CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

020193Orig1s015

Trade Name:	ELMIRON
Generic or Proper Name:	pentosan polysulfate sodium
Sponsor:	Janssen Pharmaceuticals, Inc
Approval Date:	March 12, 2021
Indication:	Elmiron is indicated for the relief of bladder pain or discomfort associated with interstitial cystitis.

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPLICATION NUMBER:

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APPROVAL LETTER

NDA 020193/S-015

SUPPLEMENT APPROVAL

Janssen Pharmaceuticals, Inc
Attention: Jenna Giacchi, M.S.
Associate Director, Global Regulatory Affairs
Janssen Research & Development, LLC
920 Highway 202
P.O. Box 300
Raritan, NJ 08869

Dear Ms. Giacchi:

Please refer to your supplemental new drug application (sNDA) dated and received August 21, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Elmiron (pentosan polysulfate sodium) capsules.

This Prior Approval supplemental new drug application provides for conversion of the patient labeling to a Medication Guide and associated revisions to the Prescribing Information and carton and container labeling.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

CARTON AND CONTAINER LABELING

We acknowledge your February 17, 2021, submission containing draft printed carton and container labeling.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Sydney Tran, Regulatory Project Manager, at 301-796-1587.

Sincerely,

{See appended electronic signature page}

Catherine Sewell, M.D., M.P.H.
Deputy Director for Safety
Division of Urology, Obstetrics, and Gynecology
Office of Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine
Center for Drug Evaluation and Research

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CATHERINE A SEWELL
03/12/2021 10:55:14 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020193Orig1s015

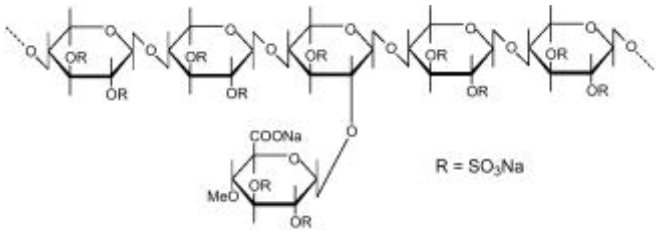
LABELING

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

Retinal Pigmentary Changes

Pigmentary changes in the retina, reported in the literature as pigmentary maculopathy, have been identified with long-term use of ELMIRON® (see ADVERSE 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 the reported cases included difficulty reading, slow adjustment to low or reduced light environments, and blurred vision. The visual consequences of these pigmentary changes are not fully characterized. Caution should be used in patients with retinal pigment changes from other causes in which examination findings may confound the appropriate diagnosis, follow-up, and treatment. Detailed ophthalmologic history should be obtained in all patients prior to starting treatment with ELMIRON®. If there is a family history of hereditary pattern dystrophy, genetic testing should be considered. For patients with pre-existing ophthalmologic conditions, a comprehensive baseline retinal examination (including color fundoscopic photography, ocular coherence tomography (OCT), and auto-fluorescence imaging) is recommended prior to starting therapy. A baseline retinal examination (including OCT and auto-fluorescence imaging) is suggested for all patients within six months of initiating treatment and periodically while continuing treatment. If pigmentary changes in the retina develop, then risks and benefits of continuing treatment should be re-evaluated, 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.

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 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

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Patients should take the drug as prescribed, in the dosage prescribed, and no more frequently than prescribed.

Patients should be informed that changes in vision should be reported and evaluated. Retinal examinations including optical coherence tomography (OCT) and auto-fluorescence imaging are suggested for all patients within six months of starting ELMIRON® and periodically during long-term treatment (see WARNINGS).

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

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

The following adverse reactions have been identified during post approval use of pentosan polysulfate sodium; because these reactions were 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:

- pigmentary changes in the retina (see WARNINGS).

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 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

Keep out of reach of children.

Product of Germany

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

Revised: 02/2021

MEDICATION GUIDE
ELMIRON® (EL ma ron)
(pentosan polysulfate sodium)
capsules, for oral use

What is the most important information I should know about ELMIRON?

