UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSY

IN RE: ELMIRON (PENTOSAN POLYSULFATE SODIUM) PRODUCTS LIABILITY LITIGATION	MDL No. 2973 Case No. 2:20-md-02973 (BRM)(ESK)
WILLIAM WEBER, on behalf of himself and all others similarly situated, Plaintiff, v. TEVA BRANDED PHARMACEUTICAL PRODUCTS R&D, INC., f/k/a Teva Global Respiratory Research, LLC.; TEVA PHARMACEUTICALS USA, INC.; JANSSEN PHARMACEUTICALS, INC., f/k/a Ortho-McNeil-Janssen Pharmaceuticals, Inc., f/k/a Janssen Pharmaceutica Inc.; ORTHO-MCNEIL PHARMACEUTICAL, LLC; JANSSEN RESEARCH & DEVELOPMENT LLC f/k/a Johnson & Johnson Research & Development, L.L.C.; ALZA CORPORATION; JANSSEN ORTHO LLC; and JOHNSON & JOHNSON, Defendants.	JUDGE BRIAN R. MARTINOTTI JUDGE EDWARD S. KIEL DIRECT FILED CLASS ACTION COMPLAINT PURSUANT TO CASE MANAGEMENT ORDER NO. 6 Civil Action No.: 2:21-cv-12464

CLASS ACTION COMPLAINT

Plaintiff WILLIAM WEBER ("Plaintiff") bring this consolidated class action on behalf of himself and all others similarly situated against TEVA BRANDED PHARMACEUTICAL PRODUCTS R&D, INC., f/k/a Teva Global Respiratory Research, LLC.; TEVA PHARMACEUTICALS USA, INC., JANSSEN PHARMACEUTICALS, INC. f/k/a Ortho-McNeil-Janssen Pharmaceuticals, Inc. f/k/a Janssen Pharmaceutica Inc.; ORTHO-MCNEIL PHARMACEUTICAL, LLC.; JANSSEN RESEARCH & DEVELOPMENT LLC f/k/a Johnson & Johnson Research & Development, L.L.C.; ALZA CORPORATION; JANSSEN ORTHO LLC;

and JOHNSON & JOHNSON;, (collectively, "Defendants") (collectively, "Defendants") and seek damages and equitable relief to remedy the harms caused by Defendants' unlawful design, manufacture, marketing, packaging, labeling, handling, distribution, and/or sale of pentosan polysulfate sodium ("PPS") as Defendants' prescription drug Elmiron® ("Elmiron"). Based upon personal knowledge as to Plaintiff's own conduct, and upon information and belief, including through investigation of counsel, as to all other matters, Plaintiff alleges as follows:

INTRODUCTION

1. This is a medical monitoring class action related to Defendants' wrongful conduct in connection with the development, design, testing, labeling, packaging, promoting, advertising, marketing, distribution and selling of Elmiron.

2. Defendants manufacture, promote and sell Elmiron as a prescription drug that treats interstitial cystitis (also known as "IC" or "bladder pain syndrome"). Elmiron is manufactured as a capsule suitable for oral consumption.

3. Defendants knew or should have known that Elmiron, when taken as prescribed and intended, causes harmful damage to the retina, including the macula, and causes a form of maculopathy now referred to as pentosan polysulfate sodium (PPS) maculopathy or Elmiron maculopathy (hereinafter "Elmiron Maculopathy"), a condition that is not seen in patients who have not ingested Elmiron and is caused only by the toxicity of Elmiron.

4. Numerous patient reports, scientific studies and even alerts by governmental agencies have established that Elmiron causes damage to the retina, including Elmiron Maculopathy.

5. Defendants failed to warn, instruct, advise, educate or otherwise inform Elmiron users about the risk of Elmiron Maculopathy or the need for medical and ophthalmological monitoring.

6. Defendants failed to warn, instruct, advise, educate or otherwise inform Elmiron prescribers about the risk of Elmiron Maculopathy or the need for medical and ophthalmological monitoring.

7. Defendants failed to warn, instruct, advise, educate or otherwise inform United States governmental regulators about the risk of Elmiron Maculopathy or the need for medical, ophthalmological monitoring.

8. At all relevant times, the U.S. label for Elmiron made no mention of risk to patients' eyes or vision or the need for baseline, annual or continuing examinations, monitoring and early detection to identify Elmiron Maculopathy.

9. Baseline, annual or continuing examinations, monitoring and early detection are necessary to identify and possibly alleviate the devastating vision issues that Elmiron is causing and will continue to cause in the years to come. Recent scientific research has identified specific imaging studies that are most suitable for identifying Elmiron Maculopathy.

10. Recent scientific publications have also suggested that Elmiron Maculopathy can continue to evolve years after drug cessation, and may not even begin to manifest itself until months and even years after a person stops taking Elmiron.

11. The recent findings make it even more essential that individuals exposed to Elmiron have medical monitoring and ophthalmological testing.

12. Plaintiff accordingly brings this class action on behalf of himself and all others similarly situated seeking redress to compensate for their economic losses; to provide for the

medical monitoring they require for early detection, treatment and study of Elmiron Maculopathy for the remainder of Plaintiff's and each Medical Monitoring Class Member's lives; and to deter the type of misconduct that caused the damages suffered by Plaintiff and the Class.

PARTY PLAINTIFF

13. Plaintiff WILLIAM WEBER is a citizen of the state of Massachusetts, residing in Berkshire County. Plaintiff WEBER was diagnosed with interstitial cystitis and subsequently took Elmiron as prescribed by his physician from approximately 2004 to 2019. During the relevant time periods, Plaintiff WEBER and his physicians were given no warning and had no knowledge of subcellular damage and the serious risk of severe damage to the retina including the macula and resulting vision impairment posed by the use of Elmiron. As a result of his exposure to Elmiron, Plaintiff WEBER demonstrates subcellular damage and is now at a significantly increased risk of contracting Elmiron Maculopathy and requires medical and ophthalmological monitoring for the early detection of this disease. Currently, Plaintiff WEBER has not been diagnosed with Elmiron Maculopathy.

PARTY DEFENDANTS

TEVA BRANDED PHARMACEUTICAL PRODUCTS R&D, INC.

14. TEVA BRANDED PHARMACEUTICAL PRODUCTS R&D, INC., f/k/a Teva Global Respiratory Research, LLC, (hereinafter "TEVA") is a Delaware corporation with a current principal place of business at 41 Moores Road, Malvern, Pennsylvania 19355.

15. Upon information and belief IVAX L.L.C. f/k/a IVAX Corporation (hereinafter "IVAX") and Baker Norton U.S., Inc. f/k/a Baker Norton Pharmaceuticals, Inc. f/k/a Baker Cummins Pharmaceuticals, Inc. (hereinafter "Baker Norton") are and have been wholly owned subsidiaries of TEVA.

16. Upon information and belief Baker Norton is and has been a wholly owned subsidiary of IVAX

17. In June, 1991, Baker Norton submitted the NDA for Elmiron to the FDA and was the named sponsor on the approval of Elmiron by the FDA. In support of the NDA for Elmiron, Baker Norton conducted the clinical trials. The validity of two of these clinical trials was seriously questioned by the FDA.

18. Baker Norton held the NDA for Elmiron from the date of approval, September 26, 1996, until approximately September 1997.

19. In September 1997, IVAX licensed the rights to Elmiron in the United States and Canada to Alza Pharmaceuticals, a division of defendant ALZA CORPORATION, for $75 Million in up-front payments. At times hereinafter relevant, ALZA CORPORATION made the $75 Million up-front payment and additional payments required under the agreement to IVAX.

20. IVAX continues to receive milestone and royalty payments as a result of the sales of Elmiron

21. Elmiron was and is a Registered Trademark of Defendant TEVA under license to Defedndant JANSSEN PHARMA.

22. At all times relevant and material hereto, TEVA was, and still is, a pharmaceutical company involved in the manufacturing, research, development, marketing, distribution, sale, and release for use to the general public of pharmaceuticals, including Elmiron, throughout the United States.

TEVA PHARMACEUTICALS USA, INC.

23. Defendant TEVA PHARMACEUTICALS USA, INC. (hereinafter "TEVA PHARMACEUTICALS USA"), is a corporation organized under Delaware law with its principal

place of business 400 Interpace Parkway, Parsippany, NJ 07054.

24. At all times relevant and material hereto, TEVA PHARMACEUTICALS USA was, and still is, a pharmaceutical company involved in the manufacturing, research, development, marketing, distribution, sale, and release for use to the general public of pharmaceuticals, including Elmiron, throughout the United States.

JANSSEN PHARMACEUTICALS, INC.

25. Defendant JANSSEN PHARMACEUTICALS, INC., f/k/a Ortho- McNeil-Janssen Pharmaceuticals, Inc., f/k/a Janssen Pharmaceutica Inc., (hereinafter "JANSSEN PHARMA") is a corporation organized under Pennsylvania law with its principal place of business at 1125 Trenton-Harbourton Road, Titusville, New Jersey 08560.

26. JANSSEN PHARMA has held the U.S. Food and Drug Administration (FDA) New Drug Application (NDA) for Elmiron since approximately August 2008.[1]

27. Elmiron is a Registered Trademark currently under license to JANSSEN PHARMA.

28. At all times all times relevant and material hereto, JANSSEN PHARMA was, and still is, a pharmaceutical company involved in the manufacturing, research, development, marketing, distribution, sale, and release for use to the general public of pharmaceuticals, including Elmiron, throughout the United States.

OTHO-MCNEIL PHARMACEUTICAL, L.L.C.

