Learning about interstitial cystitis (IC) and your treatment plan

What is IC?
IC is a chronic, yet manageable, inflammatory bladder condition, characterized by bladder or pelvic pain, pain during or after sexual intercourse, urinary urgency and frequency, and waking one or more times a night to urinate. Recent studies have shown IC to be far more prevalent than previously thought.

What causes IC?
IC may be caused by a breakdown of the protective lining of the bladder, which may allow irritating substances in the urine to aggravate and inflame the bladder wall, resulting in pain.

ELMIRON® may help address an underlying issue of IC
While the precise way ELMIRON® works is not fully understood, ELMIRON® is thought to adhere to the bladder mucosal lining, preventing potentially irritating substances in the urine from reaching the bladder wall.

IC symptom improvement may be gradual
Studies show that ELMIRON® relieves bladder pain in many patients after 3 to 6 months of continuous therapy. Generally, the longer you take ELMIRON®, the better it may work.

INDICATION
ELMIRON® is indicated for the relief of bladder pain or discomfort associated with interstitial cystitis. ELMIRON® is available by prescription only.

IMPORTANT SAFETY INFORMATION
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, heparin, high doses of aspirin, or anti-inflammatory drugs such as ibuprofen.
ELMIRON® should not be taken if you have a known hypersensitivity to the drug or similar drugs.

The most common side effects observed in clinical trials were blood in stool, diarrhea, nausea, hair loss, headache, rash, upset stomach, abdominal pain, liver function abnormalities, and dizziness. Hair loss, when it occurred, was almost always limited to a single area of the scalp, and grew back when ELMIRON® was discontinued.

Please see full Product Information for ELMIRON® at back of tear pad.
You are encouraged to report negative side effects of prescription drugs to the FDA.
Visit www.fda.gov/Medwatch, or call 1-800-FDA-1088.
It is very important that you take ELMIRON® as directed and stick with it

Symptom improvement is generally gradual and may require 3 to 6 months of continuous therapy

- A single 100-mg capsule of ELMIRON® should be taken 3 times a day
- While you may use other IC treatment options as needed, you should continue to take ELMIRON® until otherwise instructed by your healthcare professional
- Do not stop taking ELMIRON® or reduce your dosage just because you are feeling better or because you think ELMIRON® may not be working right away
- Schedule follow-up visits with your healthcare professional once a month for the first few months

While taking ELMIRON®, other therapies may be used to help with your symptoms

- Lifestyle modifications you can make to help manage symptoms
  - **Bladder training**: Practice scheduled voiding patterns
  - **Dietary changes**: Avoid spicy or acidic foods and beverages containing caffeine and alcohol
  - **Gentle exercise**: Walking, yoga, and low-impact aerobics may be beneficial
  - **Stress-reduction and relaxation techniques**: Try controlled breathing exercises, warm baths with baking soda, and applying warm or cold compresses on the lower abdomen

- Additional therapies your healthcare professional may prescribe
  - **Amitriptyline**: A drug that works to desensitize nerves and relieve pain
  - **Bladder instillations**: A combination of medicines placed directly into the bladder through a very small catheter to provide immediate, temporary relief
  - **Hydroxyzine**: An antihistamine that may mildly suppress the body’s inflammatory response, reducing symptoms
  - **Physical therapy**: Gentle stretching and pelvic floor muscle relaxation exercises

- Additional resources such as IC-friendly recipes and stress and coping techniques are available through the following:
  - **www.orthoelmiron.com**: An Ortho Women’s Health & Urology™ Web site offering a wide range of information on IC and ELMIRON® to patients
  - **Journey to Relief®**: A free e-mail support program that provides you with great tips, resources, and money-saving offers
  - **The ELMIRON® Early Assist™ program**: Most patients enrolled in this program will pay no more than $5 per month for up to 4 months of ELMIRON® treatment
  - **Interstitial Cystitis Association (www.ichelp.com)**: A national, nonprofit organization offering information and support to IC patients and their families
  - **Interstitial Cystitis Network (www.ic-network.com)**: Features patient handbooks, a research library, and information on support groups and chat rooms
Prescribing Information

DESCRIPTION
Pentosan polysulfate sodium is a semi-synthetically produced heparin-like macromolecular carbohydrate derivative, which 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:

\[
\text{R} = \text{SO}_3\text{Na}
\]

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-butyric 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.

