CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

020193Orig1s014

Trade Name: **ELMIRON**

Generic Name: pentosan polysulfate sodium

Sponsor: Janssen Pharmaceuticals

Approval Date: 06/16/2020

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

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APPROVAL LETTER

NDA 020193/S-14

SUPPLEMENT APPROVAL

Janssen Pharmaceuticals, Inc.
Attention: Jenna Giacchi
Manager, 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 June 24, 2019, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Elmiron (pentosan polysulfate sodium) 100 mg capsules. This Prior Approval labeling supplement to your application provides revisions to the package insert WARNINGS section and Post-Marketing section, as well as an update to the Patient 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, Patient Package Insert), 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.

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.

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

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

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 Maria Wasilik, Regulatory Project Manager, at 301-796-0567.

Sincerely,

{See appended electronic signature page}

Christine P. Nguyen, M.D.
Director (Acting)
Division of Urology, Obstetrics, and Gynecology
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

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/

MARIA R WASILIK
06/16/2020 11:44:46 AM

CHRISTINE P NGUYEN
06/16/2020 11:47:21 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020193Orig1s014

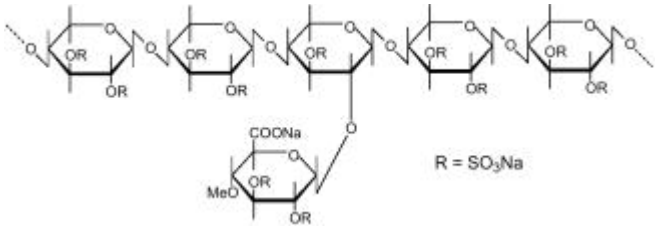
LABELING

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

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

Keep out of reach of children.

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

Product of Germany

Manufactured by:

Janssen Ortho LLC

Gurabo, Puerto Rico 00778

Manufactured for:

Janssen Pharmaceuticals, Inc.

Titusville, New Jersey 08560

Revised: June 2020

PHARMACIST: PLEASE DISPENSE ONE PATIENT LEAFLET PER PRESCRIPTION

Patient Leaflet

Questions and Answers About

ELMIRON®

(Generic name = pentosan polysulfate sodium)

Capsules

What is the most important information I should know about ELMIRON®?
ELMIRON® (pronounced EL ma ron) is used to treat the pain or discomfort of interstitial cystitis (IC). You must take ELMIRON® as prescribed by your doctor in the dosage prescribed but no more frequently than prescribed. Pigment changes in the retina of the eye (also referred to as pigmentary maculopathy in medical journal articles) have been reported with long-term use of ELMIRON®. While the cause of the pigmentary changes is unclear, continued long term dosing with ELMIRON® may be a risk factor. The consequences of these pigmentary changes in the retina are not fully understood. Visual symptoms that have been reported include: difficulty reading, slow adjustment to low or reduced light environments, and blurred vision. If you already have retinal pigment changes from other causes, it may be difficult to distinguish future retinal pigment changes if they occur. Call your doctor (including your eye doctor) if you notice any changes in your 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 since these changes may be irreversible and may progress even after stopping treatment. ELMIRON® is a weak anticoagulant (blood thinner) which may increase bleeding. Call your doctor if you will be undergoing surgery or will begin taking anticoagulant therapy such as warfarin sodium, heparin, high doses of aspirin, or anti-inflammatory drugs such as ibuprofen.

What is ELMIRON®?

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

Who should not take ELMIRON®?

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

What does your doctor need to know?

- Tell your doctor if you have a personal or family history of eye problems of the retina.
- Tell your doctors (including your eye doctor) if you experience visual changes such as reading difficulty, slower adjustment to low or reduced light, or blurred vision. (See "**WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT ELMIRON®?**")
- If you are taking anticoagulant therapy such as warfarin sodium, heparin, high doses of aspirin, or anti-inflammatory drugs such as ibuprofen.
- If you are pregnant.
- If you have any liver problems.

How should I take ELMIRON®?

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

What should I avoid while taking ELMIRON®?

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

What are the most common side effects of ELMIRON®?

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

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

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

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

Keep out of reach of children.

Product of Germany

Manufactured by:

Janssen Ortho LLC

Gurabo, Puerto Rico 00778

Manufactured for:

Janssen Pharmaceuticals, Inc.

Titusville, New Jersey 08560

Revised: June 2020

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020193Orig1s014

MEDICAL REVIEW(S)

Medical Officer's Review of NDA 20-193/S-014
Ophthalmology Consultant

NDA #20-193	Submission: 6/24/2019
Supplement 14	Submission amended: 3/24/2020
Ophthalmology Consult	Submission amended: 4/24/2020
	Submission amended: 5/18/2020
	Review completed: 5/19/2020

Name:	ELMIRON (pentosan polysulfate sodium)
Sponsor:	Janssen Research & Development, LLC
Indications:	Relief of bladder pain or discomfort associated with interstitial cystitis

Submitted: Prior Approval Supplement (PAS) proposes revisions to the ELMIRON® United States Package Insert (USPI) by adding a warning of retinal pigmentary changes which have occurred after long term use. Included in the submission was a revised version of the ELMIRON® USPI and a Clinical Overview. This supplement was subsequently amended on 24 March 2020 to propose additional labeling revisions based on information from literature and cases from JRD's Global Safety Database. The Agency and JRD agreed that long-term use of PPS may cause pigmentary changes, but initially there was disagreement on the appropriate description of the changes. On 24 April 2020, JRD provided counterproposals and accompanying rationales to the Agency's 10 April 2020, proposed labeling revisions. Following a teleconference with the Agency on 01 May 2020, JRD submitted an amendment to the PAS to provide proposals in accordance with agreements made during the discussion. On 13 May 2020, JRD received the Agency's labeling revisions. The May 18th, 2020, submission reflects the evidence currently available to describe the pigmentary changes.

MedDRA Preferred Term	Number of Events[a]
Maculopathy	51
Vision blurred	18
Amblyopia	6
Dry eye	5
Macular degeneration	5
Conjunctivitis	4
Eye pain	4
Optic neuritis	4
Visual impairment	4
Eye disorder	3
Blindness	2
Blindness unilateral	2
Photophobia	2
Visual acuity reduced	2
Age-related macular degeneration	1
Cataract	1
Choroidal neovascularisation	1
Diplopia	1
Eye haemorrhage	1
Eye irritation	1
Eye pruritus	1
Eye swelling	1
Eyelid bleeding	1
Eyelid ptosis	1
Eyelid rash	1
Eyelid sensory disorder	1
Iritis	1
Macular fibrosis	1
Mydriasis	1
Ocular vascular disorder	1
Orbital oedema	1
Refraction disorder	1
Retinal degeneration	1
Retinal haemorrhage	1
Total	**132**

o

MedDRA=Medical Dictionary for Regulatory Activities

Reviewer's Comments: *Based on the mean age of the patients, a significant portion of the blurred vision adverse events are likely to be due to cataracts or dry eye symptoms.*

Case Characteristics of Patients Reporting Eye Disorders Using Pentosan Polysulfate Sodium (n=117)

Characteristic		Number of Cases
Source	Spontaneous	63
	Literature	51
	Solicited	3
Patient Sex	Female	100
	Male	7
	NR	10
Patient Age (Years) [a] **Mean: 55.4 Median: 55 Range: 23-80**	20 to 29	5
	30 to 39	7
	40 to 49	21
	50 to 59	17
	60 to 69	19
	70 to 80	21
	Adult	9
	Elderly	1
	NR	17
Outcome (Event Level)[b]	Not resolved	24
	Resolved	16
	Resolving	5
	NR	87
Indication[c]	Cystitis interstitial	104
	Cystitis	1
	Micturition urgency	1
	Pollakiuria	1
	Urinary tract disorder	1
	NR	9
Country of Origin	United States	114
	Canada	2
	United Kingdom	1

Applicant's Review of the Literature

In 2019, the Janssen Research (Company) was informed that pigmentary maculopathy might be a potential safety signal based upon a study by Pearce et al (2018a). This study was a retrospective review of electronic medical records that identified 38 subjects treated at the Emory Eye Center between 2015 and 2017, who reported active use of PPS for a diagnosis of IC. The median cumulative PPS dose was 2,263 g (range: 1,314-2,774 g) with a median duration of exposure of 186 months (range: 144-240 months). The first literature review identified 3 relevant studies, 1 letter to the editor, 1 response to letter to the editor, and 1 editorial. All 6 publications were based on data from the Emory Eye Center. All citations described a suggestive association of a unique form of maculopathy in patients taking PPS with chronic exposure. It was noted that the authors were not able to establish a definite causal relationship between PPS and maculopathy. In fact, Pearce et al (2018a) proposed an alternative explanation for the maculopathy, which was that it may be related to the underlying condition of IC and BPS. However, Hanif et al (2019b) concluded that PPS exposure, and no other IC-related exposure, was strongly associated with this newly-described, vision-threatening macular condition. Although large-scale research and duplication of data at other centers was deemed necessary to further elucidate a causal relationship between PPS and maculopathy, the authors of these publications recommended comprehensive ophthalmic examinations with appropriate testing for patients on PPS, and that the clinicians should be informed because this condition may have been

mistaken for other well-known macular disorders, such as pattern dystrophy and AMD. As a result of the review of the literature, in 2019, the Company included new warning text in the ELMIRON PI that informed that cases of pigmentary maculopathy had been reported with long-term use of PPS; however, causality had not been established. Further, the proposed text also advised health care providers that if changes in a patient's vision occurred, an ophthalmologic exam should be considered.

In 2020, the Company identified the case report by Mishra et al (2020) in which the authors concluded that the data demonstrated that PPS exposure can be associated not only with pigmentary alterations, but also with active CNV. Following review of this literature case report, in February 2020, the Company conducted a second review of the literature to identify citations published between 2019 and 2020. A review of the search results determined that 16 citations were relevant; however, 3 were previously identified in the first search (Hanif et al [2019b], Foote et al [2019b], and Pearce et al [2018]). In addition, one article, which was not in the search output, was identified during a review of the reference section within one of the citations. A review of the 23 identified citations determined that the results from several studies align with the results from Mishra et al (2020). Shah et al (2019) studied patients with IC and reported that the unique maculopathy was identified and confirmed exclusively in the PPS-exposed group and not the unexposed group. Foote et al (2019a) identified patients with IC/BPS and self-reported current or previous use of PPS and retinal degeneration. The most commonly reported visual symptoms were difficulty reading and difficulty adapting to dim lighting. The mean daily dose was 370 mg (range: 200-592 mg) and the median cumulative exposure to PPS was 2,270 g (range: 581-4,307 g), over a median duration of 198 months (range: 36-273 months). Hanif et al (2019a) identified 35 patients with visual symptoms including metamorphopsia, blurred vision, and prolonged dark adaptation. The median duration of PPS intake was 15 (range: 3-22) years, and the median cumulative exposure was 1.61 (range: 0.44-4.31) kg. In a retrospective, cross-sectional study by Hanif et al (2019b), 80/219 (36.5%) subjects were exposed to PPS and among these, 14 subjects were diagnosed with pigmentary maculopathy. For these 14 subjects, the median duration of PPS intake and cumulative exposure were 18.3 years (range: 3-21.9 years) and 2.3 kg (range: 0.58-2.98 kg), respectively. PPS exposure was the sole statistically significant predictor of an unspecified pigmentary maculopathy. Vora et al (2020a)24 evaluated the prevalence and risk factors for maculopathy in patients with long-term exposure to PPS. Of the 117 patients identified, 27 (23.1%) had definite signs of maculopathy. Further, the mean total PPS exposure was significantly higher (1,350 g; $p<0.01$) in patients with maculopathy compared with those without signs of toxicity (1,040 g). Vora et al (2020a) concluded that their findings add strong support to the growing body of evidence that links long-term PPS use to the potential development of a toxic maculopathy.

Despite the recommended total daily dose of 300 mg; some patients reported total daily doses exceeding this recommendation (444.8±128.5 mg/day, Wang et al [2020]). Total cumulative exposure varied from 440 grams to 4,310 grams (Hanif et al [2019a]) and 1,533 to 6,023 grams (Wang et al [2020]).

In summary, multiple case series studies and a retrospective database study have been published reporting pigmentary maculopathy association with the long-term use of PPS; however, some publications include overlapping patients and data. Pigmentary maculopathy has only been reported

in patients who received long-term treatment with ELMIRON. The duration of exposure is reported to typically range from 3 to 22 years (Hanif et al 2019a11), but (Foote et al 2019b7) reported one case with pigmentary maculopathy as early as after 27 months of exposure. Further, the Committee for Medicinal Products for Human Use's Scientific Conclusion (27 June 2019) reported a case in the Vigilyse database with an exposure of less than 2 years. Pigmentary maculopathy also appears to be associated with cumulative dose. A multivariate logistic model used in Vora et al (2020a) compared patients with IC with pigmentary maculopathy to those without and showed cumulative PPS dose was the only significant factor linked to the risk of pigmentary maculopathy. The minimum cumulative PPS dose currently reported to be associated with pigmentary maculopathy is 440 grams by Hanif et al (2019a). Additionally, one case reported by Mishra et al (2020) suggested potential pigmentary maculopathy progression with CNV after 2,300 g of PPS (300 mg/day) for 21 years. Progression of pigmentary maculopathy with visual impairment that progressed for 6 years after discontinuation of PPS was reported by Huckfeldt et al (2019) in a patient whose cumulative exposure to PPS was 1,300 g to 2,000 g (200-300 mg/day) for 18 years. Cumulatively, this data provides evidence that suggests that pigmentary maculopathy may be associated with the long term use of PPS.

Applicant's Conclusions

Based on this review of literature and cases from the GMS Global Safety Database, there is sufficient evidence to support that pigmentary maculopathy is possibly associated with the long-term use of PPS. Key factors supporting this conclusion include this maculopathy being identified exclusively in patients with IC who were in the PPS-exposed group and other literature reports based on data from multiple patients describe a relationship to higher cumulative doses. The reporting frequency is 0.0003/10,000 patient-days and the CIOMS frequency category is very rare. Inclusion of an AE as an AR does not constitute an admission that medical personnel, user facility, holder of the regulatory licenses, distributor, manufacturer or product caused or contributed to a particular event. Adverse reaction determinations are not intended to be an appraisal of the medical cause of a particular event; instead, they represent an evaluation based on review of the available relevant information at the time of the evaluation according to the appropriate regulatory requirements.

Full Published Articles reviewed by Ophthalmology Reviewer

Vora RA *et al.* A case of pentosan polysulfate maculopathy originally diagnosed as stargardt disease. Am J Ophthalmol. https://doi.org/10.1016/j.ajoc.2020.100604

Mishra K *et al.* Choroidal Neovascularization Associated with Pentosan Polysulfate Toxicity. Ophthalmol Retina. 2020; 4(1), 111-113.

Sadda SR. A path to development of screening guidelines for pentosan maculopathy. Can J Ophthalmology. 2020; 55(1), 12.

Ludwig CA *et al.* Pentosan Polysulfate Sodium Exposure and Drug-Induced Maculopathy in Commercially Insured Patients in the United States. Ophthalmol. 2020 Apr;127(4):535-543. https://doi.org/10/1016/j.ophtha.2019.10.036

Hadad A *et al.* A Novel Multimethod Image Analysis to Quantify Pentosan Polysulfate Sodium Retinal Toxicity. Ophthalmology. 2020 Mar; 127 (3), 429-431.

Hanif AM *et al.* Strength of Association between Pentosan Polysulfate and a Novel Maculopathy. Ophthalmology. 2019 Oct; 126 (10), 1464-1466.

Vora RA *et al.* Prevalence of Maculopathy Associated with Long Term Pentosan Polysulfate Therapy. Ophthalmology. https://doi.org/10.1016/j.ophtha.2020.01.017

Wang D *et al.* Pentosan-associated maculopathy: prevalence, screening guidelines and spectrum findings based on prospective multimodal analysis. Can J Ophthalmol. 2019. https://doi/org/10.1016/j.jcjo.2019.12.001

Pearce WA *et al.* Pigmentary Maculopathy Associated with Chronic Exposure to Pentosan Polysulfate Sodium. Ophthalmology. 2018 Nov;125(11):1793-1802.

Jain N, *et al.* Association of macular disease with long-term use of pentosan polysulfate sodium: findings from a US cohort. Br J Ophthalmol 2019;0:1–5. doi:10.1136/bjophthalmol-2019-314765

Reviewer's Comments: *Retinal pigmentary changes have been reported; however, there is no clear evidence of harm to the visual system. Clinical testing has not established any visual deficit. Visual complaints have been non-specific and are consistent with age related changes of the lens and retina.*

Pigmentary changes have been demonstrated in multiple patients at multiple sites in patients who have taken pentosan for extended periods of time (multiple years). The changes appear to be permanent, and the visual consequences unknown. The pigmentary changes should be included in the package insert because they appear to be non-reversible.

Applicant's Proposed Labeling:

(b) (4)

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Summary Recommendations:

Supplement 14 of NDA 20-193, as amended in the May 18, 2020, submission is recommended for approval.

Wiley A. Chambers, M.D.
Supervisory Medical Officer, Ophthalmology

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WILEY A CHAMBERS
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MEDICAL OFFICER REVIEW OF LABELING SUPPLEMENT

NDA:	020193/Supplement 14/SDN 535, 542, 543, 544, 545, 546
DRUG:	ELMIRON (Pentosan Polysulfate Sodium)
COMPANY:	Janssen Pharmaceuticals, Inc
DATE OF SUBMISSION:	June 24, 2019
DATE:	May 18, 2020
REVIEWER:	Catherine Sewell, MD, MPH Medical Officer DUOG/ORPURM/OND/CDER/FDA

Background

Elmiron (pentosan polysulfate sodium, PPS) was approved in 1996 for the treatment of bladder pain associated with interstitial cystitis (IC). IC is a chronic condition characterized by urinary frequency and urgency with associated bladder pain. There are currently no other oral medical products approved by FDA for the treatment of interstitial cystitis.