29. Defendant ORTHO-MCNEIL PHARMACEUTICAL, LLC. (hereinafter "ORTHO

[1] The holder of the NDA is the party that controls the patents associated with a FDA approved drug, giving them the ability to, among other things, market and sell the subject drug. The NDA holder also has the ability and responsibility to update the product label, no matter where the update in the label is needed, to ensure that it warns of dangerous adverse events associated with its drug.

PHARMA") is a corporation organized under Delaware law with its principal place of business at 1000 US Highway 202, Raritan, New Jersey 08869.

30. ORTHO PHARMA held the NDA for Elmiron from approximately July 2004 until August 2008.

31. ORTHO PHARMA marketed, co-marketed, sold and distributed Elmiron through its division, Ortho Women's Health and Urology.

32. At all times all times relevant and material hereto, ORTHO PHARMA was, and still is, a pharmaceutical company involved in the manufacturing, research, development, marketing, distribution, sale, and release for use to the general public of pharmaceuticals, including Elmiron, throughout the United States.

JANSSEN RESEARCH & DEVELOPMENT LLC

33. Defendant JANSSEN RESEARCH & DEVELOPMENT LLC, f/k/a Johnson & Johnson Research & Development, L.L.C. (hereinafter "JANSSEN R&D") is a limited liability company organized under the laws of New Jersey with its principal place of business at One Johnson & Johnson Plaza, New Brunswick, New Jersey 08933.

34. JANSSEN R&D 's sole member is Centocor Research & Development, Inc. (hereinafter "Centocor"), a Pennsylvania corporation with its principal place of business at 800 Ridgeview Dr. Horsham, Pennsylvania 19044.

35. JANSSEN R&D held the NDA for Elmiron from approximately August 2002 until August 2004.

36. At all times relevant and material hereto, JANSSEN R&D was, and still is, a pharmaceutical company involved in the manufacturing, research, development, marketing, distribution, sale, and release for use to the general public of pharmaceuticals, including Elmiron,

throughout the United States.

ALZA CORPORATION

37. Defendant ALZA CORPORATION (hereinafter "ALZA") is a corporation organized under Delaware law with its principal place of business at 700 Eubanks Drive, Vacaville California.

38. In September 1997, IVAX licensed the rights to Elmiron in the United States and Canada to Defendant ALZA for $75 Million in up-front payments.

39. Upon information and belief, Defendant ALZA made the $75 Million up-front payment and additional payments required under the agreement.

40. Defendant ALZA held the NDA for Elmiron from approximately April 1998 until August 2002.

41. At all times all times relevant and material hereto, ALZA was, and still is, a pharmaceutical company involved in the manufacturing, research, development, marketing, distribution, sale, and release for use to the general public of pharmaceuticals, including Elmiron, throughout the United States.

JANSSEN ORTHO, LLC

42. Defendant JANSSEN ORTHO, LLC (hereinafter "JANSSEN ORTHO") is a limited liability company organized under Delaware law with its principal place of business at Gurabo 00777, Puerto Rico. JANSSEN ORTHO's sole member is OMJ PR Holdings, a corporation incorporated in Ireland with a principal place of business in Puerto Rico.

43. At all times relevant and material hereto, JANSSEN ORTHO was, and still is, a pharmaceutical company involved in the manufacturing, research, development, marketing, distribution, sale, and release for use to the general public of pharmaceuticals, including Elmiron,

throughout the United States.

JOHNSON & JOHNSON

44. Defendant JOHNSON & JOHNSON is a corporation organized under New Jersey law with its principal place of business at One Johnson & Johnson Plaza, New Brunswick, New Jersey 08933.

45. Upon information and belief, JANSSEN PHARMA, ORTHO PHARMA, JANSSEN R&D, JANSSEN ORTHO and ALZA are and have been wholly owned subsidiaries of JOHNSON & JOHNSON.

46. Upon information and belief, JOHNSON & JOHNSON maintains a controlling interest in OMJ PR Holdings and Centocor.

47. On June 22, 2001, JOHNSON & JOHNSON acquired licensing rights to Elmiron when a wholly owned subsidiary of JOHNSON & JOHNSON merged with and into ALZA, in a $10.5 billion stock-for-stock transaction.

48. JOHNSON & JOHNSON and its "family of companies" do business by, among other things, designing, developing, testing, manufacturing, labeling, packaging, distributing, marketing, selling and/or profiting from Elmiron, throughout the United States.

49. JOHNSON & JOHNSON together with its co-defendants manufactured, packaged, labeled, promoted, advertised, marketed, co-marketed, distributed and sold Elmiron at all times Plaintiff was prescribed, purchased and ingested Elmiron.

50. Defendants were jointly engaged in the business of designing, developing, manufacturing, testing, packaging, promoting, marketing, distributing, labeling and/or selling Elmiron and controlling the Elmiron NDA.

JURISDICTION & VENUE

51. This Court has original jurisdiction over this class action pursuant to 28 U.S.C. § 1332, as amended by the Class Action Fairness Act, 28 U.S.C. § 1332(d) because there are at least one hundred (100) members of the proposed class; the value of the relief sought exceeds $5,000,000; and at least one Plaintiff is a citizen of a state different from at least one Defendant.

52. The Court has personal jurisdiction over Defendants because Defendants specifically avail themselves of and maintain their headquarters, a regular presence or conduct business in this District.

53. Venue is proper in this forum pursuant to 28 U.S.C. § 1391(b)(2) and (c)(2) because a substantial part of the acts giving rise to Plaintiff's claims occurred in this District and because Defendants are subject to personal jurisdiction within this District.

54. All conditions precedent to this action have occurred, been performed, or have been waived.

FACTUAL ALLEGATIONS

A. Brief History of Elmiron

55. Elmiron, also known as Pentosan Polysulfate Sodium (PPS), is an oral heparinoid derived from beech tree bark. It is a macromolecule resembling glycosaminoglycans (GAGs) and was initially used in the 1950's as a blood thinner – similar to Heparin.

56. Elmiron was the first – and remains the only – oral drug approved by the FDA specifically for the treatment of patients with interstitial cystitis ("IC") (bladder pain).

57. However, Elmiron is not the only treatment for IC that is available to physicians and their patients.

58. IC is a diagnosis that applies to patients with chronic bladder pain in the absence of other explanatory etiologies (or causes). The symptoms associated with IC range from discomfort to severe pain and can include increased frequency and urgency of urination.

59. Under the IC treatment guidelines established by the American Urological Association ("AUA"), there are six lines of treatment for IC. According to the AUA, "first-line treatments" should be suggested to all patients and "sixth-line treatments" should be reserved for the most severe cases, with the remaining treatment options falling in between.

60. Elmiron is not a first-line treatment for IC. Rather, Elmiron is one of ten suggested second-line treatments, including three other oral medications: amitriptyline, cimetidine and hydroxyzine.

61. The guidelines further include numerous third-, fourth-, fifth-and sixth-line treatments. When first and second-line treatments fail to provide relief, the third, fourth, fifth and sixth-line treatments involve more invasive procedures such as the use of a catheter to deliver medicated solutions directly to the bladder, Botox injections to the muscle wall of the bladder, implantation of neurostimulation devices to control muscle contractions in the bladder, or, in rare cases, surgery to remove ulcers from the bladder or augment the bladder wall with an intestinal patch.

62. Defendants market Elmiron as "The Only Oral Medication FDA Approved to Treat the Bladder Pain or Discomfort of Interstitial Cystitis (IC)."[2] However, while Elmiron is the only oral medication approved by the FDA *specifically* for the purpose of treating IC, that statement is misleading in that ***1) Elmiron is not the only oral medication approved by the FDA that can be***

[2] ORTHOELMIRON, https://www.orthoelmiron.com/patient/about-elmiron (last visited Oct. 6, 2020).

used to treat IC; 2) Elmiron is not the only IC treatment option; ***and 3) Defendants knew, or should have known, that studies demonstrate there is no statistically significant difference between the treatment effect of Elmiron and a placebo.***

63. Rather, Elmiron is in fact one of *five* oral medications endorsed by the AUA Guidelines for use in treating IC, all of which are FDA-approved oral medications. Furthermore, the AUA Guidelines list *six lines* of treatment for IC, each of which contain multiple treatment options.

64. Indeed, in a March 2012 Citizen's Petition to the FDA, JANSSEN PHARMA did not make the same misrepresentation it made to the public, but rather qualified that "[a]lthough other medications may treat discrete symptoms [of IC], ELMIRON is the only ***orally-administered*** medication that is ***specifically*** approved for treatment of IC patients." (emphasis added).[3]

65. On August 7, 1985, Elmiron was designated an "orphan drug" by the FDA. At that time, non-party Medical Marketing Specialists, located in Boonton, New Jersey, was the owner of Elmiron. The "orphan drug" designation is a special status granted under the Orphan Drug Act ("ODA") to a drug used to treat a rare disease or condition upon request of a sponsor. For a drug to qualify for orphan designation, both the drug and the disease or condition must meet certain criteria specified in the ODA and FDA's implementing regulations (21 CFR Part 316). Orphan designation qualifies the sponsor of the drug for various development incentives provided by the ODA, including tax credits for qualified clinical testing. However, the granting of an orphan designation request does not alter the standard regulatory requirements and process for obtaining

[3] March 26, 2020 Janssen Citizen Petition requesting FDA adoption of appropriate bioequivalence requirements to govern approval of any abbreviated new drug application ("ANDA") relying on ELMIRON (pentosan polysulfate sodium) as its reference product (hereinafter "Janssen Citizen Petition") (emphasis added).

marketing approval. Safety and effectiveness of a drug must be established through adequate and well-controlled studies whether a drug is an "orphan drug" or not.