Serious side effects have been reported with the use of ELMIRON, including:

- **Changes in the retina of the eye (pigmentary maculopathy).** Taking ELMIRON may be associated with pigment changes in the retina of the eye that may continue even after stopping treatment with ELMIRON. Tell your healthcare provider including your eye doctor right away if you have any vision changes including any of these symptoms:
  - o difficulty reading
  - o your vision takes longer to adjust to low or reduced light
  - o blurred vision

Throughout your treatment, regular eye examinations that include retinal examinations are suggested for early detection of retinal/macular changes. Your doctor will discuss with you when to get your first eye examination and follow up exams, and whether the treatment should be continued.

- **Increased bleeding.** ELMIRON may increase bleeding. Tell your healthcare provider right away if you have any of these symptoms:
  - o bruising easily
  - o nosebleeds
  - o bleeding gums
  - o blood in your stool

  Your risk of bleeding may be increased if you take ELMIRON along with other medicines such as:
  - o warfarin sodium
  - o heparin
  - o high doses of aspirin
  - o anti-inflammatory medicines such as ibuprofen

Tell your healthcare provider if you are taking any of these medicines.

Before you start taking ELMIRON, tell your healthcare provider if you are going to have surgery. Your healthcare provider may stop ELMIRON before you have surgery. Talk to your healthcare provider about when to stop taking ELMIRON and when to start taking it again.

What is ELMIRON?

- ELMIRON is a prescription medicine used to treat bladder pain or discomfort associated with interstitial cystitis.
- It is not known if ELMIRON is safe and effective in children under 16 years of age.

Do not take ELMIRON if you:

- are allergic to pentosan polysulfate sodium or any of the ingredients in ELMIRON. See the end of this Medication Guide for a complete list of ingredients in ELMIRON.

Before your take ELMIRON, tell your healthcare provider about all of your medical conditions, including if you:

- have a personal or family history of eye problems of the retina.
- have a history of aneurysms.
- have problems with easy bleeding (thrombocytopenia).
- have hemophilia.
- have gastrointestinal problems such as ulcerations, polyps, or diverticula.
- have liver problems
- are pregnant or plan to become pregnant. ELMIRON should be used during pregnancy only if clearly needed. Tell your healthcare provider if you become pregnant while taking ELMIRON. You and your healthcare provider should decide if you should continue to take ELMIRON.
- are breastfeeding or plan to breastfeed. It is not known if ELMIRON passes into your breastmilk. You and your healthcare provider should decide if you will take ELMIRON or breastfeed.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take ELMIRON?

- Take ELMIRON exactly as your healthcare provider tells you to take it.
- Take 1 capsule of ELMIRON by mouth 3 times a day with water at least 1 hour before meals or 2 hours after meals. Each capsule contains 100 mg of ELMIRON.
- If you take too much ELMIRON, call your healthcare provider right away or go to the nearest emergency room.

What are the possible side effects of ELMIRON?

Serious side effects have been reported with the use of ELMIRON, including:
Changes in the retina of the eye
Increased bleeding

(See "What is the most important information I should know about ELMIRON?")
The most common side effects of ELMIRON are:

o hair loss	o stomach pain	o rash
o diarrhea	o upset stomach	o abnormal liver function tests
o nausea	o headache	o dizziness

These are not all of the possible side effects of ELMIRON.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ELMIRON?

- Store ELMIRON at room temperature between 68°F to 77°F (20°C to 25°C).
- **Keep ELMIRON and all medicines out of the reach of children.**

General information about the safe and effective use of ELMIRON.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ELMIRON for a condition for which it was not prescribed. Do not give ELMIRON to other people, even if they have the same symptoms you have. It may harm them. You can ask your

pharmacist or healthcare provider for information about ELMIRON that is written for health professionals.

What are the ingredients in ELMIRON?
Active ingredient: pentosan polysulfate sodium

Inactive ingredients: microcrystalline cellulose, magnesium stearate, gelatin, 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.

Product of Germany
Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, New Jersey 08560
For more information, go to www.ORTHOELMIRON.com or call 1-800-526-7736.

