MRHD in mice, on a mg/kg basis. The results of these studies in rodents showed no clear evidence of drug-related tumorigenesis or carcinogenic risk.

Pentosan polysulfate sodium was not clastogenic or mutagenic when tested in the mouse micronucleus test or the Ames test (*S. typhimurium*). The effect of pentosan polysulfate sodium on spermatogenesis has not been investigated.

Pregnancy Category B

Reproduction studies have been performed in mice and rats with intravenous daily doses of 15 mg/kg, and in rabbits with 7.5 mg/kg. These doses are 0.42 and 0.14 times the daily oral human doses of ELMIRON® when normalized to body surface area. These studies did not reveal evidence of impaired fertility or harm to the fetus from ELMIRON®. Direct *in vitro* bathing of cultured mouse embryos with pentosan polysulfate sodium (PPS) at a concentration of 1 mg/mL may cause reversible limb bud abnormalities. Adequate and well-controlled studies have not been performed in pregnant women. Because animal studies are not always predictive of human response, this drug should be used in pregnancy only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ELMIRON® is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 16 years have not been established.

ADVERSE REACTIONS

ELMIRON® was evaluated in clinical trials in a total of 2627 patients (2343 women, 262 men, 22 unknown) with a mean age of 47 [range 18 to 88 with 581 (22%) over 60 years of age]. Of the 2627 patients, 128 patients were in a 3–month trial and the remaining 2499 patients were in a long-term, unblinded trial.

Deaths occurred in 6/2627 (0.2%) patients who received the drug over a period of 3 to 75 months. The deaths appear to be related to other concurrent illnesses or procedures, except in one patient for whom the cause was not known.

Serious adverse events occurred in 33/2627 (1.3%) patients. Two patients had severe abdominal pain or diarrhea and dehydration that required hospitalization. Because there was not a control group of patients with interstitial cystitis who were concurrently evaluated, it is difficult to determine which events are associated with ELMIRON® and which events are associated with concurrent illness, medicine, or other factors.

Adverse Experience in Placebo-Controlled Clinical Trials of ELMIRON® 100 mg Three Times a Day for 3 Months

Body System/Adverse Experience	ELMIRON® n = 128	Placebo n = 130
CNS Overall Number of Patients*	3	5
Insomnia	1	0
Headache	1	3
Severe Emotional Lability/Depression	2	1
Nystagmus/Dizziness	1	1
Hyperkinesia	1	1
GI Overall Number of Patients*	7	7
Nausea	3	3
Diarrhea	3	6
Dyspepsia	1	0
Jaundice	0	1
Vomiting	0	2
Skin/Allergic Overall Number of Patients*	2	4
Rash	0	2
Pruritus	0	2
Lacrimation	1	1
Rhinitis	1	1
Increased Sweating	1	0
Other Overall Number of Patients*	1	3
Amenorrhea	0	1
Arthralgia	0	1
Vaginitis	1	1
Total Events	17	27
Total Number of Patients Reporting Adverse Events	13	19

* Within a body system, the individual events do not sum to equal overall number of patients because a patient may have more than one event.

The adverse events described below were reported in an unblinded clinical trial of 2499 interstitial cystitis patients treated with ELMIRON®. Of the original 2499 patients, 1192 (48%) received ELMIRON® for 3 months; 892 (36%) received ELMIRON for 6 months; and 598 (24%) received ELMIRON® for one year, 355 (14%) received ELMIRON® for 2 years, and 145 (6%) for 4 years.

Frequency (1 to 4%): Alopecia (4%), diarrhea (4%), nausea (4%), headache (3%), rash (3%), dyspepsia (2%), abdominal pain (2%), liver function abnormalities (1%), dizziness (1%).

Frequency (≤ 1%):

Digestive: Vomiting, mouth ulcer, colitis, esophagitis, gastritis, flatulence, constipation, anorexia, gum hemorrhage.

Hematologic: Anemia, ecchymosis, increased prothrombin time, increased partial thromboplastin time, leukopenia, thrombocytopenia.

Hypersensitive Reactions: Allergic reaction, photosensitivity.

Respiratory System: Pharyngitis, rhinitis, epistaxis, dyspnea.

Skin and Appendages: Pruritus, urticaria.

Special Senses: Conjunctivitis, tinnitus, optic neuritis, amblyopia, retinal hemorrhage.

Post-Marketing Experience

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.

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 ***CLINICAL PHARMACOLOGY*** 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 overdosage, the patient should be given gastric lavage if possible, carefully observed and given symptomatic and supportive treatment.

DOSAGE AND ADMINISTRATION

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.

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

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

HOW SUPPLIED

ELMIRON® is supplied in white opaque hard gelatin capsules imprinted "BNP7600" containing 100 mg pentosan polysulfate sodium. Supplied in bottles of 100 capsules.

NDC NUMBER 50458-098-01

Storage

Store at controlled room temperature 15°–30°C (59°–86°F).