66. In 1986, Elmiron was made available for compassionate use. Compassionate use is a potential pathway for a patient with an immediately life-threatening condition or serious disease or condition to gain access to an investigational medical product (drug, biologic, medical device, or combination product) for treatment outside of clinical trials when no comparable or satisfactory alternative therapy options are available.

67. The original NDA for Elmiron was submitted on June 11, 1991, five (5) years after it was made available for compassionate use by Baker Cummins Pharmaceuticals, Inc., now Baker Norton, which at the time was a subsidiary of IVAX.

68. On February 18, 1992, FDA Division Director Wiley A. Chambers, MD, issued his review of the Elmiron NDA. In his review, Dr. Chambers indicated the NDA was *not* recommended for approval, citing several very serious flaws with the clinical trials submitted to support approval of the drug. Specifically, Dr. Chambers stated:

> The application as submitted lacks substantial evidence consisting of adequate and well-controlled investigations, as defined in 21 CFR 314.126 that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling. Specifically, the analysis of the results of the submitted studies are not adequate to assess the effects of the drug.

He further stated:

> The purpose of conducting clinical investigations of a drug is to distinguish the effect of a drug from other influences. Based on the analyses submitted to date for studies E-001 and E-002, there appears to be significant investigator interaction. The results obtained by the first investigator listed in each study are significantly different than the results obtained by each of the other investigators in the studies. In the absence of an adequate explanation for these differences, studies E-001 and E-002 cannot be considered to be adequate and well-controlled. It is recommended that an additional clinical investigation utilizing investigators not included in previous studies be conducted and submitted as part of any resubmission of this application.

69. The investigators referenced in Dr. Chambers' review as having "significantly different" results compared to all of the other investigators were Dr. Philip Hanno and Dr. C. Lowell Parsons.

70. Dr. Parsons' results in study E-002 were particularly concerning to the FDA reviewers. Specifically, Dr. Parson's found that 10 of 15 or 66.7% of his patients treated with Elmiron described their bladder pain as "better." Interestingly, no other investigator in that study had more than 40% of patients fit into this category and collectively, the other six investigators combined reported that only 23% of patients described their bladder pain as "better." As noted by FDA reviewer Dr. John Kenealy:

> [I]n each of the studies herein presented, elimination of the results from one of the centers all but destroys the statistical significance of the results of that study. The medical reviewer has indicated that one of the two investigators is known to have a financial interest in this drug. Because of the strong influence of these centers on the outcome, Scientific Investigations has been requested to audit the records of these centers for these studies.

FDA reviewer Dr. Paul Waymack also stated:

> [I]t should be noted that when reviewing the data, it was determined that if the data from a single investigator (the champion of this therapy) was removed from the study, not only was statistical significance lost, but even the trend towards benefit was lost.

71. Both reviewers were referring to Dr. Parsons, who had both a financial interest in Elmiron, as well as connections with the sponsor at the time, Baker Norton.

72. Indeed, after Elmiron was approved, Dr. Parsons gave numerous lectures and presentations touting Elmiron as "an amazing breakthrough" to treat IC.

73. Upon information and belief, Dr. Parsons then received and still continues to receive from the Defendants, royalty payments from the sale of Elmiron.

74. Due in part to the serious flaws in the clinical studies performed by Dr. Parsons and

other concerns expressed by the FDA, on January 27, 1993, the FDA sent a letter to Baker Norton indicating the NDA for Elmiron *was not* approvable. The letter included the following statement as one of the reasons the NDA was denied:

> One purpose of conducting clinical investigations of a drug is to distinguish the effect of a drug from other influences. Based on the analyses submitted for studies E-001 and E-002, there appears to be significant investigator interaction. The results obtained by the first investigator listed in each study are significantly different than the results obtained by each of the other investigators in the studies. In the absence of an adequate explanation for these differences, studies E-001 and E-002 cannot be considered to be adequate and well-controlled. We recommend that an additional clinical investigation utilizing investigators not included in previous studies be conducted and submitted as part of any amending of this application.
>
> We recommend that you consider carrying out an additional study to demonstrate effectiveness of the drug.

75. On March 19, 1993, a meeting was held between the FDA and Baker Norton, during which the FDA again requested Baker Norton perform an additional clinical study to support the efficacy of Elmiron. During the meeting, the parameters of the recommended study were discussed in detail. However, during this meeting, FDA also agreed that Baker Norton could submit additional analyses to support their position that the existing data was adequate. This included further analysis of clinical trials E-001 and E-002, along with an analysis of the compassionate use experience. The re-analysis of the clinical trials was submitted to FDA on July 7, 1993.

76. After receipt of the new analysis submitted by Baker Norton, FDA issued a memo again declaring the NDA for Elmiron remained not approvable, citing a lack of independence by a clinical investigator, failure to meet the level of statistical significance required and a failure of the case report forms to support the scale used for analysis. FDA again requested that a new clinical trial be conducted. At this time, the compassionate use data had not yet been provided to FDA.

77. On July 20, 1993, Baker Norton submitted a brief study protocol for a proposed urinary concentration-controlled trial of Elmiron. Upon information and belief this study was not

conducted prior to approval.

78. On August 29, 1994, Dr. Waymack sent a correspondence to Division Director Patricia Love expressing further serious concerns about studies E-001 and E-002, stating:

> They have reanalyzed the data from the E-002 trial, after excluding all the data from Dr. Parsons. When this was done, the lowest p value obtained was only .107, which was for the Overall Improvement (Investigator Impression). This raises a number of possible explanations for the significant p values obtained from the studies, other than the drug having an effect. These would include a different patient population at the site of Dr. Parsons investigations, a loss of blinding, some other form of bias, or a random statistical event.

79. On October 28, 1994, FDA issued a *second* letter declining to approve Baker Norton's NDA for Elmiron. The letter indicated that study E-001 did not provide adequate evidence of effectiveness and that study E-002 provided only "some" evidence of effectiveness (as indicated above, the results of study E-002 were disproportionately affected by Dr. Parson's data). Thus, FDA requested that Baker Norton perform an additional adequate and well-controlled clinical study designed to show effectiveness and safety. FDA suggested that if the study was clearly positive and otherwise acceptable it, along with study E-002, would provide sufficient evidence for approval.

80. On February 16, 1995, yet another meeting was held between FDA and Baker Norton concerning Elmiron. During this meeting, FDA again reiterated the need for an additional clinical trial and Baker Norton continued to resist, arguing for the validity of the two trials already conducted. FDA was not convinced, stating:

> We indicated that we need replication of an adequate study. This is in part needed in order to show that other physicians can safely use the product. So far, their data shows that one physician can use Elmiron; the results from the other physicians do not show improvement. The sponsor showed a slice with pooled data from all investigators in order to support their position. This slide confirmed our point that the data is driven by one physician (Parsons).

81. For some reason, Baker Norton continued to push back against conducting an

additional trial and instead suggested that the compassionate use data would be sufficient to show the product worked. FDA noted that such an analysis would be the "third reassessment of old data that was twice deemed inadequate."

82. On August 31, 1995, Baker Norton submitted its analysis of the compassionate use experience.

83. On March 1, 1996, despite Baker Norton's refusal to conduct an additional clinical trial to demonstrate the effectiveness of Elmiron, for some yet unknown reason, FDA approved the NDA, giving Baker Norton the right to market Elmiron in the United States. Amazingly, the approval was based on study E-002, previously and repeatedly deemed inadequate and a compassionate use experience analysis, also previously deemed inadequate. The approval letter was directed to Baker Norton in Miami Florida.

84. In September 1997, Alza Corporation acquired all rights to Elmiron from Baker Norton, which at this point in time was still owned by IVAX. Baker Norton/IVAX sold the rights to Elmiron to ALZA for $75 million up front and continued to receive milestone and royalty payments thereafter.

B. Poor Bioavailability and Efficacy of Elmiron

85. Though Defendants admit that the mechanism of action for Elmiron is unknown, Elmiron is thought that it coats the epithelial cells of the bladder to provide pain relief. The drug has poor oral bioavailability and absorption, requiring users to take long-term high doses of the drug, resulting in accumulation and ultimate toxicity over time.

86. Typical users take 100mg doses, 3 times per day.

87. Only about 6% of the drug is absorbed to the epithelial cells of the bladder; the majority of the drug is excreted.

88. However, Elmiron is also absorbed into retinal epithelial cells, which can result in retinal toxicity.

89. It is suggested that users ingest Elmiron for at least 3 to 6 months—and often longer—to achieve benefit.[4] One cohort reported that pain relief occurred in only 40% to 60% of patients.[5] Populations of patients receiving extended treatment (>2 years) showed no further improvement or worsening of symptoms, yet users often continue the drug for years.[6] In other trials, the improvement of certain IC symptoms with Elmiron was significant compared to Placebo (28% of treated subjects versus 13% of placebo controls), but the overall degree of improvement was not dramatic from a clinical standpoint.[7]

90. In March 2012, a Citizen's Petition to the FDA ("Citizen Petition") requested a bioequivalence study for any new generics coming to market. In an effort to maintain its market position and block generics from coming to market, JANSSEN PHARMA admitted that as to Elmiron, "***the drug has low bioavailability, is poorly absorbed from the gastrointestinal tract and cannot be reliably assayed by determining serum levels***."[8]

91. JANSSEN PHARMA further elaborated:

> ***ELMIRON has not yet been fully characterized***. ELMIRON contains a mix of many components, which vary in chain length (molecular weight), number and

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[4] *See e.g* Elmiron Patient Brochure. Available at https://www.orthoelmiron.com/patient/patient-information

[5] Philip M. Hanno, *Analysis of Long-Term Elmiron Therapy for Interstitial Cystitis*, Vol. 49, Issue 5, Supplement 1 UROLOGY 93–99 (1997) (Exhibit "A").