This Medication Guide has been approved by the U.S. Food and Drug Administration Revised: 02/2021

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020193Orig1s015

MEDICAL REVIEW(S)

Memorandum to File

NDA:	**sNDA 020193/S015**
Drug:	**Elmiron**
Sponsor:	**Teva Branded Pharmaceutical Products R&D Inc., Manufactured for Janssen Pharmaceuticals, Inc.**
Indication:	**Relief of bladder pain or discomfort associated with interstitial cystitis.**
Date received:	**8/21/2020**
Re:	**Prior Approval Supplement: Medication Guide Labeling Proposal**

1. Background: The sponsor, Janssen Pharmaceuticals, has submitted a prior approval supplement to seek approval of a Medication Guide Proposal as per 21 CFR part 208 that is intended to accompany future dispensed prescriptions of the FDA-approved drug, Elmiron. Elmiron (pentosan polysulfate sodium) is a low molecular weight heparin-like macromolecular carbohydrate derivative, which resembles glycosaminoglycans. Elmiron has anticoagulant and fibrinolytic effects. It is indicated for the relief of bladder pain or discomfort associated with interstitial cystitis and has a long marketing history, having initially been approved by the FDA in 1996.

Due to reports of pigmentary maculopathy associated with long-term Elmiron use, the Sponsor submitted a Prior Approval Supplement for revisions to the Elmiron United States Package Insert (USPI) including the addition of a warning of retinal pigmentary changes occurring after long term use. Please refer to the Medical Officer Review of this labeling supplement, dated 5/18/2020. An Ophthalmology Consult was completed on 5/19/2020 which determined that based on a review of the literature and the Global Safety Database, there was sufficient evidence to support that pigmentary maculopathy is possibly associated with long term use of Elmiron. However, it was also noted that although retinal pigmentary changes were reported, there was no clear evidence of harm to the visual system, clinical testing had not established any visual deficit, and visual complaints were non-specific and consistent with age-related change of the lens and retina. The reviewer's recommendation was that since the pigmentary changes appeared to be permanent, non-reversible, and the consequences unknown, that they should be included in the package insert.

Subsequently, on 6/16/2020, labeling changes were made to the USPI for Elmiron, adding warnings about the association of pigmentary maculopathy with long-term Elmiron use. As per the current approved Elmiron label, all patients should undergo detailed ophthalmological history prior to starting treatment, and a baseline retinal examination is suggested for all patients within six months of starting the treatment. Elmiron is also a weak anticoagulant and bleeding complications have been reported. As per the approved Elmiron label, patients undergoing invasive procedures or with increased risk of bleeding should be evaluated for hemorrhage.

2. Current Submission: The sponsor has submitted a proposed Medication Guide following the requirements of 21 CFR part 208. This regulation describes the purpose of Medication Guides for new and refill prescriptions of drug products used on an outpatient basis. The sponsor has included information for patients about the reports of pigmentary changes in the retina with long-term use of Elmiron and suggests regular eye exams during Elmiron treatment. In addition, the Medication Guide informs patients about the risk of increased bleeding with Elmiron (b) (4)

During the review process, we sought regulatory guidance from Eric Brodsky (PLT) about whether a sponsor could propose changing a Patient Leaflet to a Medication Guide. In an email dated 1/31/2021, he advised that applicants can propose a Medication Guide for their prescription drug product.

In addition, FDA may approve a MG if the patient labeling meets any one of the following three criteria to have a MG as per 21 CFR 208.1(c):

> (1) The drug product is one for which patient labeling could help prevent serious adverse effects.
>
> (2) The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product.
>
> (3) The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.
>
> *Reviewer's Comment: Agree that part #2 applies to this Medication Guide.*

As per CFR 21, Chapter 1, Subchapter C, Subpart B (General requirements for a Medication Guide) Part 208.20: Content and format of a Medication Guide.

> (2) The Medication Guide shall be scientifically accurate and shall be based on, and shall not conflict with, the approved professional labeling for the drug product under §201.57 of this chapter, but the language of the Medication Guide need not be identical to the sections of approved labeling to which it corresponds.
>
> *Reviewer's Comment: The Proposed Medication Guide was reviewed and compared with the approved label for Elmiron. It appears to be accurate and based on the most current information in the approved label.*

3. Sponsor Question to FDA: The sponsor includes a question to the FDA in the annotated proposed label, Medication Guide section, page 14 as follows:

> Question from Sponsor to FDA: "This verbatim statement is included per 21CFR 208.20(b)(8)(i). However, because ELMIRON is only approved for one indicaton (sic) as described in this Medication Guide, please consider removing or revising this statement."
>
> "Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide."
>
> *Reviewer's comment: Recommend retaining required regulatory language.*

3. Conclusion: Provided that the Medication Guide and carton labeling are consistent with Patient Labeling Team and CMC guidelines, the Medication Guide fulfills the requirements of 21 CFR 208 and is recommended for approval for use.