The Applicant submitted a labeling supplement on June 24, 2019, to add a warning on pigmentary maculopathy. Subsequently, on March 24, 2020, the Applicant submitted an amendment to the prior approval supplement. The salient features of this amendment were to revise the label further regarding pigmentary maculopathy with:

- (b) (4)
- (b) (4)
- Update to the Warnings section
- Update to the Precautions, Information for Patients section
- Addition of a Postmarketing Adverse Reaction
- Updates to the Patient Leaflet

The impetus for these labeling changes included new information from literature and cases from Janssen's Global Safety Database.

Review

Applicant's Exposure Data

The cumulative exposure to Elmiron is estimated to be (b) (4) capsules total. See Table 1.

Table 1 Cumulative Exposure to Elmiron, launch to January 31, 2020

Country	Number of Capsules	Person-Days
Canada		(b) (4)
South Korea		
United States		
Total		

Applicant's Overview of Safety

The Applicant was informed of a study by Pearce et al[1]which reported on pigmentary maculopathy and a possible association with the use of PPS. The Applicant conducted two literature searches, in March 2019 and February 2020, using Medline, Biosis, Embase, International Pharmaceutical Abstracts and SciSearch. The searches yielded 23 relevant citations. The Applicant also conducted a search of the GMS Global Safety Database for all cases that met the following criteria:

- Pentosan polysulfate sodium as suspect, or suspect-interacting drug
- Medically confirmed cases
- Valid cases only
- All case types (e.g., spontaneous/clinical trial/registry, etc.)
- Version of case: highest version in date range
- Cases received cumulatively through 30 January 2020; cases that were in workflow at the time of the GMS Global Safety Database search were not captured as part of this search.
- Adverse events coded to the Medical Dictionary for Regulatory Activities (MedDRA version 22.1) System Order Class (SOC) Eye disorders.

All cases were retrieved independent of the reporter's relationship attribution. The Applicant further searched FAERS/WHO VigiBase data.

The Applicant's search of the GMS Global Safety Database yielded 117 case reports of eye disorders in patients who used PPS, 71 of which were not evaluated further, leaving 46 cases selected for further review. 37 of those cases were reported in the literature, leaving 9 cases for summary. The cases were deemed to have a plausible temporal relationship between exposure to PPS and the adverse event, given that the patients had used PPS for at least 6 months and an increased total cumulative dose of PPS seemed to be associated with more severe findings on exam. The findings were limited by the facts that most cases did not report genetic testing for hereditary eye conditions and no patients had documented baseline ophthalmic examinations before starting PPS. The FAERS data found 9 cases reporting maculopathy in PPS users, but most of the patients were unidentifiable and had limited information precluding causal assessment. The VigiBase data mining yielded one case of maculopathy, 5 cases of macular degeneration, 13 cases of visual impairment and 11 cases of vision blurred. The Applicant concluded that overall there was sufficient evidence to support an association between PPS and pigmentary maculopathy, and proposed to update the label.

[1] Pearce WA, Chen R, Jain N. Pigmentary maculopathy associated with chronic exposure to pentosan polysulfate sodium. Ophthalmology. 2018; 125(11): 1793-1802.

FDA Review of Safety

OSE

The Office of Surveillance and Epidemiology (OSE) was consulted and OSE's findings and conclusions are discussed in their memorandum. OSE reviewed cases of pentosan-related pigmentary maculopathy identified by searching multiple FDA databases (FAERS, NEISS-CADES, VigiBase) and the medical literature through February 2020 and analyzed drug utilization patterns for pentosan.

FDA Drug Utilization Data

FDA drug utilization data indicate the number of prescriptions for PPS is falling annually; prescriptions fell 41% in that time period. See Table 2.

Table 2 US Estimated Number of Patients with a Dispensed Prescription for PPS 2011-2018

(b) (4)

Search of the FAERS database yielded 20 cases of retinopathy, only 8 of which reported "maculopathy", "pigmentary maculopathy" or "pigmentary changes". PPS dosing was within the recommended range and time to onset of the AEs ranged from 9 to 28 years, with a mean of 21 years. Five of eight patients reported visual symptoms and one case had the potential confounder of cataract surgery. None of the cases provided fundus imaging, and many of the cases were reported after the Pearce publication, indicating the possibility of stimulated reporting. No cases were identified from NEISS-CADE. The search of the WHO VigiBase yielded 53 individual cases, 49 of which were from the US. Only one case outside the US reported maculopathy. Of the 49 US cases, 21 were received after the publication of the initial case series, indicating possible stimulated reporting.

DPV's and DEPI's literature searches identified several case reports, a retrospective analysis of patients with PPS exposure, as well as several observational studies, including one cross-sectional study, two claim-based retrospective cohort studies and two descriptive studies. (See Appendix 1 for list of studies reviewed by OSE and DTOP.)

The studies indicate that multiple ophthalmology practice sites identified pigmentary maculopathy associated with PPS. There is preliminary evidence suggesting a dose-response relationship, with pigmentary maculopathy cases reporting a significantly higher daily dose, longer duration of use, and higher cumulative dose than non-cases.

However, the data present many challenges to causality assessment, due to limited interpretability of case reports, case series, unclear temporal association, potential confounders and lack of details in the reports. Additionally, there are limitations to conclusions which can be drawn from the literature:
(1) observational studies preclude concluding a causal relationship between pentosan and pigmentary maculopathy; (2) claim-based studies are subject to major limitations such as the lack of retinal imaging confirmation and the validation of study outcome algorithms, short follow-up time, and potential residual confounding; (3) other studies lacked an unexposed comparator group and potential selection bias, potential outcome misclassification, and residual confounding.

OSE concluded that there are several compelling elements in the data that support an association between pentosan and a novel pigmentary maculopathy. The clinical consequences of this maculopathy remain unclear because the general vision complaints are commonly reported with aging. OSE finds this drug/adverse event pairing warrants inclusion in the labeling of pentosan to make all health care professionals aware of this association.
OSE recommends an update to the Warnings section of the pentosan label to reflect the potential risk of pigmentary maculopathy and include the commonly reported symptoms of blurred vision, difficulty with dark adaptation, metamorphopsia, and nonspecific visual symptoms, although their relationship to pigmentary changes is unknown.

DTOP
The Division of Urology, Obstetrics and Gynecology Products (DUOG) also consulted the Division of Transplant and Ophthalmology Products (DTOP) to review the literature as well as the Applicant's proposed labeling. (See Appendix 1 for list of studies reviewed by OSE and DTOP.)
DTOP's findings and conclusions are discussed in their memorandum. DTOP concluded that "retinal pigmentary changes have been reported; however, there is no clear evidence of harm to the vision. Clinical testing has not established any visual deficit. Visual complaints have been non-specific and are consistent with age related changes of the lens and retina.
Pigmentary changes have been demonstrated in multiple patients at multiple sites in patients who have taken pentosan for extended periods of time (multiple years). The changes appear to be permanent, and the visual consequences unknown. The pigmentary changes should be included in the package insert because they appear to be non-reversable."

Recommendation
DUOG concurs with OSE and DTOP that the data do not support a causal association between pentosan polysulfate sodium and retinopathy. The FDA believes the new information supports a revision to the Warnings and Precautions and Adverse Reactions sections of the label. The information does not change the overall favorable risk/benefit profile of pentosan polysulfate sodium in treating IC. The Agency will continue to monitor, through routine

pharmacovigilance, cases of ocular adverse events (retinal pigment changes) reported for pentosan polysulfate sodium (Elmiron).

Labeling

Labeling negotiations progressed, including a teleconference with the Applicant on May 1, 2020 in which the FDA clearly stated that a non-causal association of retinal pigmentary changes with the use of PPS (b) (4) FDA reviewed and revised the supplement and sent back to the Applicant on May 13th, 2020. The Applicant returned the label on May 15, 2020, aligning the patient information with the prescribing information and (b) (4) The Applicant requested that this term be retained for now, and they requested that this topic be decoupled from the pending PAS until they conduct a comprehensive assessment to be discussed with the Agency separately. The Agency agreed to this proposal.

The final agreed upon labeling is as follows (relevant sections only included here):

(b) (4)

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Appendix 1. Published Articles Reviewed

Vora RA *et al.* A case of pentosan polysulfate maculopathy originally diagnosed as stargardt disease. Am J Ophthalmol. https://doi.org/10.1016/j.ajoc.2020.100604

Mishra K *et al.* Choroidal Neovascularization Associated with Pentosan Polysulfate Toxicity. Ophthalmol Retina. 2020; 4(1), 111-113.

Sadda SR. A path to development of screening guidelines for pentosan maculopathy. Can J Ophthalmology. 2020; 55(1), 12.

Ludwig CA *et al.* Pentosan Polysulfate Sodium Exposure and Drug-Induced Maculopathy in Commercially Insured Patients in the United States. Ophthalmol. 2020 Apr;127(4):535-543. https://doi.org/10/1016/j.ophtha.2019.10.036

Hadad A *et al.* A Novel Multimethod Image Analysis to Quantify Pentosan Polysulfate Sodium Retinal Toxicity. Ophthalmology. 2020 Mar; 127 (3), 429-431.

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Jain N, *et al.* Association of macular disease with long-term use of pentosan polysulfate sodium: findings from a US cohort. Br J Ophthalmol 2019;0:1–5. doi:10.1136/bjophthalmol-2019-314765

Shaikh S, Shaikh N, Blumenkranz MS. Fluorescein angiographic changes in acute toxic retinopathy associated with polypharmacy. Retina-J Ret Vit Dis. 2000;20(6):685-688

Huckfeldt R, Vavvas D. Progressive Maculopathy After Discontinuation of Pentosan Polysulfate Sodium. Ophthalmic Surg Lasers Imaging Retina. 2019;50:656-659.

Ludwig CA, Vail D, Callaway NF, Pasricha MV, Moshfeghi DM. Pentosan polysulfate sodium exposure and drug-induced maculopathy in commercially insured patients in the United States. Ophthalmology. 2019 Nov 5. pii: S0161-6420(19)32211-0. doi: 10.1016/j.ophtha.2019.10.036. [Epub ahead of print]

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020193Orig1s014

OTHER REVIEW(S)

Division of Urology, Obstetrics, and Gynecology

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 020193/ S- 14

Name of Drug: Elmiron (pentosan polysulfate sodium) 100 mg Capsules

Applicant: Janssen Pharmaceuticals, Inc.

Labeling Reviewed

Submission Date: **June 24, 2019**

Receipt Date: **June 24, 2019**

Amendments: **March 24 and 31, April 24 and 28, May 8 and 18, 2020**

Background and Summary Description:
This Prior Approval supplement was submitted to add a warning of pigmentary maculopathy.. In order to support the supplement, the applicant submitted a review of the cumulative post-marketing cases reporting pigmentary maculopathy with the use of Elmiron and entered into the Global Medical Safety (GMS) global safety database, as well as a review of literature data, the Food and Drug Administration Adverse Event Reporting System (FAERS), and World Health Organization (WHO) Vigibase data.

On March 24, 2020, the applicant amended the supplement based on two literature searches and a search of all cases in their GMS Global Safety Database. The new proposed labeling was updated to included changes for (b) (4) WARNINGS, (b) (4) Precautions, Post-Marketing Adverse Reaction, and extensive changes to the Patient Leaflet.

Additional literature references were submitted March 31, April 24 and 28, 2020. On May 1, 2020, the applicant and the FDA discussed the labeling in a teleconference. As a result of the discussions in the teleconference, the applicant submitted amended labeling on May 8, 2020. On May 18, 2020, agreed upon labeling was submitted as the final amendment to the supplement.

Review

The Office of Surveillance and Epidemiology (OSE) completed a review of the labeling supplement and made the following recommendations:

> Update the Warnings section of the pentosan label to reflect the potential risk of pigmentary maculopathy and include the commonly reported symptoms of blurred vision, difficulty with dark adaptation, metamorphopsia, and nonspecific visual symptoms,

although their relationship to pigmentary changes is unknown.

The Division of Transplant and Ophthalmology Products (DTOP) also reviewed the labeling supplement. The final proposed labeling sent to the applicant included changes recommended by DTOP.

The clinical reviewer for the Division of Urology, Obstetrics, and Gynecology (DUOG) reviewed the information submitted to support the labeling changes. The DUOG reviewer concurs with OSE and DTOP that the data do not support a causal association between Elmiron and retinopathy.

Supplement 14 proposed labeling was compared to the last approved labeling (December 12, 2008). Based on the advice from DTOP and OSE, DUOG made substancial changes to the applicant's proposed labeling. The division sent the applicant the proposed labeling changes on May 13, 2020. Additions are shown with an underline and deletions are shown with strikethroughs. Minor editorial changes were also made to the labeling.

(b) (4)

Recommendations

The proposed labeling changes for NDA 020193/ S-14 were accepted by the applicant and submitted as an amendment to the NDA on May 18, 2020. An approval letter should be issued.

George Lyght, Pharm.D.
Regulatory Project Manager Date

Margaret Kober, R.Ph., M.P.A.
Chief, Project Management Staff Date

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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 Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Office of Surveillance and Epidemiology (OSE) Integrated Review

Date:	May 15, 2020
Reviewers:	Allison Lardieri, PharmD, BCPPS Karen Konkel, MD Division of Pharmacovigilance II (DPV II) Adebola Ajao, PhD Corinne Woods, RPh, MPH Division of Epidemiology II (DEPI II)
Team Leaders:	Lynda McCulley, PharmD, BCPS – DPV II Jie (Jenni) Li, PhD – DEPI II LCDR Justin Mathew, PharmD – DEPI II
Division Directors:	S. Christopher Jones, PharmD, MS, MPH – DPV II Monique Falconer, MD, MS – DEPI II (Acting Deputy) LCDR Grace Chai, PharmD – DEPI II (Deputy)
Product Name:	Elmiron (pentosan polysulfate sodium)
Subject:	Pigmentary maculopathy
Application Type/Number:	NDA 020193
Sponsor:	Janssen Pharmaceuticals, Inc.
OSE RCM #:	2019-355

Special acknowledgement to Wiley Chambers, MD, William Boyd, MD, and Manish Kalaria, MD for their contribution to this review.

TABLE OF CONTENTS

EXECUTIVE SUMMARY

Pentosan polysulfate sodium was approved by the FDA in 1996 and is indicated for the relief of bladder pain or discomfort associated with interstitial cystitis (IC). In 2018, Pearce et al. published a case series, "Pigmentary maculopathy associated with chronic exposure to pentosan", which first described this potential drug-adverse event association.[1] The sponsor for pentosan polysulfate sodium[a] submitted a prior approval supplement (PAS; see **Section 1.1**) requesting to add safety information concerning an association between pigmentary maculopathy and pentosan to the label. To assist the Division of Urology, Obstetrics, and Gynecology (DUOG) and the Division of Ophthalmology (DO) with responding to this PAS, OSE reviewed cases of pentosan-related pigmentary maculopathy[b] identified by searching multiple FDA databases[c] through February 2020, conducted epidemiological study review, and analyzed drug utilization patterns for pentosan.

On balance, our analysis of the available data indicates the presence of a new safety concern associated with pentosan. While the FAERS and literature findings from this review do not fully resolve the question of causation between pigmentary maculopathy and pentosan exposure, several compelling elements support an association (see table in **Appendix J** providing details about elements of causality assessment and currently available evidence). Retinal specialists at multiple ophthalmology practice sites have identified a novel pigmentary maculopathy associated with pentosan. The described patients had similar symptoms and fundoscopic changes that were reported to be distinct from age-related macular degeneration and other pigmentary maculopathies. No clear genetic cause was identified. There is preliminary evidence of a dose-response relationship, with pigmentary maculopathy cases reporting a significantly higher daily dose, longer duration of use, and higher cumulative dose of pentosan than non-cases. Several ophthalmologists have proposed plausible theories for potential mechanisms of action for pentosan-associated pigmentary maculopathy.

From a DPV perspective, there are challenges to causality assessment. Case reports and case series, by definition, lack a comparison group and can provide no information regarding background rate of pigmentary maculopathy in the untreated IC population. There is a long time between initiation of the drug and onset of the disease. Possible confounders were reported in some cases (i.e., smoking, concomitant medications, genetic variants of undetermined significance), and other cases lacked detail about concomitant conditions and medications.

From an epidemiology perspective, study results suggest an association, but the limitations of the observational studies preclude concluding a causal relationship between pentosan and pigmentary maculopathy. The two large claim-based studies reported no significant association between pentosan and different maculopathy outcomes but are subject to major limitations such as the lack of retinal imaging confirmation and the lack of validation of study outcome

[a] For the remainder of the document, pentosan polysulfate sodium (PPS, brand name Elmiron) will be referred to as pentosan.
[b] For completeness, we broadened our search to include all terms related to retinopathy.
[c] FDA databases used in this review include the FDA Adverse Event Reporting System, National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance, and World Health Organization VigiBase.

algorithms, short follow-up time, and potential residual confounding. Three studies that conducted multimodal retinal imaging suggested an association between pentosan exposure and pigmentary maculopathy and provided preliminary evidence of dose response among patients exposed to pentosan. However, these studies were also limited by lack of unexposed comparator and potential selection bias, potential outcome misclassification, and residual confounding. Despite these study limitations, we could not rule out a possible causal relationship between pentosan and pigmentary maculopathy.