[6] *Id.*

[7] Mulholland SG, Hanno P, Parsons CL, Snat GR, Staskin DR. Pentosan polysulfate sodium for therapy of interstitial cystitis: a double-blind placebo-controlled clinical study. Urology (1990) (Exhibit "B").

[8] *See* Janssen Citizen Petition (emphasis added).

> location of glucuronic acid sidechains and number of locations of sodium sulfate groups. ***Moreover, no definitive information exists to identify which of the components are active (i.e., responsible for the safety and efficacy of ELMIRON)*** . . . The information presented above demonstrates that due to the ***unknown etiology of IC, the inability to characterize ELMIRON and understand how it works in the body, the difficulty of measuring PPS in plasma, blood, or urine and the lack of a reliable bioassay to measure the product's effects***, conventional methods of determining bioequivalence are inadequate."[9]

92. The low efficacy and bioavailability of Elmiron are particularly troubling in light of the significant risks of permanent vision impairment and damage to the retina caused by the drug. These design defects render Elmiron more dangerous than other drugs and treatment options designed to treat IC and cause an unreasonable increased risk of serious injury, including but not limited to permanent vision and retinal injuries.

C. Defendants' Failure to Test Elmiron

93. Defendants admit that "the mechanism of action of pentosan polysulfate sodium in interstitial cystitis is not known," and to date, have failed to determine the mechanism of action of the drug.

94. In the Elmiron NDA file, the FDA noted that: "Elmiron works by binding to exposed epithelium," which may explain its apparent effect on the urinary bladder epithelium (emphasis added).

95. Defendants knew or should have known of the potential impact of the drug on other epithelial cells—particularly the retinal epithelial cells of the eye—but failed to adequately test for these adverse effects.

96. Defendants acknowledged that their Phase III testing of Elmiron was "subjective" and that "an objective measure" may be more appropriate. JANSSEN PHARMA stated:

[9] *Id.* (emphasis added).

> The Phase III studies on which the ELMIRON approval was initially based assessed the effect of the drug on subjects' pain and discomfort levels, as measured by the subjects' individual assessments. Pain and discomfort, while key symptoms of the IC diagnosis, are inherently subjective elements. Therefore, while patients' individual assessments based on these subjective impressions were useful in the Phase III ELMIRON trials to demonstrate a clinical benefit as compared to placebo, ***an objective measure is more appropriate*** for studies with clinical endpoints to assess bioequivalence.[10]

97. Furthermore, JANSSEN PHARMA not only failed to conduct pharmacokinetic ("PK") and pharmacodynamic ("PD") testing on the drug, but in fact advocated *against* such testing, stating:

> ***A PK study, while generally appropriate for drugs that are systemically absorbed, is inappropriate*** for determining bioequivalence of an oral dosage form of PPS. Although PPS is systemically absorbed and distributed to the bladder, it has extremely low bioavailability; even with the use of radioactive drug, PPS is difficult to detect in blood or plasma. Due to low serum concentration and the inherent complexity of the product, attempts by the manufacturer of the product, bene, to develop a sensitive and reliable bioassay have been futile. ***Indeed, Janssen is not aware of any analytical techniques presently available to predict or measure systemic concentration of PPS*** . . . Finally, because the mechanism of action of PPS and the pathophysiology of IC is unknown, ***there is no known pharmacodynamic marker other than clinical effect measured as reduction of pain***. (emphasis added)

98. PK and PD testing is not "inappropriate." An understanding of pharmacokinetics of a drug—including absorption, distribution, metabolism and excretion—is a critical aspect of drug design and is crucial to understanding how the drug interacts with the human body and evaluate potential risks associated with the drug.

D. Elmiron is no Better than a Placebo in Treating IC

99. As described above, Elmiron was eventually approved by the FDA based on two seriously flawed clinical trials that were determined by the FDA to be inadequate and not well

[10] Janssen Citizen Petition (emphasis added).

controlled. In part, this was due to a lack of independence, as well as compassionate use data that the FDA had twice previously determined to be inadequate.

100. Prior to approval, one of the top concerns expressed by the FDA was that when the data from a single investigator (Dr. Parsons) was *removed*, there was no proof that Elmiron was an effective treatment IC/Bladder Pain Syndrome.

101. Since the initial approval, additional data has been published that serves as further evidence of Elmiron's lack of efficacy.

102. In a March 2012 Citizen's Petition to the FDA requesting a bioequivalence study for any new generics coming to market – in an effort to maintain its market position and block generics from coming to market – Defendant JANSSEN PHARMA admitted that "the drug has low bioavailability, is poorly absorbed from the gastrointestinal tract, and cannot be reliably assayed by determining serum levels."[11]

103. JANSSEN PHARMA further elaborated:

> ***ELMIRON has not yet been fully characterized***. ELMIRON contains a mix of many components, which vary in chain length (molecular weight), number and location of glucuronic acid sidechains, and number of location of sodium sulfate groups. ***Moreover, no definitive information exists to identify which of the components are active (i.e., responsible for the safety and efficacy of ELMIRON)*** . . . The information presented above demonstrates that due to the ***unknown etiology of IC, the inability to characterize ELMIRON and understand how it works in the body, the difficulty of measuring PPS in plasma, blood, or urine, and the lack of a reliable bioassay to measure the product's effects***, conventional methods of determining bioequivalence are inadequate.[12]

104. In 2015, an article was published in the Journal of Urology comparing the efficacy

[11] March 26, 2012, Janssen Citizen Petition requesting FDA adoption of appropriate bioequivalence requirements to govern approval of any abbreviated new drug application ("ANDA") relying on ELMIRON (pentosan polysulfate sodium) as its reference product (hereinafter "Janssen Citizen Petition") (emphasis added).

[12] *Id.* (emphasis added).

and safety of the recommended dose of Elmiron with a third of that daily recommended dose and a placebo. This study involved 368 patients with IC/bladder pain syndrome and took place over the course of 24 weeks. The study found that "[t]here was no statistically significant difference between the pentosan polysulfate sodium group and the placebo group or between the 2 pentosan polysulfate sodium groups for the primary end point, defined as responder achieving a 30% or greater reduction from the baseline ICSI total score at study end." The authors concluded "[r]esults of this study in a broad population of patients with symptoms consistent with interstitial cystitis revealed no treatment effect vs placebo for pentosan polysulfate sodium at the currently established dose or at a third of the daily dose."[13]

105. The low efficacy and bioavailability of Elmiron are even more troubling in light of the significant risks of permanent vision impairment and damage to the retina caused by the drug. These design defects render Elmiron more dangerous than other drugs and treatment options designed to treat IC and cause an unreasonable increased risk of injury, including, but not limited to, permanent vision loss and retinal injuries.

E. The Dangers of Elmiron

106. Despite study after study providing clear evidence of the dangers of PPS, Defendants failed to adequately investigate the threat that PPS poses to patients' eyes and vision or warn patients of the risk that they would suffer retinal injury and vision impairment.

107. A physician's usage study of PPS conducted in the late 1980's and early 1990's noted adverse events affecting vision, including what was described at the time as optic neuritis

[13] J Curtis Nickel et al. *Pentosan Polysulfate Sodium for Treatment of Interstitial Cystitis/Bladder Pain Syndrome: Insights From a Randomized, Double-Blind, Placebo Controlled Study*, JOURNAL OF UROLOGY (published online first September 20, 2014) (Exhibit "C").

and retinal hemorrhage. Defendants relied upon this very study when seeking FDA approval for Elmiron and therefore had direct notice of the potential adverse effects on the eye.[14]

108. Reported adverse effects on vision included:[15]

> ***Blurred Vision. Left Central Optic Vein Occlusion***: A 32 year old white female without a prior history of eye trauma, hypertension, diabetes or previous significant ophthalmologic history complained of experiencing blurred vision.
>
> ***"Filmy Sensation Over Left Eye" Possible Left Optic Neuritis***: A 21 year old white female without any history of ophthalmological problems, head trauma, diabetes, or any previous neurological symptoms experienced a "filmy sensation over the left eye."

109. As early as 1991, available medical research also identified that PPS inhibits regrowth and proliferation of retinal pigment epithelial (RPE) cells,[16] and could thereby impair an important physiological pathway for retinal health.

110. Indeed, as set forth above, Defendants were on notice from the FDA of the possible effect on other epithelial cells, corroborating the risk Elmiron posed specifically to the RPE cells of the eye.

111. In fact, by 1992, PPS was also in Phase I trials for certain cancer treatments because of its "potent inhibition of cell motility," which further corroborates the role of PPS inhibiting cell regrowth and proliferation.

112. The FDA had serious concerns about Elmiron and rejected several applications for its approval, finding the conduct of some of the clinical trials "worrisome."

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[14] A Statistical and Medical Review of an Amendment to the New Drug Application for Elmiron® (Pentosan Polysulfate), NDA #20193, Appendix D (January 1996) (Exhibit "D").

[15] *Id*.

[16] Katrinka H. Leschey, John Hines, Jeff H. Singer, Sean F. Hackett, and Peter A. Campochiaro, *Inhibition of Growth Factor Effects in Retinal Pigment Epithelial Cells*, 32 INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE 1770–1778 (1991) (Exhibit "E").