Regulatory Action: The sponsor should be informed that the proposed Medication Guide meets the requirements and may be approved for use.

Jennifer Dodson, Primary Author

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/s/

JENNIFER L DODSON
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020193Orig1s015

OTHER REVIEW(S)

Division of Regulatory Operations for Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: 020193

Name of Drug: Elmiron (pentosan polysulfate sodium)

Applicant: Janssen Pharmaceuticals Inc.

Labeling Reviewed

Submission and Receipt Dates: August 21, 2020

Background and Summary Description

This prior approval supplemental application proposes the conversion of the currently approved patient labeling into a Medication Guide. Additionally, carton and container labels to reflect this change were also submitted to the Division for review and approval.

Review

The Prescribing Information (PI) and Patient Package Insert (PPI) approved June 16, 2020, were compared to the labeling submitted August 21, 2020, under S-015. The following changes were identified.

Prescribing Information (PI) Changes:

- Under section for **Information for Patients**, added "Advise the patient to read the FDA-approved patient labeling (Medication Guide)."
- Under section for **Storage**, modified to add degree measurement to storage temperature, 15°C to 30°C (59°F to 86°F).
- Changed statement on being a registered trademark of Teva Branded Pharmaceutical Products R&D Inc. used under license from "ELMIRON® is a registered trademark of Teva Branded Pharmaceutical Products R&D, Inc., used under license to Janssen Pharmaceuticals, Inc."
- Under section for **Product of Germany**, removed manufacturing information.
- Under section for **Revised date**, changed to open date format of month and year (month, 2021).

Patient Labeling Changes:

- Under section for **What is the most important information I should know about ELMIRON?**,
  - Deleted "ELMIRON® (pronounced EL ma ron) is used to treat the pain or discomfort of interstitial cystitis (IC)."
  - Deleted "You must take ELMIRON® as prescribed by your doctor in the dosage prescribed but no more frequently than prescribed."
  - Modified sentence to "(b) (4) ."
- Under section for **What is ELMIRON?**,
  - Modified sentence to "(b) (4) ."
- Under section for (b) (4),
  - Added "(b) (4) are allergic to pentosan polysulfate sodium (b) (4) or any of the (b) (4) ingredients in ELMIRON®. See the end of this Medication Guide for a complete list of ingredients in ELMIRON®."
  - (b) (4)
- Under section for (b) (4),
  - Modified sentence to (b) (4)
- Under section for **How should I take ELMIRON?**,
  - Added sentence "(b) (4) "
  - Modified sentence to "(b) (4) "
- Under section for (b) (4)**?**,
  - Modified sentence to "(b) (4) "
- Under section for **What are the** (b) (4) **possible** (b) (4) **side effects of ELMIRON?**,
  - Modified section heading to "What are the possible (b) (4) side effects of ELMIRON?"
  - Added "(b) (4)

[redacted] (see "What is the most important information I should know about ELMIRON®")

- Modified sentence "The most common side effects of ELMIRON® are hair loss, diarrhea, nausea, [redacted], headache, rash, upset stomach, abnormal liver function tests, dizziness [redacted]."
- Added "These are not all of the possible side effects of ELMIRON®."
- Added "Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088."

- Added section for **How should I store ELMIRON®?**
  - Added sentence "Store at [redacted] room temperature [redacted]."
  - Modified sentence "Keep ELMIRON® and all medicines out of the reach of children."

- Added section for **General information about the safe and effective use of ELMIRON®.**
  - Deleted sentence "This leaflet provides a summary of information about ELMIRON®."
  - Modified sentence "Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. [redacted]

- Added section for **What are the ingredients in ELMIRON®?**
  - Added "Active ingredient: pentosan polysulfate sodium"
  - Added "Inactive ingredients: microcrystalline cellulose, magnesium stearate, gelatin. [redacted] 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.

- Modified section on trademark with "ELMIRON® is a registered trademark of Teva Branded Pharmaceutical Products R&D, Inc., used under license. © 2002 Janssen Pharmaceutical Companies

  - Added "For more information, go to www.ORTHOELMIRON.com or call 1-800-526-7736."