In conclusion, there are several compelling elements from our data that support an association between pentosan and a novel pigmentary maculopathy. Although the clinical consequences of this unique maculopathy remain unclear given that the reported symptoms are general vision complaints common in the described age group, we believe this drug/adverse event pairing warrants inclusion in the labeling of pentosan. Because pentosan is typically prescribed by non-ophthalmologists, it is especially important to make all health care professionals aware of this association.

Based on this review, OSE recommends the following:

- Update the Warnings section of the pentosan label to reflect the potential risk of pigmentary maculopathy and include the commonly reported symptoms of blurred vision, difficulty with dark adaptation, metamorphopsia, and nonspecific visual symptoms, although their relationship to pigmentary changes is unknown.

[1] Pearce WA, Chen R, Jain N. Pigmentary maculopathy associated with chronic exposure to pentosan polysulfate sodium. *Ophthalmology*. 2018;125:1793-1802

1 INTRODUCTION

Pentosan polysulfate sodium was approved by the FDA in 1996 and is indicated for the relief of bladder pain or discomfort associated with interstitial cystitis (IC). In 2018, Pearce et al. published a case series, "Pigmentary maculopathy associated with chronic exposure to pentosan", which first described this potential drug-adverse event association.[1] The sponsor for pentosan polysulfate sodium[d] submitted a prior approval supplement (PAS; see **Section 1.1**) requesting to add safety information concerning an association between pigmentary maculopathy and pentosan to the label. To assist the Division of Urology, Obstetrics, and Gynecology (DUOG) and the Division of Ophthalmology (DO) with responding to this PAS, OSE reviewed cases of pentosan-related pigmentary maculopathy[e] identified by searching multiple FDA databases[f] and the medical literature through February 2020, conducted epidemiological study review, and analyzed drug utilization patterns for pentosan.

1.1 PRIOR APPROVAL SUPPLEMENT

On June 24, 2019, the sponsor submitted a PAS proposing to add a warning on pigmentary maculopathy:

Sponsor's Conclusions: "Based on the review of cases from the Global Medical Safety (GMS) global safety database, published literature, and datamining from FAERS and Vigibase, maculopathy is not considered causally associated with the use of PPS. However, considering the new available data from the literature review and the elevated EGBM's for macular lesions, the Company proposed to add pigmentary maculopathy in the Warnings section of the Elmiron RSI."

Sponsor's proposed labeling:

Warnings

(b) (4)

(b) (4)

On March 24, 2020, the sponsor submitted an amendment to the pending prior approval supplement:

"This amendment is based on the availability of new information from the literature and cases from Janssen Research & Development's (JRD) Global Safety Database which concludes that there is sufficient evidence to support that pigmentary maculopathy is possibly associated with the long-term use of PPS."

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[d] For the remainder of the document, pentosan polysulfate sodium (PPS, brand name Elmiron) will be referred to as pentosan.

[e] For completeness, we broadened our search to include all terms related to retinopathy.

[f] FDA databases used in this review include the FDA Adverse Event Reporting System, National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance, and World Health Organization VigiBase.

Sponsor proposes to incorporate revisions into the following sections: (b) (4) Update to the Warnings section, Update to the Precautions, Information for Patients section, Addition of a Postmarketing Adverse Reaction, Updates to the Patient Leaflet. (See **Appendix A** for sponsor's proposed additions to all sections of the label)

Sponsor's proposed labeling (b) (4)

(b) (4)

On May 1, 2020 DUOG, DO, and OSE met with Janssen Pharmaceuticals to discuss the labeling supplement and all agreed that inclusion in the Warnings section was appropriate.

On May 12, 2020, Janssen Pharmaceuticals resubmitted the labeling supplement to include this adverse event in the Warnings section.

1.2 BACKGROUND

1.2.1 Overview of Anatomy and Physiology of the Retina

The retina is a complex multi-layered structure that is about 0.5 mm thick and is situated at the back of the eye.[2] It transduces light entering the eye into biochemical and then electrical impulses that are transmitted via the optic nerve to the visual cortex of the brain, where visual input is interpreted.[3] A simple side-view schematic of eye anatomy is provided below (**Figure 1**)[2].

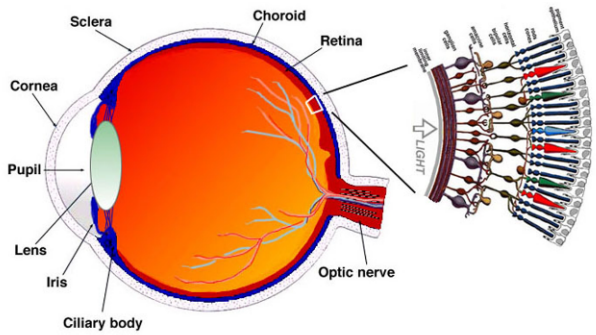

Figure 1: A drawing of a section through the human eye with a schematic enlargement of the retina

Source: Kolb, H. Simple anatomy of the retina. *Webvision*. http://webvision med.utah.edu/

Different parts of the retina carry out different functions. The central part of the retina is dominated by cones, the photoreceptors that allow for color perception and visual acuity. The fovea is the central-most portion of the macula, which is responsible for central (acuity and fine detail) vision. The peripheral retina has more rods, which allow for vision in lower light conditions, as well as detection of motion and contrast. Looking through an ophthalmoscope, one can view the fundus, another term for the back of the eye, which includes the retina, fovea, macula, retinal blood vessels, and optic nerve. A normal fundus is depicted in **Figure 2**.[2] There are many other examination techniques for anatomic and functional evaluation of the fundus, including electroretinography, fundus fluorescein angiography (FFA), fundus autofluorescence (FAF), near-infrared reflectance imaging (NIR), and (cross-sectional) optical coherence tomography (OCT).[3,4] Combining these techniques allows for a more comprehensive understanding of fundal pathology.

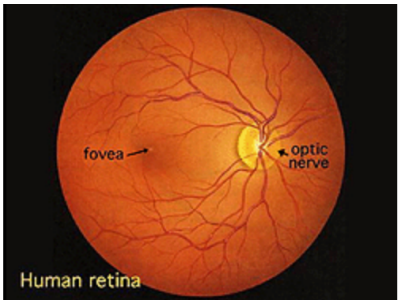

Figure 2. Normal fundus
Source: Kolb, H. Simple anatomy of the retina. *Webvision*. http://webvision.med.utah.edu/

The retinal pigment epithelium (RPE) is the deepest layer of the retina. The RPE contains two types of pigment: lipofuscin and melanin.[5] Lipofuscin is an age-related pigment that accumulates over time. Melanin is believed to protect the eye by absorbing visible light and binding free radicals.

Deep to the RPE is the choriocapillaris, an array of blood vessels that is the sole source of blood supply to the central vision. The interface between the RPE and the choriocapillaris is called Bruch's membrane (BM), a five-layered extracellular matrix.[6] These structures together effectively create the retina-blood barrier.[7]

The RPE has a multitude of functions, including light absorption, epithelial transport between the retina and the bloodstream and the retina and glial cells[g] (for nutrition and waste management), maintaining the visual cycle (the mechanism by which phototransduction occurs), phagocytosis (which repairs photo-oxidative damage to a component of the photoreceptors), and secretion (of molecules that communicate with cells of neighboring tissues and the immune system).[2] **Figure 3** depicts the anatomy and physiology of the RPE.[2]

[g] Glial cells are the supporting cells of the nervous system, including the retina.

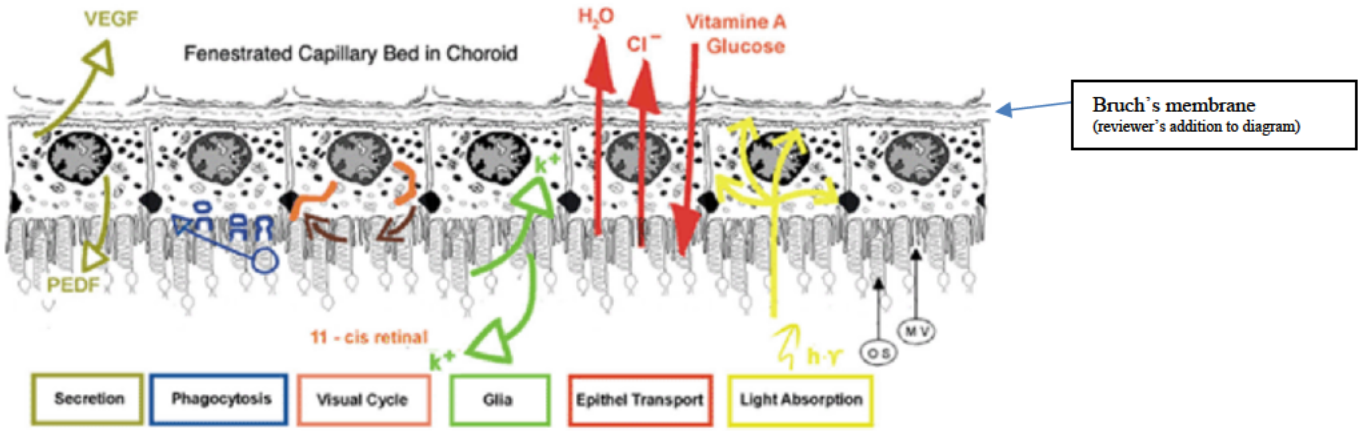

Figure 3. The anatomy and physiology of the retinal pigment epithelium
Source: Kolb, H. Simple anatomy of the retina. *Webvision*. http://webvision.med.utah.edu/

With increasing age, the retina thins as neurons are lost and photoreceptor cells shorten.[5] The RPE/BM complex undergoes gradual structural deterioration including loss of microvilli, deposition of lipofuscin and drusen (cellular debris), and thickening of BM. This deterioration may be evident on ophthalmoscopy, OCT, and wide-field AF. Once damaged, the RPE does not have much capacity for regeneration.[3]

1.2.2 Overview of Maculopathy

Retinopathy is a general term referring to retinal injury, with common causes including diabetes, hypertension, and premature birth. Maculopathy is more specific and refers to pathologic conditions of the macula, the central area of the retina associated with visual acuity. Symptoms can include decreased vision, visual scotoma (an area of lost or depressed vision within a visual field), or metamorphopsia (a disturbance of vision in which objects are seen as wavy or distorted in shape).[8] The differential diagnosis for maculopathy is broad and includes the common condition known as age-related macular degeneration (AMD). Several drugs can cause maculopathies or pigmentary degeneration including epinephrine, niacin, deferoxamine, didanosine, phenothiazines, quinolines (chloroquine, hydroxychloroquine), and quinine.[8] With deferoxamine, damage may be permanent and may occur after a single dose of medication. The American Academy of Ophthalmology has established monitoring guidelines for patients taking chloroquine and hydroxychloroquine.[9]

A subset of macular diseases historically categorized as pattern dystrophies may more appropriately be termed pigmentary maculopathies.[10] These disorders are diverse and are either genetic or acquired. In general, they have fundus abnormalities consistent with RPE degeneration, including abnormal yellow, orange or gray lipofuscin pigment deposition in the RPE and subretinal space. Despite their similarities, each disease's pattern of pigment deposition and underlying pathogenic mechanism is unique, though some clinical findings are more distinct than others. Some patients may have pigmentary disturbances that progress with no deterioration in visual function, whereas others have progressive visual disturbances including decreased visual acuity, difficulty with dark adaptation, blurred vision, visual scotoma, and/or metamorphopsia.[7, 8]

The adverse event of interest in this review is a pigmentary maculopathy described in 2018 by Pearce, et al., that is associated with the use of pentosan.[11] It has unique characteristics that include "(1) fundus photography revealing macular hyperpigmented spots, yellow-orange deposits, and/or patchy retinal pigment epithelium (RPE) atrophy; (2) AF imaging revealing a densely packed array of hyperautofluorescent and hypoautofluorescent spots involving the posterior pole; and (3) optical coherence tomography (OCT) imaging demonstrating focal thickening or elevation of the RPE with associated hyperreflectance on NIR imaging."[4] Additionally, funduscopic findings of macular pigmentary changes are more subtle than the associated AF and NIR findings, which have been described as "striking".[4] The primary symptoms of this disorder include difficulty reading and prolonged dark adaptation, with preserved visual acuity in many cases.

1.2.3 Overview of Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS)

IC/BPS is a complex, poorly understood chronic visceral pain disorder characterized by "an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than six weeks duration, in the absence of infection or other identifiable causes".[12] It most frequently presents in the fourth decade and is more common in women than in men.[13] Because criteria for diagnosis have varied, prevalence studies have been challenging. Prevalence in self-report and billing data studies has been estimated to be between 197-850/100,000 women and 41-60/100,000 men.[13] The RAND Interstitial Cystitis Epidemiology (RICE) study estimated that between 2.7-6.5% of US women have symptoms consistent with the disease.[14] IC/BPS is often associated with other chronic pain syndromes like irritable bowel syndrome, vulvodynia, and fibromyalgia.[13] Of note, retinal disease is not a described co-condition.[10]

The American Urological Association has developed a diagnostic algorithm guideline and proposed a step-wise approach to treatment, beginning with the least invasive options.[15] Diagnosis involves obtaining a careful history, performing physical and lab exams, and asking about baseline voiding symptoms and pain levels. Cystoscopy should be considered if the diagnosis is uncertain. First line treatment involves non-drug options such as patient education about the chronic nature of and challenges in treating the disease, self-care and behavioral modification, and teaching coping skills to help mitigate stress-induced exacerbations. Second line treatments include physical therapy, multimodal pain management, and a range of medications including **pentosan**, amitriptyline, cimetidine, hydroxyzine, intravesical heparin, DMSO, or lidocaine.

1.2.4 Overview of Pentosan Polysulfate Sodium

Pentosan is a low molecular weight heparin-like compound used to treat bladder pain associated with IC. It is recommended as a second-line treatment for IC by the American Urological Association's guidelines for IC and is the only FDA approved oral agent for IC.[16] In the 1950s, pentosan was originally used for its heparin-like properties, although its anticoagulant effect is 1/15th the activity of heparin.[17,18] Its proposed mechanism of action in IC is to adhere to the mucosal membrane of the bladder wall and buffer against irritants in the urine.[17]

The most common adverse events reported with pentosan in an unblinded clinical trial of 2499 IC patients treated for up to 4 years, were alopecia (4%), diarrhea (4%), nausea (4%), headache (3%), rash (3%), dyspepsia (2%), abdominal pain (2%), liver function abnormalities (1%), and dizziness (1%).[17] A post-marketing, randomized, double-blind, parallel group, Phase 4 study of 380 patients with IC treated with pentosan for 32 weeks reported rectal hemorrhage (6.3%) as the most common adverse event.[17] Several small clinical trials of pentosan use over a short duration of time (3-18 months) did not report any vision-related safety signals.[19,20,21] However, conjunctivitis, optic neuritis, amblyopia, and retinal hemorrhage were reported at a frequency of ≤1% in the clinical trial of 2,499 patients who received pentosan for up to 4 years.[17] The relatively short duration of exposure to the drug in study settings limits identification of adverse events with a long clinical latency, such as a retinal pigment disorder.

1.3 REGULATORY HISTORY

Pentosan was approved by the FDA in 1996 and is indicated for the relief of bladder pain or discomfort associated with IC. It is designated as an orphan drug for the treatment of sickle cell disease and treatment of mucopolysaccharidosis (MPS) type VI. Pentosan is also approved in Australia, Canada, Germany, Argentina, Singapore, and Italy.[22]

1.4 PRODUCT LABELING

The current pentosan product label contains the following ocular related adverse events **(bolded)**[17] :

ADVERSE REACTIONS

> 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; 598 (24%) received ELMIRON® for one year, 355 (14%) received ELMIRON® for 2 years, and 145 (6%) received ELMIRON® for 4 years.
>
> *Special Senses:* **Conjunctivitis,** tinnitus, **optic neuritis, amblyopia, retinal hemorrhage**.

2 METHODS AND MATERIALS

2.1 CASE DEFINITION

The following case definition was adapted from the OSE Retinopathy Case Definition (2006)[8] and reviewed by Dr. Wiley Chambers and Dr. William Boyd (DO). Although the adverse event of interest in this review is pigmentary maculopathy, the case definition was kept broad to include all cases of retinopathy for completeness.

Inclusion Criteria:
A case will be included if a temporal relationship exists with pentosan and it satisfies one of the following criteria:

- The term retinopathy or retinal toxicity is explicitly used in the FAERS or literature report as a possible clinical diagnosis
- The report specifies any manifestation resulting from insult to the retina (e.g., hemorrhage, edema, or pigmentary changes)
- The report specifies any evidence of findings upon visual exam such as bull's eye maculopathy, cotton wool spots, or other abnormalities of the retina
- The report specifies a diagnosis of macular degeneration

Exclusion Criteria:
A case will be excluded if it satisfies one of the following criteria:

- The report describes non-specific vision changes (i.e., abnormal vision, blurry vision or decreased vision) without a clinical diagnosis
- Alternate etiology is provided

2.2 FAERS SEARCH STRATEGY

DPV searched the FAERS database to identify case reports to evaluate the association between pentosan and retinopathy with the strategy described in **Table 1**.

Table 1. FAERS Search Strategy*	
Date of Search	March 6, 2020
Time Period of Search	All reports through February 14, 2020
Search Type	*FBIS Quick Query*
Product Terms	Product Active Ingredient: Pentosan polysulfate, pentosan polysulfate sodium
MedDRA Search Terms† (Version 22.0)	High Level Group Terms: *Congenital eye disorders (excl glaucoma); Ocular structural change, deposit and degeneration NEC; Retina, choroid and vitreous haemorrhages and vascular disorders* High Level Terms: *Ocular bleeding and vascular disorders NEC; Retinal, choroid and vitreous infections and inflammations; Visual impairment and blindness (excl colour blindness); Retinal structural change, deposit and degeneration* Preferred Terms: *Chorioretinal disorder; Posterior segment of eye anomaly; Retinal disorder; Retinal injury; Optical coherence tomography abnormal; Fundus autofluorescence; Retinogram abnormal; Retinogram; Metamorphopsia; Visual impairment; Retinal function test abnormal*
* See **Appendix B** for a description of the FAERS database. † Search strategy was reviewed by Drs. Manish Kalaria (Regulatory Science Staff), Wiley Chambers, and William Boyd (DO).	