113. Nevertheless, the FDA ultimately approved Elmiron in September of 1996. After that, new information continued to reveal the serious risk of eye and vision injuries related to Elmiron use.

114. Almost immediately after the FDA approved Elmiron, patients and doctors began reporting serious complications relating to eye and vision problems in patients taking Elmiron. According to the FDA Adverse Events Reporting System (FAERS) Public Dashboard, eight patients taking Elmiron reported serious adverse effects to their vision in the 1997 calendar year.[17]

115. From January of 1997 through March of 2020, 164 cases of eye disorders were reported to the FDA as adverse effects of Elmiron, ranging from blurred vision to maculopathy and blindness. Other reported symptoms include visual impairment, halo vision and reduced visual acuity.[18]

116. In 2018, researchers from the Emory Eye Center published their concerns about the presentation of a unique eye disease they were seeing in patients taking Elmiron in the Journal of Ophthalmology.[19]

117. The researchers also summarized their findings in a letter to the editor of the Journal of Urology:

> We wish to alert readers to a concerning new observation of ***vision threatening retinal changes associated with long-term exposure to [Elmiron]***. We recently reported our findings of retinal pigmentary changes in six patients undergoing long-term therapy with [Elmiron]. These patients primarily described difficulty reading

[17] U.S. Food and Drug Administration Adverse Events Reporting System, Elmiron (1997) https://fis.fda.gov/sense/app/d10be6bb-494e-4cd2-82e4-0135608ddc13/sheet/6b5a135f-f451-45be-893d-20aaee34e28e/state/analysis (last access June 8, 2021).

[18] To date, at least 164 patients have reported "serious" adverse effects to their vision. *Id*.

[19] William A. Pearce, Rui Chen, and Nieraj Jain, *Elmiron maculopathy Associated with Chronic Exposure to Pentosan Polysulfate Sodium*, 125 OPHTHALMOLOGY 1793–1802 (2018), https://www.ncbi.nlm.nih.gov/pubmed/29801663 (Exhibit "F").

> and/or trouble adjusting to dim lighting. Each patient had received a standard dosage of [Elmiron], ranging from 200 to 400 mg daily, for a median duration of 15.5 years. . . . ***Examination findings in patients with this condition are suggestive of injury to the retina and the underlying retinal pigment epithelium***. . . . After extensive investigations, which included molecular testing for hereditary retinal disease, ***we found these cases to resemble no other retinal disease***.[20]

118. The study, "Elmiron maculopathy Associated with Chronic Exposure to [Elmiron]," focused on six women with IC who presented to the Emory clinic between May of 2015 and October of 2017, all with Elmiron maculopathy.[21] Maculopathy is a general term referring to any pathological condition that affects the macula, the central portion of the retina upon which visual acuity and sensitivity depend.

119. Most of these patients had difficulty reading and difficulty seeing in darkness. Two patients experienced a generalized dimming of their vision as the first symptom. Two others had difficulty with near vision: one had paracentral scotomas (vision loss) in part of her eye, while the other had metamorphopsia (distorted vision where straight lines become wavy).

120. All six patients underwent rigorous diagnostic imaging and DNA testing to determine if they had any genes associated with hereditary retinal loss. None had a family history of retinal disease or the discovery of any pathogenic process.

121. What they had in common was the use of Elmiron.

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[20] William A. Pearce, Adam M. Hanif, and Nieraj Jain, Letter to the Editor Re: *FDA BRUDAC 2018 Criteria for Interstitial Cystitis/Bladder Pain Syndrome Clinical Trials*, 200 UROLOGY 1122 (2018) (emphasis added) (Exhibit "G").

[21] William A. Pearce, Rui Chen, and Nieraj Jain, *Pigmentary Maculopathy Associated with Chronic Exposure to Pentosan Polysulfate Sodium*, 125 OPHTHALMOLOGY 1793–1802 (2018), https://www.ncbi.nlm.nih.gov/pubmed/29801663 (Exhibit "H").

122. Examinations of their eyes showed clear changes: "Nearly all eyes (10 eyes of 5 patients) showed subtle parafoveal pigmented deposits at the level of the retinal pigment epithelium (RPE)."[22]

123. All eyes "showed subtle vitelliform deposits that increased in number and extended beyond the major arcade of vessels in cases judged to be more severe. Four eyes of 2 patients showed RPE atrophy that was noted to increase in area and encroach on the central fovea over time."[23] Retinal imaging also found clear diseased regions, atrophy or both.[24]

124. The youngest patient in the study was 37 years old. Diagnosed with IC at the age of 23 and on a steady dosage of Elmiron, she began showing visual symptoms (difficulty with near vision and difficulty reading) at the age of 30 — just six years after she was diagnosed with IC. She had the most severe damage in the study with deep scotomas of both eyes.[25]

125. The authors expressed concern that "the region of affected tissue may expand centrifugally over time."[26]

126. They concluded that "[c]linicians should be aware of this condition because it can be mistaken for other well-known macular disorders such as pattern dystrophy and age-related macular degeneration."[27]

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[22] *Id*. at 1798.

[23] *Id.*

[24] *Id*.

[25] *Id*. at 1795, Table 2.

[26] *Id*. at 1800.

[27] *Id*. at 1801.

127. They also encouraged "drug cessation in affected patients," and "recommend[ed] that any patient with suggestive visual symptoms undergo a comprehensive ophthalmic examination."[28]

128. IC experts Robert Moldwin and Curtis Nickel responded to the Emory findings with extreme concern: "It is quite unlikely that urologists treating patients with [IC] ever would have made this association . . . yet the implications are either frightening if our treatment is causing this condition or instructive if this condition is a previously unknown manifestation of [IC]."[29]

129. In a letter published online on April 24, 2019, five doctors from the Cleveland Clinic Cole Eye Institute responded to Pearce et al.: *Pigmentary maculopathy associated with chronic exposure to pentosan polysulfate sodium* 125 OPHTHALMOLOGY 1793–1802 (2018). The doctors suggested "…that long-term antagonism of FGF signaling in human retinas by PPS has the potential to be an underlying mechanism of toxicity." They further indicated that "[o]ne could surmise that, without the appropriate FGF signaling, and thereby activity of support cells such as Muller glia, long-term accumulation of damage without repair could be the culprit."[30]

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[28] William A. Pearce, Adam M. Hanif, and Nieraj Jain, Letter to the Editor Re: *FDA BRUDAC 2018 Criteria for Interstitial Cystitis/Bladder Pain Syndrome Clinical Trials*, 200 UROLOGY 1122 (2018) (Exhibit "G").

[29] J.C. Nickel and R. Moldwin, Reply to Letter to the Editor Re: *FDA BRUDAC 2018 Criteria for Interstitial Cystitis/Bladder Pain Syndrome Clinical Trials*, 200 UROLOGY 1122, 1123 (2018) (Exhibit "G").

[30] Tyler Greenlee, Grant Hom, Thais Conti, Amy S. Babiuch, and Rishi Singh, Letter to the Editor Re: Pearce et al.: *Pigmentary maculopathy associated with chronic exposure to pentosan polysulfate sodium* (Ophthalmology. 2018; 125:1793-1802) (Published online April 24, 2019) (Exhibit "I").

130. At the American Urology Association 2019 Annual Meeting in May of 2019, the Emory team submitted another study of ten IC patients who had taken Elmiron and experienced macular disease.[31]

131. The patients in this study had a median age of 59 years (range 38–68) and median time since IC diagnosis of 19 years (range 4–40). The most commonly reported symptoms were difficulty reading and difficulty adapting to dim lighting.

132. Eye examinations showed symmetric pigmentary changes in the retina. Retinal imaging demonstrated that the abnormalities were primarily in the retinal pigment epithelium. They noted that their clinic has seen 156 patients with IC who did not have any Elmiron exposure — *and these patients showed no pigmentary maculopathy*.

133. The Emory team concluded that structural changes of the retina are occurring in patients taking Elmironand they were unclear if stopping the medication would alter the course of the damage. *They encouraged affected patients to discontinue the use of medications and to undergo comprehensive ophthalmic examinations*.

134. On June 27, 2019, The European Medicines Agency ("EMA"), a decentralized agency of the European Union ("EU") responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU, through its Committee for Medicinal Products for Human Use ("CHMP"), published a report entitled, "Scientific conclusions and grounds for the variation to the terms of the marketing authorisation(s)", apparently reviewing data from the period June 2, 2018 through December 1, 2018 stating in relevant part:

> Taking into account the PRAC ["Pharmacovigilance Risk Assessment Committee"] Assessment Report on the PSUR(s) ["Periodic Safety Update

[31] Jenelle Foote, Adam Hanif, and Nieraj Jain, *Chronic Exposure to Pentosan Polysulfate Sodium is Associated with Retinal Pigmentary Changes and Vision Loss*, 201 UROLOGY e688 (2019), https://www.auajournals.org/doi/10.1097/01.JU.0000556315.46806.ca. (Exhibit "J").