- Modified section on product and manufacturing information to remove Janssen Ortho LLC, Gurabo, Puerto Rico 00778.

- Added “This Medication Guide has been approved by the U.S. Food and Drug Administration.” and “Revised: Month 202X”.

Carton and Container Labels:

We consulted the Labeling Policy Team (LPT), the Office of Prescription Drug Promotion (OPDP), and the Division of Medication Error Prevention and Analysis (DMEPA). Based on the advice from LPT, OPDP, and DMEPA, DUOG made changes to the applicant’s proposed labeling. We sent FDA edits to the applicant for acceptance.

Applicant accepted Division’s recommended labeling and labels.

Recommendations

The labeling submitted on February 25, 2021, represents the agreed-upon labeling. The supplement should be approved.

Sydney Tran, Pharm.D.
Regulatory Health Project Manager
Urology, Obstetrics, and Gynecology
Division of Regulatory Operations for Rare Diseases,
Pediatrics, Urologic, and Reproductive Medicine
Office of Regulatory Operations
Center for Drug Evaluation and Research

Supervisory Comment/Concurrence:
Margaret Kober, R.Ph., M.P.A.
Chief, Project Management Staff
Urology, Obstetrics, and Gynecology
Division of Regulatory Operations for Rare Diseases,
Pediatrics, Urologic, and Reproductive Medicine
Office of Regulatory Operations
Center for Drug Evaluation and Research

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/s/

SYDNEY T TRAN
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MARGARET M KOBER
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 24, 2021
Requesting Office or Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number:	NDA 020193/S-015
Product Name and Strength:	Elmiron (pentosan polysulfate sodium) capsule, 100 mg
Applicant/Sponsor Name:	Janssen Pharmaceuticals, Inc.
OSE RCM #:	2020-2764-2
DMEPA Safety Evaluator:	Denise V. Baugh, PharmD, BCPS
DMEPA Acting Team Leader:	Celeste Karpow, PharmD, MPH

1 PURPOSE OF MEMORANDUM

The Applicant submitted a revised container label on February 17, 2021 for Elmiron. The Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the revised container label for Elmiron (Appendix A) to determine if it is acceptable from a medication error perspective. The revision is in response to a recommendation that we made during a previous label and labeling review.[a] In this review we recommended the Applicant indicate the expiration date format to allow us to assess it from a medication error perspective.

2 CONCLUSION

The Applicant submitted a revision of the Elmiron container label which illustrates the expiration date format as 'YYYY-MM'. As such, our recommendation was implemented and we have no additional recommendations at this time.

[a] Baugh D. Label, Labeling, and Packaging Review for ELMIRON (NDA 020193/S-015). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JAN 22. RCM No.: 2020-2764.

APPENDIX A. IMAGE OF CONTAINER LABEL RECEIVED FEBRUARY 17, 2021

Container labels

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/s/

DENISE V BAUGH
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 10, 2021
Requesting Office or Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number:	NDA 020193/S-015
Product Name and Strength:	Elmiron (pentosan polysulfate sodium) capsule, 100 mg
Applicant/Sponsor Name:	Janssen Pharmaceuticals, Inc.
OSE RCM #:	2020-2764-1
DMEPA Safety Evaluator:	Denise V. Baugh, PharmD, BCPS
DMEPA Acting Team Leader:	Celeste Karpow, PharmD, MPH

1 PURPOSE OF MEMORANDUM

The Applicant submitted the revised container label on January 28, 2021 for Elmiron. The Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the revised container labels for (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a] In this review we recommended the Applicant indicate the expiration date format to allow us to assess it from a medication error perspective.

2 CONCLUSION

The Applicant stated that the expiration date format on the Elmiron container label will be YYYY-MM. As such, our recommendation was considered and we have no additional recommendations at this time.

[a] Baugh D. Label, Labeling, and Packaging Review for ELMIRON (NDA 020193/S-015). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JAN 22. RCM No.: 2020-2764.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JANUARY 28, 2021

Container labels

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/s/

DENISE V BAUGH
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	February 1, 2021
To:	Sydney Tran Regulatory Project Manager **Division of Urology, Obstetrics, and Gynecology (DUOG)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Maria Nguyen, MSHS, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Elvy Varghese, PharmD. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	ELMIRON (pentosan polysulfate sodium)
Dosage Form and Route:	capsules
Application Type/Number:	NDA 020193
Supplement Number:	S-015
Applicant:	Janssen Research and Development, LLC.