2.3 NATIONAL ELECTRONIC INJURY SURVEILLANCE SYSTEM – COOPERATIVE ADVERSE DRUG EVENT SURVEILLANCE (NEISS-CADES) SEARCH STRATEGY

The NEISS-CADES dataset was queried to identify cases of patients presenting to the emergency department with vision problems potentially associated with pentosan use. DPV searched the NEISS-CADES dataset to identify case reports to evaluate the association between pentosan and retinopathy with the strategy described in **Table 2**:

Table 2. NEISS-CADES Search Strategy*	
Date of Search	March 6, 2020
Time period of search	January 1, 2004 to December 31, 2018
Drug Data - Drug	Pentosan polysulfate sodium
ADE Description (MedDRA PT)	All adverse events†
* See **Appendix C** for a description of the NEISS-CADES dataset. † All adverse events were searched to cast a wide net on all possible vision disorders patients may present with to an emergency department.	

2.4 WORLD HEALTH ORGANIZATION VIGIBASE SEARCH STRATEGY

The World Health Organization (WHO) VigiBase database was queried to identify cases outside the US where pentosan is marketed. DPV searched the WHO VigiBase database to identify reports of pentosan and retinopathy with the strategy described in **Table 3**:

Table 3. WHO VigiBase Search Strategy*	
Date of Search	March 6, 2020
Time period of search	All reports through February 14, 2020
Product Terms	Pentosan polysulfate
MedDRA Search Terms† (Version 21.1)	High Level Group Terms: *Congenital eye disorders (excl glaucoma); Ocular structural change, deposit and degeneration NEC; Retina, choroid and vitreous haemorrhages and vascular disorders* High Level Terms: *Ocular bleeding and vascular disorders NEC; Retinal, choroid and vitreous infections and inflammations; Visual impairment and blindness (excl colour blindness); Retinal structural change, deposit and degeneration* Preferred Terms: *Chorioretinal disorder; Posterior segment of eye anomaly; Retinal disorder; Retinal injury; Optical coherence tomography abnormal; Fundus autofluorescence; Retinogram abnormal; Retinogram; Metamorphopsia; Visual impairment; Retinal function test abnormal*
* See **Appendix D** for a description of the Vigibase database. † Search strategy was reviewed by Drs. Manish Kalaria, Wiley Chambers, and William Boyd.	

2.5 LITERATURE SEARCH STRATEGY

DPV and DEPI searched Embase and the National Library of Medicine's PubMed database to identify case reports and observational studies in humans that evaluate the association between pentosan and retinopathy with the strategies described in **Table 4**.

Table 4. Literature Search Strategy

Date of Search	March 6, 2020*				
Database	Embase #1	Embase #2	PubMed #1	PubMed #2	PubMed #3
Search Terms	(("pentosan sulfuric polyester"[MeSH Terms] OR ("pentosan"[All Fields] AND "sulfuric"[All Fields] AND "polyester"[All Fields]) OR "pentosan sulfuric polyester"[All Fields] OR "pentosan"[All Fields]) AND adverse[All Fields]) AND (Case Reports[ptyp] AND "humans"[MeSH Terms	(("pentosan sulfuric polyester"[MeSH Terms] OR ("pentosan"[All Fields] AND "sulfuric"[All Fields] AND "polyester"[All Fields]) OR "pentosan sulfuric polyester"[All Fields] OR "pentosan"[All Fields]) AND adverse[All Fields])	(pentosan) AND (adverse)	(pentosan) AND (adverse)	((Elmiron) OR (pentosan) AND (maculopathy) OR (pigmentary maculopathy) OR (retinopathy) OR (retinal pigmentation) OR (retinal disease))
Years Included in Search	All through February 14, 2020				
Other criteria	None	None	Filtered on CASE and HUMAN	None	Filtered on HUMAN

*An additional report was identified through a literature alert on October 15, 2019.

2.6 PERIODIC SAFETY REPORT

DPV reviewed the most recent periodic adverse event drug experience report (PADER) for pentosan, dated September 26, 2018 – September 25, 2019, to identify safety issues of retinopathy or pigmentary maculopathy assessed by the sponsor.

2.7 DRUG UTILIZATION

Proprietary drug utilization databases available to FDA were used to conduct these analyses. Detailed descriptions of the databases are included in **Appendix E**. The IQVIA National Sales Perspective™ provided national estimates of manufacturer sales of pentosan bottles in 2018 to all channels of distribution. IQVIA Total Patient Tracker™ data source provided the nationally estimated number of patients who received dispensed pentosan prescriptions from outpatient retail pharmacies from 2011 through 2018. Data were stratified by patient sex and age.

3 RESULTS

3.1 FAERS CASE SELECTION

The FAERS search retrieved 102 reports. After applying the case definition in **Section 2.1** and accounting for duplicate reports, 27 cases met inclusion criteria. Of the 27 FAERS cases, 7 cases were published in 2 literature articles (Pearce et al. (n=6) and Shaikh et al. (n=1)). These 7 literature cases are discussed in **Section 3.4** below and are not included in this FAERS case series. Therefore, this **FAERS-only** case series includes **20 cases (Figure 4).**

Figure 4. FAERS Case Selection

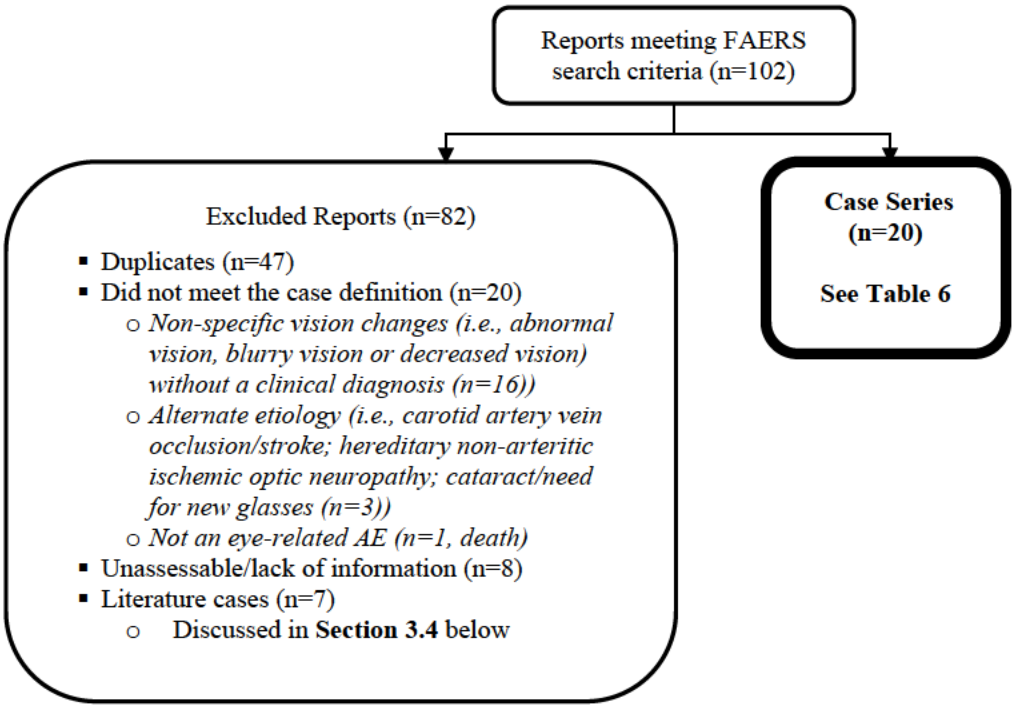

Table 6 summarizes the 20 FAERS cases of retinopathy reported with pentosan for this case series.

Appendix F contains a line listing of the 20 cases in this case series.

Table 6. Descriptive Characteristics of Retinopathy with Pentosan in this FAERS Case Series, Received by FDA through February 14, 2020 **(N=20)**	
Year received by FDA	
1997	**1**
1998	**1**
2000	**1**
2003	**1**
2009	**1**
2010	**1**
2011	**1**
2013	**1**
2015	**1**
2016	**1**
2018	**2**
2019	**6**
2020	**2**
Country	
USA	**20**
Report Type	
Expedited	**11**
Direct	**5**
Non-expedited	**4**
Age (years), n=18	
Mean	**63.2**
Median	**63**
Range	**44-82**
Sex	
Female	**17**
Male	**1**
NR	**2**
PTs Reported in ≥2 cases	
Macular degeneration	**5**
Maculopathy	**5**
Eye haemorrhage	**2**
Incorrect dose administered	**2**
Off-label use	**2**
Retinal haemorrhage	**2**
Retinal injury	**2**
Retinal pigmentation	**2**

Table 6. Descriptive Characteristics of Retinopathy with Pentosan in this FAERS Case Series, Received by FDA through February 14, 2020 **(N=20)**	
Visual impairment	**2**
Cases reporting "maculopathy", "pigmentary maculopathy*" or "pigmentary changes"*	**8**
Cases reporting diagnosis of macular degeneration	**6†**
Cases reporting diagnosis of retinal hemorrhage‡	**5**
Cases reporting adverse event diagnosed by ophthalmologist	**9**
Cases providing fundus imaging	**0**
Time to onset (n=17)	
Mean	**9.2 years**
Median	**5 years**
Range	**2 days to 28 years**
Pentosan indication	
Interstitial cystitis	**17**
NR	**3**
Pentosan dose and frequency	
100 mg BID	**2**
100 mg TID	**10**
100 mg TID – daily	**1**
100 mg QID	**2**
200 mg BID	**2**
200 mg TID	**1**
NR	**2**
Reporter	
Patient or patient's family member	**17**
Health care provider	**3**
Drug disposition	
Discontinued	**9**
Continued	**6**
Dose reduced	**1**
NR	**4**
Outcome	
Recovered	**1**
Recovering	**1**
Not recovered	**11**
NR	**7**
Dechallenge	**1**
Rechallenge	**0**

Table 6. Descriptive Characteristics of Retinopathy with Pentosan in this FAERS Case Series, Received by FDA through February 14, 2020
(N=20)
* Cases reporting "maculopathy", "pigmentary maculopathy*" or "pigmentary changes" are described in detail in **Section 3.1.2**
† One case was not coded with PT macular degeneration but coded with PT Retinal disorder. The narrative noted a diagnosis of macular degeneration.
‡ Retinal hemorrhage is labeled in the Adverse Reactions section as pentosan is known to have anticoagulant properties.

3.1.1 Key Summary Points of Patient Characteristics

- The majority (17/20) of patients are female and IC is the reported indication in the majority (17/20) of cases.
- 12/20 FAERS cases describe types of retinopathy other than pigmentary maculopathy.
- Pentosan dosing reported is within recommended dosage range (300 mg/day) in 13 cases.
- Time to onset (TTO) of the adverse event ranged from 2 days to 28 years, with a mean of 9.2 years.
    - The case with a TTO of 2 days was a retinal hemorrhage.
- None of the FAERS cases provide fundus imaging.
- FDA received 9/20 FAERS cases after the Pearce et al. case series was published in 2018. These may be a result of stimulated reporting.

*3.1.2 **Description of Cases Reporting** "Maculopathy", "Pigmentary Maculopathy", or "Pigmentary Changes**" (Subset of the FAERS cases)***

"Maculopathy", "pigmentary maculopathy" or "pigmentary changes" were reported in 8/20 FAERS cases, all of which were received after the publication of the article by Pearce et al. The 8 cases are further described in **Table 7** below.

Table 7. Description of FAERS Cases Reporting "Maculopathy", "Pigmentary Maculopathy", or "Pigmentary Changes" (Subset of the FAERS cases) through February 14, 2020 (n=8)

FAERS Case #	Year FDA Received/ Age/Sex/ Reported Indication/ Dose	Adverse Event Reported/ Symptoms Reported	Ophthalmologist Diagnosis (Y/N/NR)	Time to Onset (years)	Past Medical History	Concomitant Medications	Drug Disposition/ Outcome of event
15469252	2018 72/F IC 100 mg TID	Macular degeneration, pigmentary changes Symptoms: NR	NR	28	Bladder cancer, breast cancer, cataract surgery, right shoulder surgery, blurred vision, fibromyalgia, seasonal allergies, allergic to cats, drug allergies, smoker	Systane, cyclosporine, denosumab, cyclobenzaprine	Discontinued/ Not recovered
15678737	2018 49/F IC 100 mg TID	Elmiron toxicity, retinal pigmentation Symptoms: "seeing wavy horizontal lines where the lines were actually flat"	Y	24	Hypertension, depression, gastrointestinal reflux disease, attention deficit disorder	Aripiprazole, cetirizine, CystoProtek (contains chondroitin, glucosamine, quercetin, rutin, sodium hyaluronate, and olive kernel oil),	Discontinued/ Recovering (Positive dechallenge)

Table 7. Description of FAERS Cases Reporting "Maculopathy", "Pigmentary Maculopathy", or "Pigmentary Changes" (Subset of the FAERS cases) through February 14, 2020 (n=8)							
FAERS Case #	**Year FDA Received/ Age/Sex/ Reported Indication/ Dose**	**Adverse Event Reported/ Symptoms Reported**	**Ophthalmologist Diagnosis (Y/N/NR)**	**Time to Onset (years)**	**Past Medical History**	**Concomitant Medications**	**Drug Disposition/ Outcome of event**
						diindolylmethane, escitalopram, lamotrigine, methylphenidate extended release, metoprolol/HCTZ, pantoprazole, a multivitamin, and a probiotic	
16242978	2019 63/F IC 200 mg BID	Pigmentary maculopathy Symptoms: NR	Y	22	Asthma	Urelle (hyoscyamine sulfate, methenamine, methylene blue, phenyl salicylate, sodium phosphate monobasic), hydroxyzine, atorvastatin, advair inhaler	Discontinued/ Not recovered
16343089	2019 51/F IC 100 mg QID	Hyperpigmentation, retinal damage Symptoms: vision deteriorated over last 3 years, trouble seeing in low light, blurry vision, photo sensitivity, "hard to see"	Y	12	Non-smoker, alcohol user, sulfa drug allergy	Pantoprazole, amitriptyline	Dose reduced/ Not recovered
16432860	2019 61/F IC 100 mg TID	Pigment changes, macular dystrophy Symptoms: couldn't see colors, trouble driving	NR	NR	None	NR	NR/ Not recovered
16612747	2019 NR/F IC 100 mg QID	Maculopathy/retinal dystrophy Symptoms: NR	NR	9	NR	NR	NR/ Not recovered
17225077	2020 44/F IC 100 mg BID	PPS maculopathy "secondary to long term use of Elmiron" Symptoms: blurry vision, central distortion in both eyes up close and at a distance for 5 years that has progressively worsened	Y; Notes findings consistent with "recent study presented by American Academy of Ophthalmology in	20	NR	NR	NR/NR

Table 7. Description of FAERS Cases Reporting "Maculopathy", "Pigmentary Maculopathy", or "Pigmentary Changes" (Subset of the FAERS cases) through February 14, 2020 (n=8)							
FAERS Case #	**Year FDA Received/ Age/Sex/ Reported Indication/ Dose**	**Adverse Event Reported/ Symptoms Reported**	**Ophthalmologist Diagnosis (Y/N/NR)**	**Time to Onset (years)**	**Past Medical History**	**Concomitant Medications**	**Drug Disposition/ Outcome of event**
			October of 2019"				
17419932	2020 NR/NR NR NR	Macular toxicity and permanent vision damage Symptoms: Permanent damage to vision	Y	NR	NR	NR	NR/NR
Abbreviations: NR=not reported; IC=interstitial cystitis							

Key Summary Points of FAERS Cases Reporting "Maculopathy", "Pigmentary Maculopathy", or "Pigmentary Changes" (n=8)

- In 7/8 cases, patients were female and the reported indication was IC. Pentosan dosing reported is within recommended dosage range (300 mg/day) in 4/8 cases and is 400 mg per day in 3/8 cases. (dose NR in one case)
- Visual symptoms were reported in 5/8 cases.
- Time to onset (TTO) of the adverse event ranged from 9 to 28 years (n=6), with a mean of 19 years, and median of 21 years.
- None of the FAERS cases provide fundus imaging.
- 1 case reported a patient with previous history of cataract surgery, a potential confounder.

3.1.3 Representative Case Narrative

The following case narrative was selected as a representative case. It is a direct report from a patient received by FDA after the Pearce et al. study was published in 2018.

Case 15678737, Direct, 2018, USA, "Elmiron toxicity"

A 49-year-old female with IC on pentosan for 24 years reported visual problems including "seeing wavy horizontal lines where the lines were actually flat." She had a PMH of hypertension, depression, GERD, and ADHD. Concomitant medications included aripiprazole, cetirizine, CystoProtek (contains chondroitin, glucosamine, quercetin, rutin, sodium hyaluronate, and olive kernel oil), diindolylmethane, escitalopram, lamotrigine, methylphenidate extended release, metoprolol/HCTZ, pantoprazole, a multivitamin, and a probiotic. She had no family history of eye problems. She was noted by an ophthalmologist to have drusen and retinal pigment epithelium changes in the central macula of both eyes and was diagnosed with Stargardt disease[h,23, 24]. Upon receiving this diagnosis, she researched online and found the Pearce et al.