> Report"] for pentosan polysulfate sodium (for centrally authorised product), the scientific conclusions of CHMP are as follows:
>
> In literature, pigmentary maculopathy has been reported rarely, with pentosan polysulfate sodium, especially after long-term use. Visual symptoms might include complaints of reading difficulty and prolonged adjustment to low or reduced light environments. After extensive investigations, which included molecular testing for hereditary retinal disease, the authors of the study found these cases to resemble no other known retinal disease. Additionally, from the EudraVigilance database, at least one case describes similar findings on macula. There are a further 10 cases under SOC "eye disorders", including visual impairment, blindness, retinopathy or optic neuritis.
>
> Pending further investigation, it remains unclear whether drug cessation will halt or alter the course of the retinal disease.
>
> Although majority of the reports available in literature describe a minimum exposure to PPS of 12 years and a higher dosage than recommended in the SmPC, 1 case occurred with the recommended daily dose of 300 mg (Pierce et al). Moreover, 3 cases retrieved from Vigilyse included also the recommended dosage of 300 mg/day. Regarding the time of exposure to PPS, Foote et al article includes 1 patient exposed during 27 months and a case from Vigilyse describes an exposure of less than 2 years. Therefore, based on the available data it cannot be concluded that the pathophysiologic changes cannot be detected earlier (perhaps in an asymptomatic, reversible stage), even with the recommended daily dosage of 300 mg.
>
> In the light of this information, the PRAC recommended an update of the product information to warn about this risk and recommend regular ophthalmic examinations for early detection of pigmentary maculopathy, particularly in patients taking pentosan polysulfate sodium long-term.
>
> Additionally, the PRAC recommended the distribution of a DHPC, since even if rare, it is a potentially irreversible, serious condition, which might not be easily recognized by the urology community. [32]

135. The CHMP also recommended a Direct Healthcare Professional Communication, the equivalent of what is often referred to as a "Dear Doctor Letter" in the U.S., due to the fact that the condition at issue is "a potentially irreversible, serious condition, which might not be easily

[32] European Medicines Agency: EMA/342325/2019 - Scientific conclusions and grounds for the variation to the terms of the marketing authorisation(s) https://www.ema.europa.eu/documents/scientific-conclusion/elmiron-h-c-psusa-00010614-201812-epar-scientific-conclusions-grounds-variation-terms-marketing_en.pdf (last visited, June 8, 2021).

recognized by the urology community."[33]

136. Shortly after the recommendation by the CHMP was issued, the product labeling in the EU for Elmiron was updated to specifically warn that "[a]ll patients should have regular ophthalmic examinations for early detection of pigmentary maculopathy, particularly those with long term use of PPS. In such situations, treatment cessation should be considered."[34]

137. Shortly thereafter, the Emory team published a study in the Review of Ophthalmology in July 2019.[35]

138. "Our subsequent investigations," the team wrote, "demonstrated that this unique maculopathy is strongly associated with chronic [Elmiron] exposure, not IC itself or its other therapies. In fact, ***this characteristic maculopathy has, to date, been exclusively diagnosed in patients reporting prior [Elmiron] exposure***."[36]

139. The team further observed that claims data from a nationally present U.S. insurance company suggested that hundreds of thousands of individuals have likely been exposed to Elmiron in the U.S. The team also recognized a study finding that Elmiron-exposed patients had a significantly increased risk of being diagnosed with a new macular disease after seven years.

140. In September 2019, the Emory team published additional research in the Journal of American Medical Association Ophthalmology ("JAMA Ophthalmology"), concluding that

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[33] *Id.*

[34] European Medicines Agency: Elmiron 100 mg hard capsules, Annex I, Summary of Product Characteristics https://www.ema.europa.eu/en/documents/product-information/elmiron-epar-product-information_en.pdf.

[35] Adam M. Hanif and Nieraj Jain, *Clinical Pearls for a New Condition. Pentosan Polysulfate Therapy, a Common Treatment for Interstitial Cystitis, Has Been Associated with a Maculopathy*, REVIEW OF OPHTHALMOLOGY (July 10, 2019) (Exhibit "K")

[36] *Id*. (emphasis added).

Elmiron maculopathy "is a vision-threatening condition that can manifest in the setting of long-term exposure to the drug."[37]

141. Further, on September 23, 2019, the Canadian Product Monograph for Elmiron was updated to include the following in the "Warnings and Precautions" section:

> **Ophthalmologic**
>
> 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.[38]

142. Shortly thereafter, Health Canada issued a Health Product Advisory informing the Canadian public of the new warnings added to the Elmiron Product Monograph, but only in Canada.[39]

143. On October 1, 2019, two physicians from Harvard Medical School published a case study that observed a very concerning serious medical issue – they noted that damage caused by Elmiron continues to progress long after cessation of the drug.[40] In their study, a patient continued to exhibit worsening symptoms of PPS-associated retinal maculopathy for at least 6 years after she stopped taking Elmiron.

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[37] Adam Hanif et al., *Phenotypic Spectrum of Pentosan Polysulfate Sodium-Associated Maculopathy: A multicenter Study*, 137 JAMA OPHTHALMOLOGY 1275, 1282 (Sep. 5, 2019) (Exhibit "L").

[38] https://pdf.hres.ca/dpd_pm/00053268.PDF

[39] https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/health-product-infowatch/health-product-infowatch-october-2019.html#elmiron

[40] Rachel M. Huckfeldt and Demetrios G Vavvas, *Progressive Maculopathy After Discontinuation of Pentosan Polysulfate Sodium*, 50 OPHTHALMIC SURGERY, LASERS AND IMAGING RETINA 656–59 (2019), ncbi.nlm.nih.gov/pubmed/31671200 (Exhibit "M").

144. In November of 2019, a team from Emory and the University of Pennsylvania published an epidemiological study in the British Journal of Ophthalmology which concluded that "PPS users had significantly increased odds of having [maculopathy]."[41]

145. Also in 2019, a team from Kaiser Permanente Northern California treated a patient who was previously misdiagnosed with Stargardt disease, but was actually suffering from Elmiron-associated maculopathy.[42] In their case report, the ophthalmologists stressed that "***failure to diagnose a medication toxicity in a timely fashion may lead to preventable irreversible vision loss***."[43]

146. Another team of researchers found a 20% prevalence of a unique PPS-associated maculopathy among a cohort of patients being treated at the University of California, Los Angeles.[44] Their study suggests "a significant risk of macular toxicity for PPS-treated patients," and that "more significant PPS exposure was associated with more severe atrophy."

147. In another publication, two physicians from Harvard Medical School published a case study indicating that the damage caused by Elmiron continues to progress long after cessation

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[41] Nieraj Jain et al., *Association of Macular Disease with Long-Term Use of Pentosan Polysulfate Sodium: Findings from a U.S. Cohort*, BRITISH JOURNAL OF OPHTHALMOLOGY (published online first, November 6, 2019), https://bjo.bmj.com/content/early/2019/11/06/bjophthalmol-2019-314765 (Exhibit "N").

[42] Robin A. Vora et al., *A Case of Pentosan Polysulfate Maculopathy Originally Diagnosed as Stargardt Disease*, 17 AMERICAN JOURNAL OF OPHTHALMOLOGY CASE REPORTS 100604 (published online first, January 2020) (Exhibit "O").

[43] *Id*. (emphasis added).

[44] Derrick Wang et al., *Pentosan-Associated Maculopathy: Prevalence, Screening Guidelines and Spectrum of Findings Based on Prospective Multimodal Analysis*, CANADIAN JOURNAL OF OPHTHALMOLOGY (in press, published online January 2020) (Exhibit "P")

of the drug.[45] In their study, a patient continued to exhibit worsening symptoms of PPS-associated retinal maculopathy for at least 6 years after she stopped taking Elmiron. The doctors noted "the present case adds a new layer of concern by demonstrating progressive maculopathy continuing for up to 6 years after cessation of PPS . . . this case emphasizes the need for a screening regimen that balances the demands on patients and physicians with the importance of prompt identification of early toxicity."[46]

148. On January 20, 2020, another team of researchers published a paper in which they found a 20% prevalence of a unique PPS- associated maculopathy among a cohort of patients being treated at the University of California, Los Angeles.[47] Their study suggests "a significant risk of macular toxicity for PPS-treated patients," and that "more significant PPS exposure was associated with more severe atrophy."

149. The Interstitial Cystitis Network, a health publishing company dedicated to IC, launched its own patient survey on the heels of the Emory Eye Center findings. As of April of 2019, the IC Network had almost 1,000 survey participants, of which 53% reported eye disease.

150. Patient reports on the IC Network Support Forum include (all [*sic*]):[48]

a. June 23, 2019: "I have been diagnosed with macular degeneration and no one in my family has it. I have been on elmiron for 15 years. I decided even though the correlation is not extremely strong to go off it for the sake of my eyes . . . am hoping the degeneration will slow if not stop. Am not looking

[45] Rachel M. Huckfeldt and Demetrios G Vavvas, *Progressive Maculopathy After Discontinuation of Pentosan Polysulfate Sodium*, 50 OPHTHALMIC SURGERY, LASERS AND IMAGING RETINA 656–59 (2019), ncbi.nlm.nih.gov/pubmed/31671200 (Exhibit "M").

[46] *Id*. at 658.

[47] Derrick Wang et al., *Pentosan-Associated Maculopathy: Prevalence, Screening Guidelines, and Spectrum of Findings Based on Prospective Multimodal Analysis*, CANADIAN JOURNAL OF OPHTHALMOLOGY (in press, published online January 2020) (Exhibit "P").

[48] Interstitial Cystitis Network Patient Support Forum, https://forum.ic-network.com/.

for it reverse course. Am also hoping that I do not go back to the pain . . . all I can do is try. I feel to be between a rock and a hard place. I am an artist so my eyes are truly needed to continue my work."

b. February 3, 2019: "I saw the article too and took it to my ophthalmologist. She was very excited to see the research. She said that my macular degeneration that had occurred after 18 years of taking Elmiron was an unusual shape that they had not seen before. She said that while it won't heal me, they hoped that they could stop this from happening to other patients."

c. March 25, 2019: "After 4 excruciating years, I was diagnosed with IC in 2003. I started on Elmiron and have taken it since then. I was diagnosed with macular degeneration in 2014. My severity is mild to moderate. The left eye is definitely worse. I can no longer drive at night. I'm pretty comfortable driving to places I am familiar with during the day. I am only 58. I dread the day I will not be able to drive."