1 INTRODUCTION

On September 11, 2020, Janssen Research and Development, LLC., submitted for the Agency's review a Prior Approval Supplement (PAS) for their New Drug Application (NDA) #020193/S-015 ELMIRON (pentosan polysulfate sodium). This supplement proposes to convert the currently approved ELMIRON Patient Leaflet to a Medication Guide under 21CFR208.1(c).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Urology, Obstetrics, and Gynecology (DUOG) on January 22, 2021 and January 25, 2021, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for ELMIRON (pentosan polysulfate sodium) capsules.

2 MATERIAL REVIEWED

- Draft ELMIRON (pentosan polysulfate sodium) MG received on September 11, 2020, revised by the Review Division throughout the review cycle, and received by DMPP on January 22, 2021.
- Draft ELMIRON (pentosan polysulfate sodium) MG received on September 11, 2020, revised by the Review Division throughout the review cycle, and received by OPDP on January 25, 2021.
- Draft ELMIRON (pentosan polysulfate sodium) Prescribing Information (PI) received on September 11, 2020, revised by the Review Division throughout the review cycle, and received by DMPP on January 22, 2021.
- Draft ELMIRON (pentosan polysulfate sodium) Prescribing Information (PI) received on September 11, 2020, revised by the Review Division throughout the review cycle, and received by OPDP on January 25, 2021.
- Approved ELMIRON (pentosan polysulfate sodium) labeling dated June 16, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible

- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

MARIA T NGUYEN
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DMPP-OPDP review of pentosan polysulfate sodium (ELMIRON) NDA 20193 S-015 MG

ELVY M VARGHESE
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MARCIA B WILLIAMS
02/01/2021 04:10:23 PM

LASHAWN M GRIFFITHS
02/02/2021 06:16:55 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: February 1, 2021

To: Jennifer Dodson, M.D., Clinical Reviewer
Division of Urology, Obstetrics, and Gynecology (DUOG)

Sydney Tran, Pharm.D.
Regulatory Project Manager, DUOG

From: Elvy Varghese, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, Pharm.D.
Team Leader, OPDP

Subject: OPDP Labeling Comments for ELMIRON- pentosan polysulfate sodium capsule, gelatin coated

NDA: 020193/ S-15

In response to DUOG's consult request dated January 25, 2021, OPDP has reviewed the proposed Medication Guide (MG) and carton and container labeling for ELMIRON- pentosan polysulfate sodium capsule, gelatin coated (Elmiron). This supplement (S-15) is a labeling revision that converts the patient leaflet to a MG.

Labeling: A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on February 1, 2021.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on August 21, 2020, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Elvy Varghese at (240) 402-0080 or Elvy.Varghese@fda.hhs.gov.

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/s/

ELVY M VARGHESE
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LABEL, LABELING, AND PACKAGING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	January 22, 2021
Requesting Office or Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number:	NDA 020193/S-015
Product Name, Dosage Form, and Strength:	Elmiron (pentosan polysulfate sodium) capsule, 100 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Janssen Pharmaceuticals, Inc.
FDA Received Date:	August 21, 2020
OSE RCM #:	2020-2764
DMEPA Safety Evaluator:	Denise V. Baugh, PharmD, BCPS
DMEPA Acting Team Leader:	Celeste Karpow, PharmD, MPH

1 REASON FOR REVIEW

On August 21, 2020, Janssen Pharmaceuticals, Inc submitted a Prior Approval Supplement (PAS), for Elmiron (pentosan polysulfate sodium) capsules, NDA 020193. Supplement S-015 provides for a change of the approved patient leaflet to a Medication Guide (MG). Janssen proposes changes to the Prescribing Information (PI) based on reports in the literature of pigmentary changes in the retina. As a result, the Applicant has decided that a MG is warranted per 21 CFR 208.1(c).