[h] Stargardt disease is an inherited disorder of the retina that typically causes vision loss during childhood/adolescence, although in some forms vision loss may not be noticed until later in adulthood. The disease

case series. She shared this study with her ophthalmologist, who subsequently stated that her disease "is likely related to Elmiron toxicity." He recommended she follow up with her urologist and discontinue pentosan at this time. She discontinued pentosan and after 3 months, noted that the "wavy lines are getting 80% better."

Reviewer's comments: Causality is difficult to establish in this case with such a long time to onset as 24 years. The patient's report of a ***positive dechallenge*** *supports a potential causal relationship between pentosan and the visual problems she describes. In most instances of pigmentary degradation related to drugs, reversibility is possible; however, some patients may have continued depigmentation and functional loss over several years after the drug has been stopped.*[8] *It is not clear if there were corresponding fundus changes that are consistent with improvement in vision. Additionally, concomitant disease states and medications could have contributed to development of the visual problems. Hypertension can trigger retinopathy and lead to visual changes. Lamotrigine is labeled in Warnings and Precautions for "binding in the eye and other melanin-containing tissues." The warning notes that prescribers should be aware of the possibility of long-term ophthalmologic effects.*[25] *This case provides an example of an ophthalmologist diagnosing "Elmiron toxicity" retinopathy in a patient on pentosan. It is important to note that this report was stimulated by the publication of the Pearce et al. case series.*

3.2 NEISS-CADES

The NEISS-CADES search retrieved (b) (4) reports. After applying the case definition in **Section 2.1**, there were no cases included in this case series.

3.3 VIGIBASE

The VigiBase search retrieved (b) (4) de-duplicated individual case safety reports (ICSRs). Reports may be duplicates of the FAERS cases already identified. Narratives are not available for the cases identified in VigiBase, and therefore we are unable to apply our case definition. **Appendix G** contains a line listing of the (b) (4) ICSRS from Vigibase.

Table 8 lists the most commonly reported PTs in VigiBase ICSRs for pentosan and the adverse events of interest.

Table 8. Most Common PTs reported in VigiBase ICSRs through February 14, 2020, (n= (b) (4))*	
PT	**Count**
Visual impairment	(b) (4)
Maculopathy	
Macular degeneration	
Dizziness	
Off label use	

causes progressive damage of the macula and is also called Stargardt macular dystrophy, juvenile macular degeneration or fundus flavimaculatus.

Alopecia	(b) (4)
Drug ineffective	
Dry eye	
Eye haemorrhage	
Incorrect dose administered	
Retinal haemorrhage	
Retinal injury	
Visual acuity reduced	
Blindness unilateral	
Cataract	
Cystitis interstitial	
Decreased appetite	
Headache	
Insomnia	
Retinal pigmentation	
***Only PTs reported in (b) (4) ICSRs were included in this table. Of note, the PTs Blindness, Retinal disorder, Retinal drusen, and Retinal dystrophy were reported in (b) (4).**	

3.3.1 Key Summary Points

- (b) (4) is from Korea, Germany, United Kingdom, and Turkey and the remaining (b) (4) reports are from the US.
- Of the non-US reports, only the report from the United Kingdom included the adverse event of interest:
  - UMC report ID# (b) (4), United Kingdom: This report includes the PTs *Adjustment disorder, Maculopathy, Eyelid margin crusting, and Dry eye* in a 53-year-old female on pentosan 300 mg (frequency NR) for 12 years for IC. Concomitants included hydroxychloroquine and amitriptyline. Pentosan was withdrawn and the outcome of *Maculopathy* was not recovered.
- (b) (4) reports were received in 2019, after the Pearce et al. case series was published in 2018. These may be a result of stimulated reporting.
- Overall, the VigiBase cases do not provide evidence that pigmentary maculopathy is an adverse event reported with pentosan in countries outside the U.S.

3.4 DPV LITERATURE

DPV's literature search identified four pertinent case reports involving 37 patients: Shaikh et al. 2000 (n=1, reported to FAERS); Pearce et al. 2018 (n=6, reported to FAERS); Hanif et al. 2019 (n=35, includes the six patients reported in Pearce et al.); and Huckfeldt 2019 (n=1). DPV's summary and comments on the published case reports are presented below.

3.4.1 **Shaikh S** *et al., Retina-J Ret Vit Dis. 2000*[26]

Case Summary:
A 38-year-old female with IC developed acute retinal toxicity after receiving multiple medications during a hospital admission. Her PMH included ischemic colitis, non-insulin

dependent diabetes mellitus, chronic pelvic pain and depression. Her pre-admission medications were oral and intrathecal morphine sulfate, pentosan, gabapentin, lorazepam, hydroxyzine, glimepiride, and promethazine. She was admitted to the hospital for continued management of pain and depression, and in addition to receiving her home medications while admitted, she received a single-dose infusion of intravenous lidocaine, daily oral mexiletine, and pain "cocktails" consisting of oral baclofen, clonidine and methadone. She was also started on fluoxetine, sucralfate, and trazodone while admitted. She began to experience visual symptoms during the admission at the time of treatment with IV lidocaine and oral mexiletine and 4 days later was referred to ophthalmology for bilateral central scotomas. She was noted to have funduscopic changes, in particular, "significant hypofluorescent angiographic lesions that stained markedly in the late frames of the study circa the onset of visual loss." Due to acute retinal changes, she was advised to stop all drugs. After discontinuation of all drugs, her visual acuity improved, and she was noted to have "resolution of the acute hyperpermeable angiographic changes noted earlier and their replacement by diffuse retinal pigment epithelia atrophy associated with pigment clumping." Her medications were reinitiated over the next few months and during this time, she reported loss of vision upon taking oral mexiletine, which was immediately discontinued. The authors noted they were unable to "establish unequivocally which drug or combination of drugs was responsible" for the patient's presentation, but a "toxic basis is most likely."

DPV Reviewer's Comments

This literature case, although confounded by multiple medications, describes retinal toxicity in a young woman with IC on pentosan. Polypharmacy in this case makes causality assessment difficult; however, given the positive rechallenge with mexiletine, and reported visual effects associated with this drug, mexiletine most likely played a prominent role in causing the retinopathy in this patient. In addition, phenothiazines, a class of drugs to which mexiletine is structurally related, have been reported to cause acute retinal toxicity.[27] This patient also received promethazine, a phenothiazine, as a home medication.

3.4.2 **Pearce WA et al.,** *Ophthalmology. 2018*[1]**;** **Hanif AM et al.,** *JAMA Ophthalmology. 2019*[4]

**Note: Because Hanif et al. included all patients described in Pearce et al. case series, we describe the Hanif et al. case series as it is the most complete.*

Case Series Summary

This multi-site retrospective case series of 35 patients from four sites included the six patients previously published in the case series by Pearce et al. Each of the four participating institutions conducted a medical records review to identify patients with pentosan exposure. These charts were then reviewed by ophthalmologists with subspecialty expertise in retinal disease to determine the presence and severity of characteristic features noted in the 2018 case series by Pearce et al. These features were 1) fundus photography revealing macular hyperpigmented spots, yellow-orange deposits, and/or patchy retinal pigment epithelium (RPE) atrophy; 2) Autofluorescence imaging revealing a densely packed array of hyperautofluorescent and hypoautofluorescent spots involving the posterior pole; and 3) optical coherence tomography

(OCT) imaging demonstrating focal thickening or elevation of the RPE with associated hyperreflectance on NIR imaging. The authors note that the RPE findings are easily distinguished from drusen seen in age-related macular degeneration, allowing for differentiation between the two disorders.

A total of 70 eyes from 35 patients were identified with pentosan-associated maculopathy from a larger pool of 404 patients who reported active pentosan use at one of the sites. Most of the patients were female 34/35 (97%), most identified as white 32/35 (94%), and the median (range) age was 60 (37-70) years. The median (range) of pentosan intake duration was 15 (3-22) years and the median (range) daily dose of pentosan was 300 (150-592) mg. The most commonly reported symptoms were blurred vision (n=17), subjectively prolonged dark adaptation (n=17), and metamorphopsia (n=4). Severity was graded on a three-level scale based upon extent of fundus involvement and presence of RPE atrophy; cases were fairly evenly distributed between the three grades. None of the cases had evidence of subretinal or intraretinal hemorrhage or of macular drusen typical of AMD. No associations were found between cumulative pentosan dose and severity grade or visual acuity, or between exposure and disease extent or atrophy. One patient experienced symptoms several years after drug cessation. See **Appendix H** for Table from Hanif et al., describing case level demographic information, medical history, and clinical features of identified cases of pentosan-associated maculopathy.

Concomitant medications reported by patients included tricyclic antidepressants (n=11), gabapentin and its analogues (n=11), cyclobenzaprine (n=8), bladder relaxants (n=7), pyridium (n=5), hyoscyamine or hyoscyamine-containing compounds (n=3), and hydroxychloroquine (n=1). Past medical history reported included smoking (n=8), chronic kidney disease (n=3), fibromyalgia (n=3), arthritis (n=2), ulcerative colitis (n=2), and prior splenectomy (n=1). No cases noted positive dechallenge or rechallenge. Molecular testing was performed in 17/35 patients and returned a single pathogenic variant (ABCA4)[i] in one patient, several variants (ABCA4, ADAM9, IMPG2, MPZ, and TIMP3) of unknown significance in 5 patients, and a nonsense IMPG2 variant in a patient whose phenotype was not typical for IMPG2-associated disease. See **Appendix H** for Table from Hanif et al., describing risk factors, other IC therapies, and molecular testing results for patients in this case series.

Overall, the authors observed evidence of a unique pattern of RPE disease based on parafoveal pigmentary changes and patchy areas of RPE atrophy. Though some of the clinical findings were suggestive of a genetically based retinal pattern dystrophy, genetic testing was negative or of unknown significance in almost all patients tested. In addition, the authors note a "unique and clinically important" imaging finding that may help differentiate this condition from hereditary maculopathies is the peripapillary AF pattern. They noted there was often a peripapillary hypoautofluorescent halo, which is distinct from the peripapillary sparing often seen in other hereditary retinopathies. The authors also identified no other predisposing factors for macular disease.

[i] ABCA4 codes for a protein called N-retinylidene-PE which removes toxic products of phototransduction from photoreceptor cells, preventing damage to them. Mutations in this gene are associated with cone-rod dystrophy, Stargardt macular degeneration, age-related macular degeneration, and retinitis pigmentosa. (Source: https://ghr.nlm.nih.gov/gene/ABCA4. Accessed January 29, 2020.)

They conclude that their findings suggest pentosan-associated maculopathy is a vision-threatening condition that can manifest in the setting of long-term exposure to pentosan. They note that of the patients evaluated, many experience prominent visual symptoms of difficulty reading and prolonged dark adaptation despite generally well-preserved visual acuity. However, in some cases, central atrophy resulted in "substantial visual disability". The authors note that the pathogenesis of this condition remains unclear, and that additional work is warranted to establish causality and guide screening recommendations.

DPV Reviewer's Comments:
A strength of this case series is that it contains cases from multiple sites, adding validity to the initial 6 cases from Emory published by Pearce et al. The authors note that the characteristic RPE lesions are distinguishable from age-related macular degeneration and that a unique peripapillary AF pattern allows distinction from other maculopathies, suggesting this disorder is a separate entity. Other strengths of the case series are that all cases include clinical diagnosis based on funduscopic examination and specialized retinal testing by an ophthalmologist sub-specializing in retinal disorders, most genetic testing for hereditary maculopathies was negative or of uncertain significance, and no other predisposing factors for macular disease were identified.

There are also several limitations. This is a case series, which by definition does not have the comparator necessary to detect a difference between treated and untreated IC patients. The case series describes 35 patients with pigmentary maculopathy identified from a total database pool of 404 patients receiving pentosan. Though the authors stated that many of the identified subjects did not have sufficient evaluation to assess macular status, it would be useful to have a more detailed explanation of the 369 exclusions. There is inherent selection bias in this case series, as all the patients included are those who visited a retinal specialist and had detailed macular testing performed. Many of the tests performed for diagnosis are advanced imaging and may not be available in a general ophthalmology clinic, limiting the case series. Furthermore, nine cases were confounded by smoking (8) and hydroxychloroquine use (1), both of which can contribute to retinal disease.

3.4.3 **Huckfeldt** and Vavvas, *Ophthalmic Surg Lasers Imaging Retina. 2019.*[28]

Case Report
This report describes a 62-year-old woman with a history of fibromyalgia, ulcerative colitis, chronic fatigue syndrome, prior breast cancer treated with ongoing aromatase inhibitor, and interstitial cystitis treated with pentosan. She was referred to the authors' retinal specialty clinic because of blurry vision in her left eye and difficulty seeing at night, associated with abnormal visual field testing in the left eye and an abnormal funduscopic exam. Her visual acuity was normal OD[j] (20/20) and decreased OS[f] (20/50). Testing with fluorescein angiography and OCT were abnormal and a toxic etiology was suspected, though there was no history of exposure to retinal toxins. She was also noted to have a choroidal nevus OS. Three months later, her symptoms and findings were stable. She then returned at age 67 complaining of worsening vision in both eyes with progression and evolution of the abnormalities in her visual acuity

[j] OD refers to the right eye, OS refers to the left eye, and OU refers to both eyes.

(20/30 OD and 20/60 OS), funduscopic, AF, and OCT testing. Her medical history was now significant for excision of a localized cutaneous melanoma. Genetic testing for hereditary maculopathies was ordered and the patient returned again at age 69. At that point, she had been diagnosed with a melanoma metastatic to her temporal lobe (laterality not reported), treated with radiation and surgical excision. She described worsening vision, particularly on the left, and her visual acuity was 20/80 OD and 20/400 OS. Additional testing showed worsening central scotomas and progressive atrophy OU.[f] Genetic testing was normal, and the etiology of the disease remained elusive.

Upon reading the article by Pearce, et al.[1], the authors re-evaluated the patient's case and believed that her disease characteristics were consistent with pentosan-associated maculopathy. They confirmed with the patient that she had discontinued the pentosan at age 63, after about 18 years of use. The authors highlighted in their report that the patient experienced disease progression despite drug cessation and that a screening regimen should be considered in order to identify early evidence of toxicity.

DPV Reviewer's Comments:
This article describes an additional case with characteristics consistent with Pearce's description of pentosan-associated maculopathy in a patient with a history of chronic pentosan exposure, no evidence of genetic retinal disease, and findings consistent with a toxic etiology that were previously inexplicable. Possible confounders are the temporal lobe melanoma and its associated radiation and surgical treatments, fibromyalgia, ulcerative colitis, and history of breast cancer.

3.4.4 **Mishra**, et. al, *Ophthalmol Retina.2020.*[29]

This report describes a 56-year-old woman who reported visual blurring OU with distorted vision OS for the prior four months. She had a long-standing history of interstitial cystitis for which she had been taking 300 mg of pentosan polysulfate sodium daily for 21 years, with a cumulative dose of about 2300 grams. She reported no family history of degenerative or heritable retinal disease. Her visual acuity was 20/20-1 OD and 20/40-2 OS. The authors described exam findings like those reported by Pearce et. al., with the additional finding of choroidal neovascularization, which they successfully treated with intravitreal bevacizumab, an anti-vascular endothelial growth factor (anti-VEGF). They highlight this case as an example that choroidal neovascularization can co-occur with pentosan-associated maculopathy and may be amenable to treatment with anti-VEGF.

DPV Reviewer's comments:
This case report comes from a retinal specialty group at Johns Hopkins Wilmer Eye Institute, which is outside the original group describing pentosan-associated maculopathy. It describes the first associated case of choroidal neovascularization. The patient had prolonged exposure to pentosan and had no reported risk for retinal disease. The report lacked information about risk factors for choroidal neovascularization. Whether choroid neovascularization is another risk of PPS exposure is uncertain, but this case illustrates another example of PPS-associated maculopathy

3.4.5 **Vora, et. al**, *Am J Ophthalmol Case Rep. 2020.*[30]

This report describes a 41-year-old female on pentosan for 18 years who presented to the authors' clinic with a diagnosis of Stargardt disease and requested a second opinion. Her visual acuity was preserved but she reported difficulty with reading and night vision. Exam findings were consistent with those reported by Pearce et. al., and genetic testing was negative. The authors diagnosed her condition as pentosan-associated maculopathy and referred her to Urology to discontinue pentosan.

DPV Reviewer's comments:
This case illustrates the difficulty that may exist in either recognizing pentosan-associated maculopathy or differentiating it from a hereditary maculopathy like Stargardt disease. It is possible that other patients with chronic pentosan exposure could have been misdiagnosed with a hereditary maculopathy.

*3.4.6 **Hadad*** et. Al, *Ophthalmology*. 2019.[31]

Although this was not a case report, DPV reviewed this article because of its clinical nature. The authors searched the electronic health record of the University of Massachusetts Medical School for individuals with a diagnosis of IC with at least 3 years of pentosan exposure at a dose of 100 mg daily. Fifty-two patients were identified and 17 consented to participate. Visual acuity was preserved among all patients and only one had visual complaints (admitted to near-sighted vision and slow dark-to-light adaptation when specifically asked.) All patients underwent NIR, OCT, and AF testing, which was then subjected to computerized quantitative image manipulation and analysis that used software adapted to purpose by the authors. They correlated the image data with standardized cumulative pentosan dose adjusted to weight. In NIR testing, an inverse relationship was found between background macular entropy and pentosan dose, attributed to RPE damage and loss of normal NIR. In AF testing, with an accumulated pentosan dose of more than 20 g/kg, the macular hypo-autofluorescence defect pattern was similar to that reported by Pearce et al. Additionally, at lower doses up to a peak, AF increased, and following the peak, AF decreased. This is reportedly consistent with expected AF findings as RPE damage progresses. In the OCT images, the ratio between thickness of the fovea and the thickness of the parafovea was correlated inversely and exponentially with cumulative pentosan dose. This is reportedly similar to findings in hydroxychloroquine retinal toxicity. The authors concluded that the study demonstrated an exponential dose-response correlation between pentosan exposure and retinal toxicity. Novel image analysis techniques developed and discussed present an opportunity to investigate further and quantify correlations between chronic medication exposure and retinal toxicity without obvious morphologic macular changes.