151. On June 16, 2020, Defendants' Supplemental New Drug Application ("sNDA"), seeking to revise the Warnings and Post-Marketing Experience sections of the label and to update the Patient labeling for Elmiron to include warnings relating to vision threatening retinal changes and maculopathy was approved by FDA.

152. On that date, the label was amended to include the following in the "Warnings" section:

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.

153. The "Post-Marketing Experience" section was also amended to include the following:

> **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).

154. The recently added warnings in the US label remain inadequate, however, as they fail to warn, instruct and advise current or past patients who are or were taking Elmiron, as to what they should do and what procedures they should follow, in order to properly screen, test and monitor for vision and/or damage to the retina including the macula as a result of their use of Elmiron.

155. In July 2020, a team from Emory, the University of Michigan and the Oregon Health and Science University published the results of a retrospective study in JAMA Ophthalmology which concluded that "[t]hese retrospective data among 11 patients suggest PPS-associated maculopathy continues to evolve after drug cessation for at least 10 years. In some cases, progressive retinal pigment epithelium atrophy encroaches on the foveal center and thus may pose a long-term threat to central vision".[49]

[49] Rachel Shah et al., *Disease Course in Patients With Pentosan Polyysulfate Sodium-Associated Maculopathy After Drug Cessation*, JAMA OPHTHALMOLOGY (Published online July 9, 2020) (Exhibit "Q").

156. Another article published in Retinal Cases and Brief Reports describes the case of a patient with new onset of damage to the retina consistent with Elmiron-related maculopathy 38 months after she stopped taking the drug. In discussing the significance of the findings in this patient, the authors stated:

> This report highlights that there is potential for onset of clinically detectable PPS maculopathy years after cessation of the drug. The patient developed new visual symptoms and characteristic imaging findings of PPS maculopathy approximately 3 years after stopping the drug. If corroborated, this finding would have important implications for PPS prescribing and ophthalmic screening guidelines.[50]

157. A recent study published by Dr. Jain and his colleagues at Emory University examined the correlation between patients with Elmiron-related maculopathy and visual impairment. The authors noted that initial studies described patients with prominent visual symptoms despite relatively spared visual acuities by traditional measures of vision. The authors concluded that their findings "demonstrate that these patients do indeed perform poorly on numerous tests of visual function…even in the setting of normal visual acuity" and that Elmiron-related maculopathy "…results in visual dysfunction comparable to intermediate or advanced AMD."[51]

158. Another recent study found the prevalence of PPS maculopathy to be 15 – 20% among PPS users that agreed to participate in the study. The authors also recommended "baseline examination of all patients starting treatment with PPS to include multimodal retinal imaging…" and further that "[p]atients with cumulative dosages over 500 grams should receive annual

[50] Barnett JM, Jain N. *Potential new onset clinically detectable pentosan polysulfate maculopathy years after drug cessation*, Retin Cases Brief Rep. (November 17, 2020) (Exhibit "R")

[51] Lyons RJ, Brower J, Jain N. *Visual function in pentosan polysulfate sodium maculopathy*, Invest Ophthalmol Vis Sci. 2020;61(13):33 (Exhibit "S").

multimodal imaging and those with dosages over 1000 grams, especially over 1500 grams, should be vigilantly monitored for macular toxicity."[52]

159. A case report published by the American Academy of Optometry described A 55-year-old White woman presented with a painless, bilateral loss of vision and bilateral pigmentary maculopathy that was initially diagnosed as pattern macular dystrophy. The authors concluded that "[b]ecause toxic maculopathies are an uncommon diagnosis, screening and recognition of PPS maculopathy are critical in the primary eye care setting. Discontinuation of the insulting agent may be necessary to prevent potentially severe and irreversible vision loss in the at-risk population."[53]

160. A brief article published in the Canadian Medical Association Journal offered "five things to know about Maculopathy caused by pentosan polysulfate" these included the following: "(1) Penstosan polysulfate (PPS) is a mainstay for treatment of bladder pain associated with interstitial cystitis; (2) Maculopathy is associated with longer duration of PPS use; (3) Maculopathy caused by PPS may masquerade as age-related macular degeration; (4) Macular disease may progress even after cessation of PPS; and (5) Patients exposed to PPS who report disturbed vision should undergo ophthalmic screening".[54]

161. An article published in May 2021 in the Survey of Ophthalmology demonstrates the evolving science surrounding Elmiron-related maculopathy and the need for medical

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[52] Derrick Wang et al., Pentosan polysulfate maculopathy: Prevalence, spectrum of disease, and choroidal imaging analysis based on prospective screening, *American Journal of Ophthalmology* (2021), doi: https://doi.org/10.1016/j.ajo.2021.02.025 (Exhibit "T")

[53] Aaron W. Case, et al., *Case Report: Pentosan Polysulfate Sodium Maculopathy Originally Diagnosed as Pattern Macular Dystrophy*, Optom. Vis. Sci. (2021) (Exhibit "U")

[54] Daniel Rosenberg, et al., *Five things to Know about Maculopathy Caused by Pentosan Polysulfate*, CMAJ 2021 May 3;193:E645. doi: 10.1503/cmaj.201900 (Exhibit "V").

monitoring. The authors state:

> All patients initiating treatment with PPS should undergo comprehensive retinal evaluation with fundus photography, FAF, OCT, and NIR imaging where available, ideally within six months of starting treatment. We and others have previously advocated repeat screening at three to five years after drug initiation, assuming a standard daily dose. We now favor annual screening for PPS maculopathy for the following reasons: a) PPS maculopathy has been described in as little as three years of exposure to a standard dosing regimen, and a conservative approach is preferred in the absence of a more complete understanding of risk factors and potential modifiers for disease development, b) a large proportion of patients will develop irreversible and potentially progressive macular disease once they exceed a certain exposure level, c) there is greater potential for loss to follow-up if annual evaluations are not performed, and each annual visit is an opportunity to re-engage the patient and prescriber to discuss the goal of minimizing total exposure, d) not all patients are on standard doses and it is difficult for ophthalmologists to track and target exams based on each individual's cumulative exposure with potentially evolving screening guidelines, and e) screening exams for PPS maculopathy are relatively inexpensive and noninvasive, incurring minimal cost to the patient and healthcare system.[55]

162. A letter to the editor published in Mayo Clinic Proceedings in June 2021 recommends ophthalmic screening of patients when the cumulative PPS dose approaches or exceeds 500 g. The authors also encourage "discussion of this side effect with patients, a review of past medical and ocular history, inquiry regarding any visual symptoms or changes, and prompt ophthalmologic referral in case of any concerns – even at low doses – to allow for early detection of maculopathy, which may reduce the risk of irreversible loss of vision."[56]

163. On December 15, 2020, Health Canada mandated that the Elmiron Product Monograph be updated to include a contraindication for use of the drug in patients with a personal history of any macular pathology, as well as to further strengthen the existing warnings regarding the risk of pigmentary maculopathy. This included advising healthcare professionals to obtain a

[55] Aaron Lindeke-Myers , Adam M. Hanif, ,Nieraj Jain, *Pentosan Polysulfate Maculopathy*, Survey of Ophthalmology (May 3, 2021) (Exhibit "W").

[56] Konstantin Astafurov, et al., *Letter to the editor: Ocular Toxicity Associated with Pentosan Polysulfate Sodium*, Mayo Clin. Proc. (June 2021) (Exhibit "X").

detailed ophthalmologic history in all patients before starting treatment with Elmiron and to perform baseline and regular retinal examinations for early detection of macular pathology. Health Canada also issued a letter to healthcare professionals to advise the medical community of the contraindication, heightened warnings and monitoring recommendations.

164. In total, there are now dozens of articles published in professional medical and scientific journals detailing the serious adverse events caused by Elmiron.

165. All of the information as cited above was known by and available to Defendants at all relevant times.

166. Despite numerous signs of the potential for severe retinal side effects; multiple studies conducted at top research institutes; research being published in major peer-reviewed journals; and public warnings from a prominent EU health agency, ***Defendants failed to reasonably investigate the issue and warn patients and healthcare providers at all relevant times***.

167. At all relevant times, Defendants also failed to alert patients to the need for ophthalmological monitoring while taking Elmiron or whether risks increase with higher doses or longer durations.

168. Other medications affecting vision have included instructions and warnings for users and prescribers. For example, the anti-malaria drug Plaquenil (hydroxychloroquine) is likewise associated with retinal toxicity. In the labeling for Plaquenil, manufacturer Concordia Pharmaceuticals, Inc., provides the following warning:

> Irreversible retinal damage has been observed in some patients who had received hydroxychloroquine sulfate. Significant risk factors for retinal damage include daily doses of hydroxychloroquine sulfate greater than 6.5 mg/kg (5 mg/kg base) of actual body weight, durations of use greater than five years, subnormal glomerular filtration, use of some concomitant drug products such as tamoxifen citrate and concurrent macular disease.