The Division of Urology, Obstetrics, and Gynecology (DUOG) requested we evaluate the proposed changes to the container label and prescribing information (PI) from a medication error perspective.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed changes to the Elmiron (pentosan polysulfate sodium) capsules prescribing information (PI) and the container label to identify risks that may lead to medication errors.

We note that the sections of the PI titled 'Dosage and Administration' and 'How Supplied' were not changed and we agree that no changes are necessary to support this supplement. Our review of the section titled 'Information for Patients' notes that this section has been updated appropriately to provide for the information in the PAS supplement and the proposed change is acceptable from a medication safety perspective. Additionally, the section of the PI titled 'Storage' has been updated to add the unit of measure for each numerical temperature and the hyphen has been replaced with 'to' to more clearly express the range of storage temperatures. These changes minimize confusion and are appropriate from a medication error perspective.

Additionally, as part of our evaluation, we considered whether the proposed changes to the PI require updates to the container labels to ensure consistency, decrease the risk of medication error, and minimize the risk of confusion. We note the addition of the statement: 'Attention: Dispense the enclosed Medication Guide to each patient' to the container label (Appendix G) and this statement supports the PAS supplement as proposed. Additionally, the MG statement is presented in bold black font on the principal display panel and appears immediately below the strength statement which gives it prominence. This is appropriate from a medication error perspective.

Finally, although the proposed revisions do not require changes to the presentation of the name, strength, or route of administration, our review of the container label (see Appendix G) notes that the expiration date format is not defined. Therefore, we are unable to assess the expiration date format from a medication error perspective. See our recommendations in Section 4.1 below.

4 CONCLUSION AND RECOMMENDATIONS

The proposed changes to the Elmiron PI are acceptable from a medication safety perspective. However, the expiration date on the container label does not include an expiration date format which precludes our assessment. We provide our recommendation in Section 4.1 for consideration prior to approval of this supplement.

4.1 RECOMMENDATIONS FOR JANSSEN PHARMACEUTICALS, INC

We recommend the following be implemented prior to approval of this NDA Supplement:

A. Container Label
   1 As currently presented, the format for the expiration date is not defined. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. Additionally, we recommend that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. We recommend that a hyphen or a space be used to separate the portions of the expiration date. Please indicate the intended expiration date format.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Elmiron received on August 21, 2020 from Janssen Pharmaceuticals, Inc.

Table 2. Relevant Product Information for Elmiron	
Initial Approval Date	September 26, 1996
Active Ingredient	pentosan polysulfate sodium
Indication	Relief of bladder pain or discomfort associated with interstitial cystitis
Route of Administration	oral
Dosage Form	capsule
Strength	100 mg
Dose and Frequency	100 mg orally three times daily 1 hour before meals or 2 hours after meals
How Supplied	Bottles of 100 capsules
Storage	15˚C to 30˚C (59˚F to 86˚F)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On January 19, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, 'Elmiron' and '020193'. Our search identified no previous reviews.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Elmiron labels and labeling submitted by Janssen Pharmaceuticals, Inc.

- Container label received on August 21, 2020
- Prescribing Information (Image not shown) received on August 21, 2020, available from \\CDSESUB1\evsprod\nda020193\0060\m1\us\draft-labeling-text.pdf

G.2 Label and Labeling Images

(b) (4)

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

DENISE V BAUGH
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020193Orig1s015

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:
PLT

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Sydney Tran, DUOG RPM
301-796-1587

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
1/22/2021		020193 SDN552	electronic	8/21/2020

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Elmiron capsule		weak anticoagulant activity/like low molecular weight heparin	02/16/2021

NAME OF FIRM: Janssen Pharmaceuticals Inc

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- x☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

Applicant is proposing to convert Patient Leaflet to a Med Guide; we are requesting general input and advice. This submission has due date of 2/21/21. We are requesting completion by 2/16/21.

SIGNATURE OF REQUESTOR

Sydney Tran

METHOD OF DELIVERY (Check all that apply)
x☐ DARRTS x☐ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

06/18/2013

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/s/

SYDNEY T TRAN
01/22/2021 07:52:26 AM

From:	Tran, Sydney
To:	Giacchi, Jenna [JRDUS]
Cc:	Tran, Sydney
Subject:	NDA 020193/Emiron Supplement 015
Date:	Monday, January 25, 2021 8:19:00 AM

Dear Ms. Giacchi:

Please refer to your supplemental new drug application sNDA 020193, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for Elmiron (pentosan polysulfate sodium).