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(logo)

Manufactured by:
Janssen Ortho LLC
Gurabo, Puerto Rico 00778

Product of Germany

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, New Jersey 08560

Revised August 2012

PHARMACIST: PLEASE DISPENSE ONE PATIENT LEAFLET PER PRESCRIPTION

Patient Leaflet

Questions and Answers About

ELMIRON®
(Generic name = pentosan polysulfate sodium)
Capsules

What is the most important information I should know about ELMIRON®?
ELMIRON® (pronounced EL ma ron) is used to treat the pain or discomfort of interstitial cystitis (IC). You must take ELMIRON® as prescribed by your doctor in the dosage prescribed but no more frequently than prescribed. ELMIRON® is a weak anticoagulant (blood thinner) which may increase bleeding. Call your doctor if you will be undergoing surgery or will begin taking anticoagulant therapy such as warfarin sodium, heparin, high doses of aspirin, or anti-inflammatory drugs such as ibuprofen.

What is ELMIRON®?

ELMIRON® is used to treat the pain or discomfort of interstitial cystitis (IC). It is not known exactly how ELMIRON® works, but it is not a pain medication like aspirin or acetaminophen and therefore must be taken continuously for relief as prescribed.

Who should not take ELMIRON®?

- Patients undergoing surgery should speak with their doctor about when to discontinue ELMIRON® prior to surgery.
- ELMIRON® should be used during pregnancy only if clearly needed.

What does your doctor need to know?

- If you are taking anticoagulant therapy such as warfarin sodium, heparin, high doses of aspirin, or anti-inflammatory drugs such as ibuprofen.
- If you are pregnant.
- If you have any liver problems.

How should I take ELMIRON®?

You should take 1 capsule of ELMIRON® by mouth three times a day, with water at least 1 hour before meals or 2 hours after meals. Each capsule contains 100 mg of ELMIRON®.

What should I avoid while taking ELMIRON®?

Anticoagulant therapy such as warfarin sodium, heparin, high doses of aspirin or anti-inflammatory drugs such as ibuprofen until you speak with your doctor.

What are the most common side effects of ELMIRON®?

The most common side effects are hair loss, diarrhea, nausea, blood in the stool, headache, rash, upset stomach, abnormal liver function tests, dizziness and bruising.

Call your doctor if these side effects persist or are bothersome or if there is blood in your stool.

If you suspect that someone may have taken more than the prescribed dose of this medicine, contact your local poison control center or emergency room immediately. This medication was prescribed for your particular condition. Do not use it for another condition or give the drug to others.

This leaflet provides a summary of information about ELMIRON®. Medicines are sometimes prescribed for uses other than those listed in a Patient Leaflet. If you have any questions or concerns, or want more information about ELMIRON®, contact your doctor or pharmacist. Your pharmacist also has a longer leaflet about ELMIRON® that is written for health professionals that you can ask to read.

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Janssen Pharmaceuticals, Inc.
Titusville, New Jersey 08560

Revised August 2012

PRINCIPAL DISPLAY PANEL - 100 mg Bottle Label

NDC 50458-098-01

ELMIRON®
(pentosan polysulfate sodium)
CAPSULES

Content: 100 Capsules

Each capsule contains 100 mg pentosan polysulfate sodium.

Rx only

100 mg

ELMIRON® is a registered trademark of Teva Branded Pharmaceutical Products R&D, Inc. under license to Janssen Pharmaceuticals, Inc.

Revised August 2012

ELMIRON

pentosan polysulfate sodium capsule, gelatin coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:50458-098
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
PENTOSAN POLYSULFATE SODIUM (PENTOSAN POLYSULFATE)	PENTOSAN POLYSULFATE SODIUM	100 mg

Inactive Ingredients

Ingredient Name	Strength
CELLULOSE, MICROCRYSTALLINE	
MAGNESIUM STEARATE	
FERROSOFERRIC OXIDE	
FD&C BLUE NO. 2	
ALUMINUM OXIDE	
FD&C RED NO. 40	
FD&C BLUE NO. 1	
D&C YELLOW NO. 10	
BUTYL ALCOHOL	
PROPYLENE GLYCOL	
TITANIUM DIOXIDE	

Product Characteristics

Color	WHITE (WHITE OPAQUE)	**Score**	no score
Shape	CAPSULE	**Size**	18mm
Flavor		**Imprint Code**	BNP7600
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:50458-098-01	100 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020193	09/26/1996	

Labeler - Janssen Pharmaceuticals, Inc. (063137772)

Establishment

Name	Address	ID/FEI	Business Operations
Janssen Ortho, LLC		805887986	ANALYSIS(50458-098), MANUFACTURE(50458-098)

Establishment

Name	Address	ID/FEI	Business Operations
bene pharmaChem GmbH & Co. KG		332479380	API MANUFACTURE(50458-098)

Revised: 9/2012 Janssen Pharmaceuticals, Inc.