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 comparable. See also PRECAUTIONS- Hepatic Insufficiency.

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 surface. The drug may act as a buffer to control cell permeability preventing irritating solutes in the urine from reaching the bladder wall.

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 4 weeks. Clinical improvement in bladder pain was based upon the patient’s own assessment. In this study, 28/43 (66%) of patients received ELMIRON® and 12/43 (28%) of patients 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, 1195 (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 with 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 2498 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.

1. At 3 months, 722/2498 (28%) 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 116/2498 (5%) of patients had improved pain scores. After 6 months, the percent of patients who reported sustained 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=2498)

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>3 months¹</th>
<th>6 months²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Rating of Overall Change in Pain (Reckoning of difference between current pain and baseline)³</td>
<td>N=1161</td>
<td>N=724</td>
</tr>
<tr>
<td>Median=6</td>
<td>Median=4</td>
<td></td>
</tr>
<tr>
<td>CI: (3.37, 3.51)</td>
<td>CI: (3.83, 3.99)</td>
<td></td>
</tr>
<tr>
<td>Change in Pain/Discomfort Score (Global differed in scores at the time point and baseline)⁴</td>
<td>N=1440</td>
<td>N=904</td>
</tr>
<tr>
<td>Median=-1</td>
<td>Median=1</td>
<td></td>
</tr>
<tr>
<td>CI: (0.45, 0.57)</td>
<td>CI: (0.66, 0.71)</td>
<td></td>
</tr>
</tbody>
</table>

¹Trial not designed to detect onset of pain relief
²First-time Improvement in pain/discomfort score by 1 or 2 categories
³CI = 95% confidence interval
⁴Number (%) of patients with improvement of pain/discomfort score at 3 months when compared to baseline
⁵Number (%) 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

PRECAUTIONS

General: ELMIRON® is a weak anticoagulant (1/15 the activity of heparin). At a dose of 300 mg (n = 128), fecal excretion was reported as an adverse effect in 3.3% of patients. When 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.

ELMIRON® did not affect prothrombin time (PT) or partial thromboplastin time (PTT). INR for warfarin + placebo and warfarin + ELMIRON® did not differ statistically. See also PRECAUTIONS- Hepatic Insufficiency.

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

ELMIRON® 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 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. Increases in PTT and PT (<1% for both) or thrombocytopenia (0.2%) were noted.

Information for Patients:
If the drug should be used in pregnant women, the drug is contraindicated and should not be used.

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 in F344 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 tumorigenicity 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 0.2% 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 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.

<table>
<thead>
<tr>
<th>Body System/Adverse Experience</th>
<th>ELMIRON®</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Number of Patients*</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>CNS</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Insomnia</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Severe Emotional Lability/Depression</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nystagmus/Dizziness</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hypokinesia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>GI</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Dyspepsa</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Jaundice</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Skin/Allergic/Overall Number of Patients*</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Lactation</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vaginitis</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Total Events</td>
<td>17</td>
<td>27</td>
</tr>
<tr>
<td>Total Number of Patients Reporting Adverse Events</td>
<td>13</td>
<td>19</td>
</tr>
</tbody>
</table>

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, 219 (8%) received ELMIRON® for 3 months; 892 (36%) received ELMIRON® for 6 months; and 598 (24%) received ELMIRON® for 16 weeks in a clinical trial. At a daily dose of 300 mg (n = 128), rectal hemorrhage was reported as an adverse event in 6.3% of patients. The seventy 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 4 study conducted in 360 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 seventy 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 antiocoagulation, 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 “BNP7660” containing 100 mg pentosan polysulfate sodium. Supplied in bottles of 100 capsules.

NDC NUMBER 0062-9800-01

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

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Ortho Women’s Health & Urology, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.

Raritan, New Jersey 08869

Manufactured by:

Janssen Ortho LLC

Gurabo, Puerto Rico 00778

Manufactured for:

Ortho Women’s Health & Urology, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.

Raritan, New Jersey 08869

Revised December 2008 10110402

U.S. Patent 5,180,715

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 cystis (IC).

You must take ELMIRON® as prescribed by your doctor in the dosage prescribed but no more frequently than prescribed.

ELMIRON® is weak anti-coagulant (blood thinner) which may increase bleeding.

What is ELMIRON® used for? ELMIRON® is used to treat the pain or discomfort of interstitial cysts (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 anti-coagulant 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 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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Raritan, New Jersey 08869

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