DPV Reviewer's comments:
This publication provides preliminary evidence of a dose-response relationship, but limitations include lack of validation of the image analysis technique, and potential selection bias by inclusion of a small fraction of pentosan-exposed patients who were willing to participate in the study.

3.5 DEPI LITERATURE

DEPI's literature search identified five published observational studies, including one cross-sectional study by Hanif et al. 2019,[32] two claim-based retrospective cohort studies by Jain et al. 2019[33], Lugwig et. al. 2019, and two descriptive studies by Wang et al. 2019 and Vora et al. 2020. DEPI's summary and comments on all five observational studies are presented below.

3.5.1 **Hanif AM** et al., *Ophthalmology*. 2019[32]

Methods

A cross-sectional study was conducted to evaluate risk factors for development of a unique maculopathy among patients diagnosed with IC in a U.S. Medical Eye Center. The authors first queried billing records, electronic medical records, and pharmacy databases to identify patients seen at the Emory Eye Center (EEC) between May 2014 and October 2018 with a diagnosis of IC. For each IC patient, electronic medical records and the Emory Healthcare Network pharmacy database were queried for exposure to IC therapies including pentosan, hydroxyzine, tricyclic antidepressants, gabapentin, pregabalin, cyclobenzaprine, methenamine, phenazopyridine, oxybutynin, and hydroxychloroquine. Expert reviewers masked to the exposure history reviewed all available ophthalmic images to identify pigmentary maculopathy cases among the patients with IC. Cases were assessed for characteristic features of pigmentary maculopathy and grouped into four categories (see outcome definition below). Fisher's exact tests and independent two-sample T-tests were used to assess the association between categorical and continuous variables (IC treatment group and other patient characteristics) and the study outcome (pigmentary maculopathy). Multiple logistic regression was not performed due to low number of cases for each independent variable examined.

Outcome Definition

Characteristic features of pentosan-associated pigmentary maculopathy were defined as: (1) bilateral pathology centered on the fovea, (2) fundus photography revealing paracentral macular hyperpigmented spots, pale yellow deposits, and/or patchy RPE atrophy, (3) a dense array of hyper- and hypo-auto fluorescent spots and reticular AF imaging abnormalities, and (4) foci of nodular RPE enlargement on OCT imaging corresponding to hyper-reflectance on NIR imaging. Patients were grouped into four categories. Category one was defined as cases fulfilling the defined criteria above for pentosan-associated pigmentary maculopathy, while category two cases were nonspecific macular pigment changes that did not closely match the case definition. Category three were patients that were not similar to the phenotype described, while category four were patients with fewer than two available imaging that was not adequate to assess pathology. Categories one and two were combined into an "Unspecified Pigmentary Maculopathy" group, while categories three and four were combined into a "No Pigmentary Maculopathy" group.

Results

The study investigators reviewed medical records for 219 patients diagnosed with IC who underwent an examination at the EEC during the study period. The mean age of the patients was 60.8 years (standard deviation: 15.1) and 195 (89%) of the patients were females. Of the 219 IC patients, expert reviewers masked to exposure history adjudicated 24 as cases of unspecified

pigmentary maculopathy (categories one and two), and 195 were classified as non-cases (categories three and four). Cases and non-cases were similar in gender (88% and 89% females, respectively), mean age (61 years-old) and ethnicity (70% White). Cases reported a higher frequency of pentosan use than non-cases (83.3% vs. 30.8%), making pentosan exposure the sole statistically significant predictor of the unspecified pigmentary maculopathy with an odds ratio (OR) of 11.25 (95% Confidence Interval (CI): 3.69 – 34.33, $p < 0.0001$). No other IC medications demonstrated a statistically significant association. The reported OR for hydroxyzine was greater than two but was not statistically significant (OR: 2.12 (95% CI: 0.87, 5.18)).

DEPI Reviewer's Comments

This cross-sectional study suggests a strong association between pentosan exposure and pigmentary maculopathy in a univariate analysis. However, we could not determine a causal relationship because the cross-sectional study design assessed exposure to IC therapies and identified pigmentary maculopathy cases at the same time and does not allow for an assessment of temporality of exposure relative to the study outcome. It would take an analytic design, such as a case control study or a retrospective cohort study to assess a causal association more rigorously between pentosan and pigmentary maculopathy. Secondly, there is potential for misclassification of the study outcome. There were 144 IC patients designated as category four (non-cases) owing to insufficient retinal imaging to allow assessment of macular structure. Of these, four pentosan exposed patients and 11 unexposed patients had descriptions of macular pigmentary changes within their medical charts but were classified as non-cases. If these 15 non-cases were true cases, the crude OR would have dropped to 3.54 as opposed to the observed 11.25. This potential outcome misclassification would exaggerate the observed OR and bias the risk estimate away from the null. Thirdly, this study did not compare the characteristics of pentosan exposed and unexposed patients, therefore, it is unclear how different these patient groups were with regards to potential confounders. Further, the study was limited by a small sample size which precluded the use of multiple logistic regression to control for other potential confounders such as age and use of other IC therapy.

3.5.2 **Jain** et al. *Pharmacoepidemiology and drug safety,* 2019[33]

Methods

This retrospective cohort study was conducted in a US medical claims database (OptumInsight Eden Prairie, Minneapolis USA) to assess the association between pentosan use and maculopathy disease. The exposed cohort were patients who filled a first prescription for pentosan (index date) between January 2002 and December 2016. Patients were excluded for not having at least two years of insurance plan prior to index date or for having any previous diagnoses of retinal toxicity, hereditary retinal degeneration, age related macular degeneration (AMD), or drusen. An unexposed cohort was matched 5:1 for every exposed patient on age ($\pm$ 5years), gender, race, and insurance start date ($\pm$ 3 years). The primary analysis required patients to have at least five years of follow-up after the index date while the secondary analysis required at least 7 years of follow-up. The primary study outcome was defined as presence of ICD9/10 diagnoses code for atypical maculopathy (defined as any new diagnoses of a hereditary or secondary pigmentary maculopathy), while the secondary study outcome was any new diagnoses

of dry AMD or drusen in addition to atypical maculopathy (i.e. atypical maculopathy + AMD). Multivariate logistic regression was conducted to evaluate the odds of developing a macular disease at 5 and 7 years of follow-up. Variables were entered into the multivariable model if they are associated with pentosan exposure at p <0.2 in the univariate model. Variables entered into the univariate model were age, hypertension, diabetes, transient ischaemic attack or stroke, index year, peripheral vascular disease, malignancy, atrial fibrillation, congestive heart failure, previous myocardial infarction, arrhythmia, yearly income, education level, and geographic region. Analyses were conducted for both 5-year and 7-year follow-ups and a sub-analysis was conducted for IC patients only.

Results

At 5-year follow-up, 3,012 pentosan users were compared to 15,060 unexposed patients. Nine (0.3%) pentosan users had maculopathy compared to 32 (0.2%) unexposed patients, while 103 (3.4%) pentosan users had maculopathy plus AMD compared to 440 (2.9%) unexposed patients. None of the 5-year follow-up results were statistically significant. At the 7-year follow-up, 1,604 pentosan users were compared to 8,017 unexposed patients and 10 (0.6%) pentosan users had maculopathy compared to 25 (0.3%) unexposed patients, while 87 (5.4%) pentosan users had maculopathy plus AMD compared to 328 (4.1%) unexposed patients. At 7-year follow-up, pentosan users had significantly increased OR for maculopathy plus AMD (OR: 1.41, 95% CI: 1.09 -1.83) but not for maculopathy (OR: 1.87, 95% CI: 0.87 - 3.99). For the IC population sub analysis, the study reported increased OR of maculopathy at 5 years follow-up (OR: 2.91, 95% CI: 1.15, 7.36, p =0.02), but not at 7 years follow-up (OR: 1.46, 95% CI: 0.66, 3.24, p =0.35).

3.5.3 **Ludwig** et. al. *Ophthalmology,* 2019.[34]

Methods

This retrospective cohort study was conducted using Truven Health MarketScan commercial insurance claims database to evaluate the association between pentosan exposure and maculopathy. Patients were selected for the study if they were newly diagnosed with IC between 2007 and 2016, have at least 365 days of insurance coverage before and after IC diagnosis, and no maculopathy diagnosis prior to the IC diagnosis. Exposure to pentosan was evaluated as both binary (pentosan vs. no pentosan) and categorical (0 prescription days, 1 – 30 days, <1 year, 1 – 2 years, 2 – 3 years, 3 – 4 years, 4 – 5 years >=5 years) variables. Maculopathy was defined as any diagnosis of drusen, non-exudative age-related macular degeneration (AMD), exudative AMD, toxic maculopathy, or hereditary dystrophy using ICD-9 and ICD-10 diagnosis codes. Cox proportional hazards was used to model the association between pentosan exposure and maculopathy in a five-year follow-up study controlling for gender, age at IC diagnosis, and diabetes. A sensitivity analysis was conducted excluding all patients with diabetes.

Results

In Market Scan, 227,325 patients were diagnosed with IC during the study period. Of these, 49,899 met the study inclusion criteria. Most patients with IC were women (90%) and between the ages of 40 and 60 years (47%). Seventeen percent had diabetes and 23% filled pentosan

prescription. Pentosan prescription was filled an average of 125 days from index IC diagnosis and was filled for an average of 1230 days. Among patients with IC, 2.7% (n= 1335) were diagnosed with maculopathy with the most common diagnoses being exudative AMD (1.5%), followed by drusen (0.8%), non-exudative AMD (0.3%), toxic maculopathy (0.1%), and hereditary dystrophy (0.04%). Similar proportion of patients were diagnosed with a maculopathy among pentosan exposed (277 (2.37%)) and unexposed (1058 (2.77%) patients. Study reported no significant association between pentosan binary exposure and any maculopathy outcome after controlling for age, gender, and diabetes. Model that used a categorical pentosan exposure showed that exposure to pentosan longer than 4 years was associated with 8.78-fold increased risk of hereditary dystrophy (95% CI 1.12 - 68.81). Length of pentosan exposure was otherwise not associated with diagnoses of drusen, non-exudative AMD, exudative AMD, toxic maculopathy, or any other maculopathy. Patient age at IC diagnosis was associated with diagnosis of AMD, drusen, and any maculopathy in both exposure models.

DEPI Reviewer's Comments on the Claim-based Retrospective Studies (Ludwig 2019 and Jain 2019)

Both retrospective claims-based studies are large studies that built on the limitations of the previous cross-sectional study by assessing IC exposure prior to determining the study outcomes, matching exposed to unexposed patients on select covariates, and/or conducting multivariable analyses to control for potential confounders. However, both studies did not validate their ICD9/ICD10-based outcome algorithms in the administrative claims databases, and they did not conduct multi-modal retinal imaging to confirm that study outcomes match the pigmentary maculopathy under investigation. Therefore, it is not clear if any of the study outcomes are pigmentary maculopathy, which has been described as distinct from age-related macular degeneration and other pigmentary maculopathies. Furthermore, both studies are limited by short patient follow-up. FAERS cases labelled as pigmentary maculopathy reported a median time to disease onset of 21 years (range of 9 – 28 years). Therefore, follow-up period in these database studies may not be sufficient to identify pigmentary maculopathy. Ludwig et al. reported that exposure to pentosan longer than four years was associated with 8-fold increased risk of hereditary dystrophy; however, this study only accounted for age, gender, and diabetes in the multivariable analysis. It is likely that the observed increased risk may be due to potential confounders such as concurrent medications and co-morbidities that were not adjusted for in the multivariate analysis. Although both retrospective claims studies did not report significant associations between pentosan and the different maculopathy outcomes examined, with the exception of hereditary dystrophy, we still cannot rule out the association between pentosan and pigmentary maculopathy.

*3.5.4 **Wang** et al. Ophthalmology,* 2019[35]

Methods

This observational study evaluated the prevalence of pentosan-associated maculopathy among patients exposed to pentosan at a single large University. Electronic medical records at the University of California, Los Angeles (UCLA) was searched to identify patients prescribed pentosan between March 2013 and October 2019. Patients previously or currently exposed to

pentosan were contacted for complete eye exam and standard multimodal retinal imaging. Information on demographics (age, sex, race, body mass index (BMI)), ocular and medical history, smoking history, medication history including duration of use, and daily dosage of pentosan were obtained from each patient using a questionnaire. Visual symptoms including the nature and timing of problems since starting pentosan were also queried. Severity of pentosan maculopathy was graded according to presence or absence of atrophy.

Results

Seven hundred and thirty-five patients were prescribed pentosan during the study period at UCLA. Of these, the first 440 patients (60%) were contacted to request participation in the study after verbal confirmation of pentosan use. Fifty patients (7%) who reported previous or current use of pentosan enrolled in the study. All 50 patients underwent complete eye examination and a standard multimodal retinal imaging protocol. Of the 50, 46 (92%) were females, and 43 (86%) were white. Median age of the study cohort was 60 years (range 23 – 93 years). Mean duration of exposure was 9.1 $\pm$ 8.6 years, mean daily dose was 330.4 $\pm$ 214.3 mg, and mean cumulative dose was 1228.4 + 1439.9 g. Pentosan associated maculopathy was identified in 10 of the 50 patients (20%) with a median age of 69.5 (range 41 – 76) years. The most common symptoms reported by maculopathy cases were nyctalopia/night blindness (n=5), blurry vision (n=2), and distortion (n=1) with two patients having no symptoms. Visual acuity was preserved with a median Snellen visual acuity of 20/20 OD. When maculopathy cases were compared to non-cases, there was no statistically significant difference in age, sex, smoking history, BMI, and visual acuity. However, mean duration of exposure, mean daily dose, and mean cumulative dose were significantly higher in cases (20.3 years, 444 mg/daily, 3375 g) than non-cases (6.3 years, 301 mg/day, 691 g) $p<0.001$. Among cases, there was a trend of increased duration of use, increased daily dose, and increased cumulative dose in more severe cases. Median duration of pentosan use was 16, 20, and 22.9 years in mild, moderate, and severe cases. Similarly, median daily pentosan dose was 300 mg, 400 mg, and 555.2 mg in mild, moderate, and severe cases and median cumulative dosages were 2847, 3285, and 4015.3 g in mild, moderate and severe cases.

3.5.5. Vora et al. *Ophthalmology*, 2020[36]

Methods

This observational study evaluated the prevalence and risk factors for maculopathy in patients with long term exposure to pentosan in Kaiser Permanente Northern California (KPNC). The electronic medical record at KPNC was queried for patients diagnosed with IC during the prior 20 years. The authors contacted patients who had been dispensed at least 500 g of pentosan in the prior 20 years and still had an active prescription in 2018. These patients were invited and screened with OCT and fundus photography. Two experts masked to total medication use classified patients as definite or no definite signs of maculopathy. Cases were considered definite maculopathy if they met published clinical criteria and if both retinal specialist scores were concordant. Demographics such as sex, age, race, height, weight, BMI, and smoking history were also determined from the electronic medical records.

Results

At KPNC, there were 1,120 patients diagnosed with IC in the prior 20 years. Of these, 475 (42%) patients were actively taking pentosan. The authors reached out to 138 patients dispensed at least 500 g of pentosan in the prior 20 years and actively taking pentosan. One hundred and seventeen of 138 patients (25%) were screened with OCT and fundus photography and 27 **(23.1%)** had definite signs of maculopathy, while 90 (76.9%) did not. The 21 patients that were not screened were slightly younger and had lower cumulative exposure. Visual acuity was generally preserved in all maculopathy cases with only 3 patients with reduced central vision due to geographic atrophy. When maculopathy cases were compared to non-cases, there was no statistically significant difference in sex, race, age, weight, BMI, duration of therapy, and daily dose. However, there was significant difference in mean cumulative dose between maculopathy cases (1,350 g) and non-cases (1,040 g), $p < 0.01$. The proportion of maculopathy increased significantly with increasing pentosan dose, 12.7% in 500 - 999 g group, 30% in 1000 - 1500 g, and 41.7 % in >1,500 g groups ($p<0.01$). Multivariate analysis comparing cases to non-cases suggested that cumulative pentosan dose was significantly associated with maculopathy (OR: 3.05 (95% CI: (1.08, 8.67)) after adjusting for age, race, BMI, and daily dose.