We are currently reviewing the supplement 015 submitted on August 21, 2020 and we have a recommendation.

We recommend the following be implemented to the container label:

> As currently presented, the format for the expiration date is not defined. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. Additionally, we recommend that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. We recommend that a hyphen or a space be used to separate the portions of the expiration date. Please indicate the intended expiration date format.

We request that you submit this information by January 28, 2021, to the NDA application.

Please confirm receipt.

Regards,

Sydney Tran, Pharm.D.
Regulatory Health Project Manager
Urology, Obstetrics, and Gynecology
Division of Regulatory Operations for Rare Diseases, Pediatrics,
Urologic, and Reproductive Medicine
Office of Regulatory Operations
Center for Drug Evaluation and Research
Sydney.Tran@fda.hhs.gov
Office: 301-796-1587

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/s/

SYDNEY T TRAN
01/25/2021 08:43:36 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO: **CDER-OPDP-RPM**	FROM: (Name/Title, Office/Division/Phone number of requestor) Sydney Tran, DUOG RPM 301-796-1587

REQUEST DATE:	IND NO.	NDA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
1/25/2011		020193/S015 SDN 552	Electronic

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Elmiron capsule		weak anticoagulant activity/like low molecular weight heparin	February 12, 2021

NAME OF FIRM:	
Janssen Pharmaceuticals Inc	PDUFA Date: February 21, 2021

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☐ PRESCRIBING INFORMATION (PI)
xx☐ PATIENT PACKAGE INSERT (PPI)
xx☐ CARTON/CONTAINER LABELING
xx☐ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA
☐ IND
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☐ INITIAL PROPOSED LABELING
xx☐ LABELING REVISION

For OSE USE ONLY
☐ REMS

EDR link to submission:

\\CDSESUB1\\evsprod\NDA020193\0060

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.

COMMENTS/SPECIAL INSTRUCTIONS:

Applicant is proposing to convert Patient Leaflet to a Med Guide; we are requesting general input and advice. This submission has due date of 2/21/21.

Mid-Cycle Meeting:

Labeling Meetings: Wrap-Up Meeting:	
SIGNATURE OF REQUESTER Sydney Tran	
SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☐ eMAIL ☐ HAND

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/s/

SYDNEY T TRAN
01/25/2021 10:57:44 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:
OSE-DMEPA

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Sydney Tran, DUOG RPM
301-796-1587

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
1/06/2021		020193 SDN552	electronic	8/21/2020

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Elmiron capsule		weak anticoagulant activity/like low molecular weight heparin	02/16/2021

NAME OF FIRM: Janssen Pharmaceuticals Inc

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
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- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Applicant is proposing to convert Patient Leaflet to a Med Guide

We will need the PI, Medguide, and cartons and containers reviewed.
This submission has due date of 2/21/21. We are requesting completion by 2/16/21.

SIGNATURE OF REQUESTOR

Sydney Tran

METHOD OF DELIVERY (Check all that apply)
x☐ DARRTS x☐ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

SYDNEY T TRAN
01/06/2021 12:09:09 PM

NDA 020193/S-015

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

Janssen Pharmaceuticals, Inc
Attention: Jenna Giacchi, M.S.
Associate Director, Global Regulatory Affairs
Janssen Research & Development, LLC
920 Highway 202
P.O. Box 300
Raritan, NJ 08869

Dear Ms. Giacchi:

We have received your supplemental new drug application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for Elmiron (pentosan polysulfate sodium).

This supplemental application proposes the deletion of the Patient Leaflet and addition of a Medication Guide.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 20, 2020, in accordance with 21 CFR 314.101(a).

If the application is filed, the goal date will be February 21, 2021.

If you have questions, call Sydney Tran, Regulatory Project Manager, at 301-796-1587.

Sincerely,

{See appended electronic signature page}

Margaret M. Kober, R.Ph., M.P.A.
Chief, Project Management Staff
Division of Regulatory Operations for Urology, Obstetrics, and Gynecology
Office of Regulatory Operations
Center for Drug Evaluation and Research

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/s/

MARGARET M KOBER
09/11/2020 02:39:44 PM
Chief, Project Management Staff