DEPI Reviewer's comment on the Descriptive Studies

Both descriptive studies assessed the prevalence of maculopathy among patients exposed to pentosan. No unexposed comparators were included in these studies. A small proportion (7 – 25%) of patients exposed to pentosan were evaluated using standard multimodal retinal imaging. This could potentially introduce selection bias and possibly overestimate the prevalence of maculopathy especially if patients with higher pentosan exposure or more severe maculopathy were enrolled. However, both studies provide preliminary evidence of a dose response relationship among patients exposed to pentosan with maculopathy cases reporting significantly higher daily dose, longer duration of use, and higher cumulative dose than non-cases

3.6 PERIODIC SAFETY REPORT

The most recent PADER submitted by the sponsor (dated September 26, 2018 – September 25, 2019) noted the pending PAS submitted in June 2019 proposing the addition of a Warning on pigmentary maculopathy. In this PADER, the sponsor reported 12 ICSRs with the PT *Maculopathy* and one ICSR with the PT *Retinal pigmentation.*

3.7 FOREIGN REGULATORY ACTIONS

In September 2019, the United Kingdom updated the Special Warnings and Precautions for Use section of pentosan product labeling to contain information about the rare risk of pigmentary maculopathy.[37] They then recommended an update in January 2020 (new text in ***underlined bold***)[37]:

- *Rare cases of pigmentary maculopathy have been reported with use of pentosan polysulfate sodium (PPS), especially after long term use. Visual symptoms might include complaints of difficulty **when reading, visual distortions, altered colour vision** and/**or** slow adjustment to low or reduced light environments.*

- *All patients should have **an** ophthalm**ologi**c examination **after 6 months of use of PPS** for early detection of pigmentary maculopathy, **and, if there are no pathologic findings, regularly after 5 years of use (or earlier, in case of visual complaints)**. **However, in case of relevant ophthalmologic findings, a yearly examination should be conducted.** In such situations, treatment cessation should be considered.*

In October 2019, Health Canada added the risk of pigmentary maculopathy to the Warnings and Precautions, Post-Market Adverse Drug Reactions, and Consumer Information sections of the Canadian product monograph for Elmiron.[38] The label states:

- *Post-market cases of pigmentary maculopathy have been reported with chronic use of pentosan polysulfate sodium (PPS). Visual symptoms in these cases included difficulty reading and prolonged dark adaptation. All patients should have regular ophthalmic examinations for early detection of pigmentary maculopathy, particularly those with long-term use of PPS. If pigmentary maculopathy is confirmed, treatment discontinuation should be considered.*

3.8 DRUG UTILIZATION

In 2018, an estimated (b) (4) bottles of pentosan were sold from manufacturers, primarily ((b) (4)%) to outpatient retail pharmacies.[k] Accordingly, the analysis below included only prescriptions dispensed from outpatient retail pharmacy settings and not other health care settings (e.g. mail-order, specialty pharmacy, long-term care, or non-retail settings).

In 2018, an estimated (b) (4) patients received a prescription for pentosan dispensed from an outpatient retail pharmacy (**Table I1** in **Appendix I**). This was a (b) (4)% decrease from (b) (4) patients in 2011. During the time examined, approximately (b) (4)% of all patients who received pentosan prescriptions were female.

Patients 40 years old or younger comprised (b) (4)% or less of all patients who received pentosan prescriptions in 2018 (**Figure 5**). Patients 41-60 years comprised the largest proportion, roughly (b) (4)% of all patients in 2018, followed by patients 61-70 years old ((b) (4)%).

[k] IQVIA National Sales Perspective™. Data year 2018. Data accessed March 2019. File: NSP pentosan.xlsx.

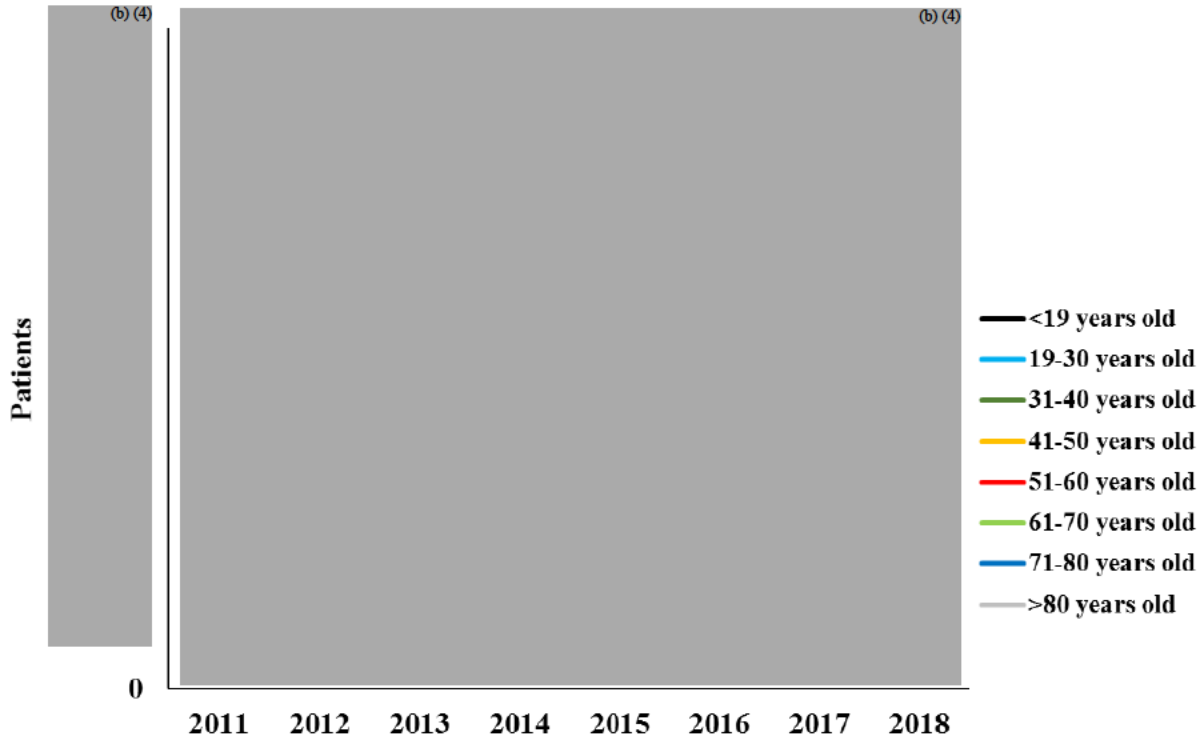

Figure 5. Nationally estimated number of patients with pentosan prescriptions dispensed from U.S. outpatient retail pharmacies, stratified by age, 2011 through 2018.

Source: IQVIA Total Patient Tracker™. 2011- 2018. Data extracted February 2019. File: TPT pentosan xlsx. Patient counts are estimates for each time period and age group and should not be summed, at the risk of double-counting patients who appear in multiple time periods or multiple age groups during the times evaluated.

4 DISCUSSION

On balance, our analysis of the available data indicates the presence of a new safety concern associated with pentosan. While the FAERS and literature findings from this review do not fully resolve the question of causation between pigmentary maculopathy and pentosan exposure, several compelling elements support an association (see table in **Appendix J** providing details about elements of causality assessment and currently available evidence). Retinal specialists at multiple ophthalmology practice sites have identified a novel pigmentary maculopathy associated with pentosan. The described patients had similar symptoms and fundoscopic changes that were reported to be distinct from age-related macular degeneration and other pigmentary maculopathies. No clear genetic cause was identified. There is preliminary evidence of a dose-response relationship, with pigmentary maculopathy cases reporting a significantly higher daily dose, longer duration of use, and higher cumulative dose than non-cases. Several ophthalmologists have proposed plausible theories for potential mechanisms of action for pentosan-associated pigmentary maculopathy.

Proposed theories include:

- Pearce et al. postulated that since pentosan accumulates in the uroepithelium and less so in other visceral organs, perhaps the RPE abnormalities could represent accumulating byproducts of the visual cycle as the RPE cells are dying (presumably from pentosan-associated toxicity).[1] Another possibility is that pentosan or one of its metabolites could be accumulating in the RPE.
- Greenlee et al. hypothesized that the mechanism could relate to pentosan's ability to antagonize Fibroblast Growth Factor (FGF) signaling pathways.[39] FGF's are important in maintaining retinal health and regeneration in vertebrate retinas. An experimental model in zebrafish and mice involving FGF antagonism resulted in degeneration of retinal structure and photoreceptor cell loss. These authors therefore suggest that long-term interference with FGF signaling could either directly damage retinal cells or interfere with normal repair processes. They point out that other pharmaceuticals known to interfere with FGF signaling have been associated with ocular side effects including RPE detachment, central serous retinopathy, and dry eye.
- Hanif et al. hypothesize that the mechanism of action involves the RPE or the RPE-photoreceptor interface.[4] Pentosan may be directly toxic to the RPE, impairing its capacity to process photoreceptor outer segments. Alternatively, pentosan might disrupt the interphotoreceptor matrix, which is important in maintaining the photoreceptor-RPE interaction. It is particularly interesting to note that the interphotoreceptor matrix is primarily made up of glycosaminoglycans that are structurally similar to pentosan.

From an epidemiology perspective, study results suggest an association, but the limitations of the observational studies preclude concluding a causal relationship between pentosan and pigmentary maculopathy. The two large claim-based studies reported no significant association between pentosan and different maculopathy outcomes but are subject to major limitations such as the lack of retinal imaging confirmation and the lack of validation of study outcome algorithms, short follow-up time, and potential residual confounding. Three studies that conducted multimodal retinal imaging suggested an association between pentosan exposure and pigmentary maculopathy and provided preliminary evidence of dose response among patients exposed to pentosan. However, these studies were also limited by lack of unexposed comparator and potential selection bias, potential outcome misclassification, and residual confounding. Despite these study limitations, we could not rule out a possible causal relationship between pentosan and pigmentary maculopathy.

From a DPV perspective, there are challenges to causality assessment. Case reports and case series, by definition, lack a comparison group and can provide no information regarding background rate of pigmentary maculopathy in the untreated IC population. There is a long time between initiation of the drug and onset of the disease. Possible confounders were reported in some cases (i.e., smoking, concomitant medications, genetic variants of undetermined significance), and other cases lacked detail about concomitant conditions and medications.

Although some cases report vision changes, the clinical consequences of pentosan associated pigmentary maculopathy appear uncertain at this time as it is difficult to distinguish these changes from age-related vision changes that occur in the population. Further investigation of these complaints requires specialized retinal exams (i.e., OCT, FAF etc.), which are unlikely to be available in spontaneous adverse event reports (i.e., FAERS). The majority of cases reported

in the literature and FAERS do not report vision loss. The most commonly reported symptoms were blurred vision and difficulty with dark adaptation. Other reported symptoms included alteration in color vision, flashes, floaters, light sensitivity, metamorphopsia, peripheral vision impairment, and scotomas.

Estimated drug utilization patterns show that the largest proportion of prescriptions appear to be dispensed to patients 41-60 years of age. Pentosan usage has trended downward for several consecutive years and we considered potential explanations for this observation. We note that non-pharmacologic interventions are the preferred treatment options over oral drug therapy, and among drug treatment options, amitriptyline is generally regarded as having better evidence to support its use over pentosan.[15,16,40] While incidence trends of IC in the United States are currently unknown, considering that IC incidence increases with age, and the US population is aging, increasing use of pentosan would be expected. However, the decreased pentosan use trend could potentially be explained by changes in IC treatment approaches by clinicians with preference to non-pentosan treatment options. Nevertheless, in 2018, an estimated (b) (4) patients received a prescription for pentosan dispensed from an outpatient retail pharmacy. Regardless of the secular trend, this indicates that many patients may be at potential risk for this disorder.

According to FDA labeling guidance[41], in order to include an adverse event in the WARNINGS AND PRECAUTIONS section of the label, "there should be reasonable evidence of a causal association between the drug and the adverse event, but a *causal relationship need not have been definitively established*[l]." Our guidance goes on to state that "Adverse reactions that do not meet the definition of a serious adverse reaction but are otherwise clinically significant because they have *implications for prescribing decisions or patient management* [h], should also be included in WARNINGS AND PRECAUTIONS.

This guidance, along with the following considerations, are the basis for our recommendations described in **Section 6**.

1. Several compelling elements in the data we reviewed support an association between pentosan and a novel pigmentary maculopathy.
2. The Sponsor has requested a change in labeling to reflect this drug-event association.
3. Two foreign regulatory agencies have acted to change labeling to reflect this drug-event association.
4. Though the clinical consequences are not clear, some patients have reported vision changes and have fundoscopic abnormalities. In cases in which a patient taking pentosan experiences visual disturbances or has fundoscopic abnormalities, the prescriber can discuss drug discontinuation or other treatment options suggested in treatment guidelines[m] with the patient, allowing patients to make a more informed decision. Through labeling changes, prescribing clinicians will more likely be aware of the potential adverse event and be more vigilant for assessing eye health.

[l] Emphasis added.
[m] See **Section 1.2.3** for overview of the American Urological Association's step-wise approach to treatment.[15, 16]

5 CONCLUSION

In conclusion, there are several compelling elements from our data that support an association between pentosan and a novel pigmentary maculopathy. Although the clinical consequences of this unique maculopathy remain unclear given that the reported symptoms are general vision complaints common in the described age group, we believe this drug/adverse event pairing warrants inclusion in the labeling of pentosan. Because pentosan is typically prescribed by non-ophthalmologists, it is especially important to make all health care professionals aware of this association.

6 RECOMMENDATION

Based on this review, OSE recommends the following:

- Update the Warnings section of the pentosan label to reflect the potential risk of pigmentary maculopathy and include the commonly reported symptoms of blurred vision, difficulty with dark adaptation, metamorphopsia, and nonspecific visual symptoms, although their relationship to pigmentary changes is unknown.

7 REFERENCES

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8 APPENDICES

8.1 APPENDIX A. SPONSOR'S PROPOSED LABELING

On March 24, 2020, the sponsor submitted an amendment to the pending prior approval supplement (S-0014), proposing the labeling changes in the attached document.

Sponsor
3-24-2020-annots

8.2 APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8.3 APPENDIX C. NATIONAL ELECTRONIC INJURY SURVEILLANCE SYSTEM-COOPERATIVE ADVERSE DRUG EVENT SURVEILLANCE (NEISS-CADES)

The National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project collects data on ED visits for adverse drug events (ADEs) in the outpatient setting. The NEISS-CADES project is a joint effort of the Centers for Disease Control and Prevention, the U.S. Consumer Product Safety Commission, and the U.S. Food and Drug Administration and provides data from a national stratified probability sample of approximately 60 hospitals with a minimum of six beds and a 24-hour emergency department (ED) in the U.S. and its territories. The NEISS-CADES project is described in detail elsewhere[n,o,p]

[n] Jhung MA, Budnitz DS, Mendelsohn AB, et al. Evaluation and overview of the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project (NEISS-CADES). Med Care 2007; 45(Suppl 2):S96-102.
[o] Budnitz DS, Pollock DA, Weidenbach KN, Mendelsohn AB, Schroeder TJ, Annest JL. National surveillance of emergency department visits for outpatient adverse drug events. JAMA 2006; 296:1858–66.
[p] Schroeder TJ, Ault K. National Electronic Injury Surveillance System (NEISS) sample design and implementation from 1997 to present. Washington, DC: US Consumer Products Safety Commission; 2001. Available at: http://www.cpsc.gov/neiss/2001d011-6b6.pdf.

All the cases in NEISS-CADES are ED visits for a condition that the treating clinician explicitly attributed to the use of a drug or a drug-specific effect. Data are currently available for the period 2004-2016.

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8.4 APPENDIX D. VIGIBASE, THE WORLD HEALTH ORGANIZATION (WHO) INTERNATIONAL DATABASE OF SUSPECTED ADVERSE DRUG REACTIONS

Uppsala Monitoring Centre (UMC) in its role as the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO Programme for International Drug Monitoring. The information is stored in VigiBase, the WHO global database of individual case safety reports (ICSRs). It is important to understand the limitations and qualifications that apply to this information and its use. The reports submitted to VigiBase generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proved that a specific medicine product (rather than, for example, underlying illness or other concomitant medication) is the cause of an event. Reports submitted to National Centres come from both regulated and voluntary sources, and therefore the probability that the suspected adverse event is drug-related is not the same in all cases. The information from VigiBase does not represent the option of the UMC or the WHO.

8.5 APPENDIX E. DRUG UTILIZATION DATABASES DESCRIPTION AND LIMITATIONS

IQVIA National Sales Perspectives™: Retail and Non-Retail

The IQVIA National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IQVIA Total Patient Tracker™ (TPT)

IQVIA Total Patient Tracker (TPT) is a national-level projected service designed to estimate the total number of unique (non-duplicated) patients across all drugs and therapeutic classes in the retail outpatient setting from U.S. retail pharmacies. Data are available back to January 2002 and are available 20 days after the close of the month. TPT uses prescription activity as part of its projection and integrates information from pharmacies and payers to eliminate duplicate patients and multiple prescription fills, producing quick and reliable unique patient counts. IQVIA has 92% coverage and a sample of ~58,900 retail pharmacies. IQVIA captures about 3.8 billion transactions annually. TPT is projected to the known universe of retail pharmacies.

Of note, the estimated prescription and/or patient counts provided are based on projections of sample prescription claims data and therefore have some degree of inherent sampling error. These estimates are not intended to be representations of exact enumerations and should be interpreted with caution particularly if they are based on a small sample size. In addition, the data cannot be validated due to lack of access to medical records in the data sources.

8.6 APPENDIX F. FAERS LINE LISTING OF PENTOSAN AND RETINOPATHY CASE SERIES (N=20)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
1	1/27/1997	5520181	1	96110018	Non-Expedited	67.00	FEMALE	USA	OT
2	7/28/1998	3201795	1	0002724	Non-Expedited	77.00	FEMALE	USA	OT
3	11/13/2000	3571010	1	6391	Non-Expedited	63.00	FEMALE	USA	OT
4	1/24/2003	3895795	1	NSADSS2003002667	Expedited (15-Day)	71.00	FEMALE	USA	OT
5	10/23/2009	7156905	1	US-JNJFOC-20091006996	Expedited (15-Day)	68.00	FEMALE	USA	OT
6	9/2/2010	7575946	1		Direct	67.89	FEMALE	USA	
7	12/7/2011	8278037	3	US-JNJFOC-20111112445	Expedited (15-Day)	53.00	NULL	USA	OT
8	7/16/2013	9401859	3	US-JNJFOC-20130705645	Expedited (15-Day)	63.00	FEMALE	USA	OT
9	2/24/2015	10861302	1	US-JNJFOC-20150210793	Expedited (15-Day)	82.00	MALE	USA	OT
10	11/10/2016	12930776	2	US-JNJFOC-20161107737	Expedited (15-Day)	59.56	FEMALE	USA	OT
11	10/5/2018	15469252	2	US-JNJFOC-20180934847	Expedited (15-Day)	72.20	FEMALE	USA	OT
12	12/1/2018	15678737	1		Direct	49.00	FEMALE	USA	OT
13	1/28/2019	15882007	1	US-JNJFOC-20190133302	Expedited (15-Day)	60.44	FEMALE	USA	HO
14	3/26/2019	16118665	2	US-JNJFOC-20190329872	Expedited (15-Day)	65.83162	FEMALE	USA	OT
15	4/25/2019	16242978 (Duplicate: 16278289)	1	US-JNJFOC-20190440794	Direct	63.00	FEMALE	USA	

16	5/22/2019	16343089	3	US-JNJFOC-20190521206	Expedited (15-Day)	51.00	FEMALE	USA	DS,OT
17	6/14/2019	16432860	2	US-JNJFOC-20190612271	Non-Expedited	61	FEMALE	USA	
18	7/22/2019	16612747	1		Direct	nr	FEMALE	USA	DS
19	1/1/2020	17225077	1		Direct	44		USA	DS
20	2/14/2020	17419932	1	US-JNJFOC-20200208282	Expedited (15-Day)	nr		USA	DS

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case may have more than one serious outcome.
Abbreviations: HO=Hospitalization, OT=Other medically significant, DS=Disability

8.7 APPENDIX G. WHO VIGIBASE LINE LISTING OF PENTOSAN AND RETINOPATHY CASE SERIES (N=53)

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8.8 APPENDIX H. DESCRIPTIVE TABLES FROM HANIF ET AL. CASE SERIES

Table. Demographic Information, Medical History, and Clinical Features of Identified Cases of Pentosan Polysulfate Sodium (PPS)–Associated Maculopathy

Patient No.	Sex/Race/Age, y	Referral Diagnosis	BMI[a]	IC Symptom Duration, y	Duration of PPS Intake, y	Mean Daily Dose, mg	Cumulative Exposure, kg	Visual Symptoms	Visual Symptom Duration, y	LogMAR VA		Grade
										OD	OS	
1	F/white/late 40s	AMD	23.5	14	13	231	1.10	Blurred vision	9	0	0.1	2
2	F/white/late 60s	AMD	25.5	13	13	323	1.55	Blurred vision	7	0	0.2	3
3	F/white/early 70s	Cone dystrophy vs AMD	26.1	15	15	300	1.64	Transient vision loss in the left eye and flashes, ringed scotomas, prolonged dark adaptation, impaired color vision, and light sensitivity in both eyes	8	0.6	0.9	3
4	F/American Indian/early 50s	Drusen vs AZOOR	24.9	16	12	450	2.04	Decreased near and peripheral vision and prolonged dark adaptation	2	0	0	2
5	F/white/mid-50s	Self-referral	24.7	8	7	400	1.02	Blurred vision and floaters	1	0	0	2
6	F/white/mid-50s	Metamorphopsia	30.2	6	Unknown	300	Unknown	Blurred vision, flashes, floaters, and decreased near vision	4	0.1	0	1
7	F/white/early 60s	Macular dystrophy	20.7	18	17	218	1.35	Prolonged dark adaptation and light sensitivity	6	0.1	0.1	2
8	F/white/early 50s	AMD	26.9	9	6	400	0.88	Metamorphopsia and light sensitivity	8	0	0	1
9	F/white/late 70s	Type 2 diabetes	29.3	6	6	300	0.68	Blurred vision	6	0.1	0.3	1
10	F/white/mid-50s	Type 2 diabetes	28.3	20	20	300	2.19	Blurred vision	Unknown	0	0	2
11	F/white/early 40s	Macular dystrophy	22.3	20	6	300	0.68	Metamorphopsia	1	0	−0.1	1
12	F/white/late 40s	Macular dystrophy	24.2	9	7	300	0.77	Blurred vision	1	0	0.2	2
13	F/white/early 60s	AMD	28.3	20	15	300	1.64	Blurred vision	2	0.2	0.3	NA
14	F/white/early 60s	Vitamin A deficiency	21.0	9	9	400	1.29	Prolonged dark adaptation	3	0	0.2	3
15	F/white/early 60s	AMD	18.1	10	10	300	1.10	Transient vision loss in the right eye	5	0.6	0.1	1
16	F/white/late 70s	AMD	26.7	35	15	150	0.82	Prolonged dark adaptation	Unknown	0.1	0.3	2
17	F/white/mid-40s	Metamorphopsia	25.4	43	3	400	0.44	None reported	NA	0	0	1
18	F/white/late 50s	AMD	26.0	18	18	457	2.98	Prolonged dark adaptation	5	0.3	0.3	3
19	F/white/early 60s	Macular dystrophy	26.1	18	18	389	2.56	Generalized dimming of vision, blurred vision, and prolonged dark adaptation	5	0.1	0.1	2
20	F/white/mid-60s	Pattern dystrophy	22.9	28	22	200	1.57	Blurred vision, spots in vision, and central scotomas	5	0.5	1.3	3
21	F/white/early 60s	Macular dystrophy	18.7	20	20	380	2.77	Paracentral scotoma and prolonged dark adaptation	4	0	0	1
22	F/white/early 60s	Pattern dystrophy	27.8	29	19	400	2.74	Prolonged dark adaptation, intermittent metamorphopsia, and spots in vision	6	0	0.1	3
23	F/white/early 60s	Macular dystrophy	19.7	39	12	300	1.31	Generalized dimming of vision, blurred vision, and prolonged dark adaptation	4	0.6	0.4	3
24	F/white/mid-40s	Macular dystrophy	35.4	14	14	400	2.04	Decreased near vision, blurred vision, and prolonged dark adaptation	4	0	0	2
25	F/white/late 30s	Macular dystrophy	36.3	13	14	400	2.04	Decreased near vision, blurred vision, and prolonged dark adaptation	7	0	0	3
26	F/white/mid-70s	AMD	18.8	22	22	300	2.40	None reported	NA	0.1	0.1	1
27	F/African American/late 30s	Macular dystrophy	21.5	25	9	300	0.99	Paracentral scotomas and blurred vision	1	0.2	0.4	3
28	F/white/late 60s	Urologist referral	28.7	30	20	300	2.18	Prolonged dark adaptation and impaired color vision	1	0.1	0	3
29	F/white/early 60s	Macular dystrophy	27.2	20	17	400	2.48	Metamorphopsia and prolonged dark adaptation	2	0	0	1

Table. Demographic Information, Medical History, and Clinical Features of Identified Cases of Pentosan Polysulfate Sodium (PPS)–Associated Maculopathy (continued)

Patient No.	Sex/Race/Age, y	Referral Diagnosis	BMI[a]	IC Symptom Duration, y	Duration of PPS Intake, y	Mean Daily Dose, mg	Cumulative Exposure, kg	Visual Symptoms	Visual Symptom Duration, y	LogMAR VA		Grade
										OD	OS	
30	F/white/early 60s	Pattern dystrophy	23.0	20	20	400	2.92	Blurred vision	3	0.1	0.1	1 OD; 2 OS
31	M/white/late 70s	Pattern dystrophy	28.1	44	20	592	4.31	Blurred vision, prolonged dark adaptation, and spots in vision	5	1.2	0.5	1
32	F/white/early 70s	Macular dystrophy	21.0	20	20	400	2.92	Prolonged dark adaptation	Unknown	0.1	0.1	2
33	F/white/mid-50s	Pigment dispersion	36.3	20	Unknown	Unknown	Unknown	None reported	NA	0.1	0.1	NA
34	F/white/early 60s	Uveitis	21.6	Unknown	Unknown	200	Unknown	Blurred vision	Unknown	0.7	0	3
35	F/white/mid-60s	AMD	27.1	8	7	300	0.81	Prolonged dark adaptation and generalized dimming of vision	Unknown	0.1	0.1	3
Median	60.0	NA	25.5	19.0	14.5	300	1.61	NA	4.0	0.1	0.1	NA
Mean (SD)	59.1 (10.9)	NA	25.5 (4.6)	19.4 (10.0)	13.9 (5.5)	338 (87)	1.76 (0.90)	NA	4.2 (2.4)	0.2 (0.3)	0.2 (0.3)	NA

Abbreviations: AMD, age-related macular degeneration; AZOOR, acute zonal occult outer retinopathy; BMI, body mass index; F, female; IC, interstitial cystitis; M, male; NA, not applicable; VA, visual acuity.

[a] Calculated as weight in kilograms divided by height in meters squared.

eTable 2. Risk factors, other IC therapies, and molecular testing results

Pt No	Smoking History	Other IC Therapies	Kidney/Liver/Spleen Comorbidities	Molecular Testing
1	Never Smoker	None	None	Macular Dystrophy Gene Panel: Negative
2	Never Smoker	None	None	Macular Dystrophy Gene Panel: Negative
3	Never Smoker	Pregabalin	CKD Stage III	Single VOUS IMPG2 and ADAM9 found.
4	Former Smoker: 5 pack years	Oxybutynin, Cystohydrodistension, Amitriptyline, Cyclobenzaprine, Gabapentin, Hydroxyzine	None	ABCA4 VOUS
5	Never Smoker	Gabapentin/pregabalin, Hydroxyzine	None	Macular Dystrophy Gene Panel: Negative
6	Never Smoker	Hydroxyzine	None	Mitochondrial Myopathy Panel: Negative
				Glycogen Storage Disease Profile: Negative
7	Former Smoker: 40 pack years	Tolterodine, Vaginal Diazepam, Amitriptyline, Cyclobenzaprine, Gabapentin, Hydroxyzine	CKD Stage I	Macular Dystrophy Gene Panel: Negative
8	Never Smoker	Cyclobenzaprine	None	Macular Dystrophy Gene Panel: Negative
9	Current Smoker	Gabapentin, Nortriptyline	None	None Performed
10	Never Smoker	None	None	None Performed
11	Never Smoker	Amitriptyline	None	ABCA4 VOUS, PROM1
12	Current Smoker	Gabapentin, Hydroxyzine, Pyridium, Promethazine	None	ABCA4 Pathogenic Variant
13	Never Smoker	None	None	None Performed
14	Never Smoker	Hydroxyzine, Gabapentin	None	None Performed
15	Never Smoker	Pyridium, Ca glycerophosphate	None	None Performed
16	Never Smoker	Amitriptyline	None	None Performed
17	Never Smoker	Gabapentin, Pyridium	None	None Performed
18	Never Smoker	None	None	None Performed
19	Former Smoker: 5 pack years	Oxybutynin, Hyoscyamine	Non-Cirrhotic Portal Hypertension	*MTTL1* wnl
20	Never Smoker	Gabapentin, Oxybutynin, Pyridium	CKD Stage III	IMPG2 Likely Pathogenic Variant
21	Current Smoker: <1 pack-year	None	None	*MTTL1* wnl
22	Never Smoker	Amitriptyline	None	None Performed
23	Never Smoker	Gabapentin, Hyoscyamine	None	Heterozygous MPZ VOUS; MTTL1 wnl
24	Never Smoker	None	None	No Pathogenic Variants; *MTTL1* wnl
25	Never Smoker	Amitriptyline	None	No Pathogenic Variants; *MTTL1* wnl
26	Never Smoker	None	Splenectomy, post-splenic rupture	None Performed
27	Never Smoker	None	None	None Performed
28	Never Smoker	Cystohydrodistension, DMSO, Amitriptyline,	None	None Performed

29	Never Smoker	Amitriptyline, Pyridum, Uribel, Cystohydrodistention	None	*TIMP3* VOUS; *MTTL1* wnl
30	Never Smoker	Amitriptyline	None	None Performed
31	Former Smoker: 74 pack years	None	None	None Performed
32	Never Smoker	Topical diphenhydramine, Oxybutynin	None	None Performed
33	Current Smoker	Oxybutynin	None	None Performed
34	Never Smoker	None	None	No Pathogenic Variants
35	Never Smoker	Amitryptiline, Lidocaine + PPS bladder installations, pyridium, fluconazole, tadalafil	None	None Performed

IC = interstitial cystitis; PPS = pentosan polysulfate sodium; DMSO = dimethyl sulfoxide; CKD = chronic kidney disease; VOUS = variant of unknown significance; wnl = within normal limits.

8.9 APPENDIX I. DRUG UTILIZATION TABLE

Table I1. Nationally estimated number of patients with a dispensed prescription for pentosan from U.S. outpatient retail pharmacies, stratified by age and sex, from 2011 through 2018.

	2011					2012					2013					2014				
	All patients (N)	**Share (%)**	Male	Female	Unsp. sex	**All patients (N)**	**Share (%)**	Male	Female	Unsp. sex	**All patients (N)**	**Share (%)**	Male	Female	Unsp. sex	**All patients (N)**	**Share (%)**	Male	Female	Unsp. sex
All ages																				(b) (4)
<19 years old																				
19-30 years old																				
31-40 years old																				
41-50 years old																				
51-60 years old																				
61-70 years old																				
71-80 years old																				
>80 years old																				
Unspecified age																				

	2015					2016					2017					2018				
	All patients (N)	**Share (%)**	Male	Female	Unsp. sex	**All patients (N)**	**Share (%)**	Male	Female	Unsp. sex	**All patients (N)**	**Share (%)**	Male	Female	Unsp. sex	**All patients (N)**	**Share (%)**	Male	Female	Unsp. sex
All ages																				(b) (4)
<19 years old																				
19-30 years old																				
31-40 years old																				
41-50 years old																				
51-60 years old																				
61-70 years old																				
71-80 years old																				
>80 years old																				
Unspecified age																				

Source: IQVIA Total Patient Tracker™. July 2012-June 2018. File: TPT testosterone 2018-1411 xlsx. Patient counts are estimates for each time period and age group and should not be summed, at the risk of double-counting patients who appear in multiple time periods or multiple age groups during the times evaluated. Of note, the estimated prescription and/or patient counts provided are based on projections of sample prescription claims data and therefore have some degree of inherent sampling error. These estimates are not intended to be representations of exact enumerations and should be interpreted with caution particularly if they are based on a small sample size. In addition, the data cannot be validated due to lack of access to medical records in the data sources.

8.10 APPENDIX J: ELEMENTS OF CAUSALITY ASSESSMENT FOR AN ASSOCIATION BETWEEN PENTOSAN AND PIGMENTARY MACULOPATHY

Element	Data Source	Supporting	Lacking
Analogy	Literature	Pentosan antagonizes fibroblast growth factor (FGF) signaling pathways. A selective FGF inhibitor (AZD4547) is associated with central serous retinopathy and RPE detachment.[34] In general, drug-associated toxic retinopathy is a known entity. Examples include hydroxychloroquine and deferoxamine.	
Biologic plausibility	Literature	Proposed mechanisms: 1. RPE cell death from PPS toxicity could cause accumulating byproducts of visual cycle resulting in RPE abnormalities[1] 2. Accumulation of PPS or metabolite in the RPE[1] 3. PPS antagonism of Fibroblast Growth Factor signaling pathways which normally maintain retinal health and regeneration in vertebrate retinas[39] 4. Toxic effects of PPS may interfere with RPE capacity to process photoreceptor outer segments[4] 5. PPS may disrupt photoreceptor-RPE interaction given that interphotoreceptor matrix is made up of glycosaminoglycans that are structurally similar to PPS[2]	
Consistency	Literature	Increasing number of reports from other ophthalmologists at different sites describe similar findings.	

Element	Data Source	Supporting	Lacking
Dechallenge-Rechallenge	FAERS	Single case of patient who described improvement in visual disturbance after stopping PPS	Huckfeldt[28] reported a case of progression of maculopathy despite cessation of PPS; confounded by interval craniotomy and XRT for melanoma; doesn't rule out PPS-related
Dose-response	Literature	Observational studies by Hanif, Ludwig, Vora, and Wang [32, 34, 36, 35] show preliminary evidence of a dose-response relationship. Hadad's computer analysis also described a dose-response relationship[31]	
Specificity	Literature	Cases appear to represent a unique maculopathy in patients exposed to long-term PPS. Many cases had genetic testing with either no pathogenic mutations or mutations of uncertain significance.	• No data available about a comparator group from either the general population or from unexposed patients with IC. • Confounding factors in case reports include age, non-specific visual complaints attributable to a range of eye disease, use of hydroxychloroquine, smoking, brain metastases, T2DM. • Some reports lack detail about concomitant diseases and medications.
Strength of association	Literature	Epidemiology studies suggest an association between long-term PPS exposure and pigmentary maculopathy.	Data are insufficient to evaluate the strength of the association. Need more robust studies that include a comparator group. Limitations of epidemiology studies precludes concluding a causal association.
Temporality	Literature	Observational studies suggest an association between higher cumulative dose, longer duration of use, and higher daily dose and pigmentary maculopathy.	The long duration of PPS use by most subjects makes it difficult to evaluate temporal association.

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/s/

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020193Orig1s014

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 020193/S-14

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

Johnson Research & Development, LLC
Attention: Jenna Giacchi
Manager, Global Regulatory Affairs
920 US Highway 202
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 the following:

NDA NUMBER: 020193

SUPPLEMENT NUMBER: 14

PRODUCT NAME: ELMIRON® (pentosan polysulfate sodium) 100 mg capsules

DATE OF SUBMISSION: June 24, 2019

DATE OF RECEIPT: June 24, 2019

This supplemental application proposes a change to the labeling, to add a warning on pigmentary maculopathy.

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 August 23, 2019, in accordance with 21 CFR 314.101(a).

If the application is filed, the goal date will be December 24, 2019.

If you have questions, call me, at 301-796-0948.

Sincerely,

{See appended electronic signature page}

George Lyght, Pharm.D.
Senior Regulatory Project Manager
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

GEORGE A LYGHT
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