> A baseline ocular examination is recommended within the first year of starting PLAQUENIL. The baseline exam should include: best corrected distance visual acuity (BCVA), an automated threshold visual field (VF) of the central 10 degrees (with retesting if an abnormality is noted) and spectral domain ocular coherence tomography (SD-OCT).
>
> For individuals with significant risk factors (daily dose of hydroxychloroquine sulfate greater than 5.0 mg/kg base of actual body weight, subnormal glomerular filtration, use of tamoxifen citrate or concurrent macular disease) monitoring should include annual examinations which include BCVA, VF and SD-OCT. For individuals without significant risk factors, annual exams can usually be deferred until five years of treatment.
>
> In individuals of Asian descent, retinal toxicity may first be noticed outside the macula. In patients of Asian descent, it is recommended that visual field testing be performed in the central 24 degrees instead of the central 10 degrees. It is recommended that hydroxychloroquine be discontinued if ocular toxicity is suspected and the patient should be closely observed given that retinal changes (and visual disturbances) may progress even after cessation of therapy.[57]

169. In stark contrast, until June of 2020, the Elmiron label read:[58]

> **WARNINGS**
>
> None.

170. At all relevant times, Defendants have failed to adequately warn or instruct patients, the medical community, or prescribers in the United States that Elmiron causes, is linked to and is associated with vision threatening retinal changes, including vision impairment.

171. At all relevant times, Defendants have failed to adequately warn or instruct patients, the medical community, or prescribers in the United States that patients taking Elmiron should

[57] Plaquenil Patient Package Insert, revised June 2018, Concordia Pharmaceuticals, Inc., https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/009768Orig1s051lbl.pdf.

[58] Elmiron Patient Package Insert, revised August 2004.

undergo regular ophthalmological testing to detect pigmentary changes and discontinue use if such changes occur.

172. Defendants failed to mention vision-threatening retinal changes or the need for ophthalmological monitoring in any of the patient materials—including the Patient Education Flyer and Patient Brochure—the sources of information most likely viewed by physicians and patients.

173. At all relevant times, the labeling for Elmiron listed serious side effects that have been reported with Elmiron, but did not list vision threatening retinal changes.

174. At all relevant times, the labeling for Elmiron failed to provide adequate warnings and instructions, failed to caution that patients should be closely monitored, failed to adequately inform patients and physicians that vision threatening retinal changes have been associated with Elmiron useand failed to contain any proper dosing considerations.

175. At all relevant times, JANSSEN PHARMA maintained a website promoting Elmiron, www.orthoelmiron.com, which included, among other topics, "About Elmiron," "How Elmiron Works," "Important Safety Information," and "Patient Information." Nowhere on the website did Defendants mention the potential for vision-threatening retinal changes associated with Elmiron use.

176. On June 24, 2019, Defendant JANSSEN PHARMA submitted its Supplemental New Drug application (sNDA) under section 505(b) of the Federal Food, Drug and Cosmetic Act for Elmiron (PPS) 100 mg capsules. This Prior Approval labeling supplement to its application provided revisions to the package insert Warnings section and Post-Marketing section, as well as an update to the Patient Labeling finally addressing the risk of vision threatening retinal changes associated with Elmiron use.

177. Defendants' sNDA, dated June 24, 2019, was not approved by the FDA until June 16, 2020. Defendants did not provide warnings anywhere on its product label or packaging referencing the risk of vision threatening retinal changes associated with Elmiron use or the need for medical and ophthalmological monitoring until June 16, 2020.

178. As of no later than June 24, 2019, when Defendants submitted their sNDA to include warnings referencing the risk of vision threatening retinal changes associated with Elmiron use, Defendants knew of the risk of injury associated with their drug and failed to warn consumers and physicians, including Plaintiff, Plaintiff's physicians and the public in general, of same.

179. The FDA has established reporting categories for post-approval changes to a drug's label. The Changes Being Effected supplement ("CBE") (21 CFR § 314.70(c)(3)) allows for changes in the labeling of a drug product to reflect newly acquired information without prior approval from the FDA.

180. The CBE process allows for drug manufacturers to change a drug label more quickly than the sNDA process based on newly acquired information about the drug.

181. Defendants should have changed the Elmiron label to include warnings and instructions addressing the risk of injury associated with the drug as soon as they had notice of adverse reports relating to same.

182. Defendant's failure to amend the Elmiron label under the CBE regulations resulted in unnecessary further delay in disseminating important safety information to physicians and patients. This additional, needless delay prevented physicians and patients from obtaining this critical information in the timeliest manner possible, which could have guided their care and treatment and allowed for an earlier diagnosis of the relevant condition.

183. By failing to use the FDA's CBE supplement to warn Plaintiff, consumers and physicians, of the risk of vision threatening retinal changes associated with using Elmiron, Defendants acted in a gross and flagrant character, evincing reckless disregard of human life and of the safety of persons exposed to its dangerous drug.

184. Additionally, by failing to use the FDA's CBE supplement to warn Plaintiff, consumers and physicians, of the risk of vision threatening retinal changes associated with using Elmiron, Defendants showed wantonness, recklessness, or a grossly careless disregard for the public's safety and welfare.

F. Defendants Had a Duty to Protect U.S. Consumers, But Did Not

185. At all relevant times, Defendants had a duty to craft an adequate label with respect to Elmiron.

186. At all relevant times, Defendants had a duty to ensure that the warnings on the Elmiron label were adequate, at all times, for so long as the drug remained available for sale in the United States.

187. At all relevant times, Defendants had a responsibility to conduct post-marketing surveillance and to continue to study the safety and efficacy of Elmiron after the Elmiron NDA was approved, for so long as the drug remained available for sale in the United States.

188. At all relevant times, Defendants had a duty to revise the Elmiron label to include a warning regarding the risk of serious vision-related injuries as soon as there was reasonable evidence of a causal association between vision- related injuries and Elmiron use.

189. Upon information and belief, despite reasonable evidence of causal association, Defendants knowingly withheld or misrepresented information required to be submitted under FDA NDA regulations, concerning the safety and efficacy of Elmiron, including, but not limited

to, raw data sets, documents, data analyses and/or other information related to the risk of Elmiron users suffering vision-related injuries as a result of their Elmiron use. Such information was material and relevant to the risk of patients, like Plaintiff, developing serious vision-related injuries as a result of taking Elmiron.

190. Upon information and belief, despite understanding that Elmiron could cause vision-related injuries, Defendants knowingly withheld or misrepresented information required to be submitted under FDA NDA regulations concerning the safety and efficacy of Elmiron, including, but not limited to, raw data sets, documents, data analyses and/or other information related to the risk of Elmiron users suffering vision-related injuries as a result of their Elmiron use. Such information was material and relevant to the risk of patients, like Plaintiff and the class members, developing serious vision-related injuries as a result of taking Elmiron.

G. How Defendants' Misconduct Endangered U.S. Consumers

191. Upon information and belief, had Defendants exercised reasonable care in testing and studying Elmiron, they would have discovered prior to seeking FDA approval, that long-term Elmiron use can cause serious vision and retinal injuries, including, but not limited to, Elmiron Maculopathy.

192. Upon information and belief, despite understanding that patients who would take Elmiron would likely remain on the medication for long periods of time, Defendants failed to test and study the long-term safety and efficacy of Elmiron prior to seeking FDA approval.

193. Upon information and belief, despite post-approval adverse event reports and other clinical evidence, Defendants failed to continue to test and study the safety and efficacy of Elmiron, particularly in patients who used the drug for long periods of time.

194. Upon information and belief, from the date all Defendants received FDA-approval to market Elmiron in the United States, Defendants each made, distributed, marketed and sold Elmiron without an adequate warning to Plaintiff or Plaintiff's prescribing physicians that Elmiron was associated with or could cause serious vision and retina damage in patients who used it and that all Defendants had not adequately conducted complete and proper testing and studies of Elmiron with regard to retina damage.

195. Upon information and belief, Defendants concealed or failed to completely disclose their knowledge that Elmiron was associated with or could cause retina damage together with their knowledge that they had failed to fully test or study said risk.

196. Upon information and belief, all Defendants ignored the association between the use of Elmiron and the risk of developing permanent and disfiguring visual complications, including, but not limited to, Elmiron Maculopathy and retina damage.

197. Upon information and belief, all Defendants failed to provide adequate instructions to U.S. healthcare professionals and patients regarding how to safely monitor and identify signs of potentially serious visual complications associated with long-term Elmiron use.

198. Upon information and belief, all Defendants failed to warn U.S. healthcare professionals and patients, including Plaintiff's prescribing physicians and Plaintiff, regarding how to safely monitor and identify signs of potentially serious visual complications associated with long-term Elmiron use.

199. Upon information and belief, all Defendants failed to warn or provide adequate instructions to U.S. healthcare professionals and patients, including Plaintiff's prescribing physicians and Plaintiff, regarding how to safely stop taking Elmiron in the event that potentially serious visual complications developed while using Elmiron.

200. Upon information and belief, all Defendants failed to warn U.S. healthcare professionals and patients, including Plaintiff's prescribing physicians and Plaintiff, of the true risk of retina damage to patients taking Elmiron as compared to other similarly efficacious pharmaceutical products.

201. All of Defendants' failures to provide adequate instructions or disclose information which Defendants each possessed, regarding the failure to adequately test and study Elmiron for the risk of serious visual complications—further rendered the Elmiron Package Insert, Medication Guide and other educational or promotional materials inadequate.

202. Despite Adverse Event Reports ("AERs") from healthcare professionals and consumers around the world, beginning at least as early as 1997 until approximately September of 2019, Defendants never warned in any country or market of the risk of serious visual complications, including, but not limited to, Elmiron Maculopathy or the need for medical and ophthalmological monitoring.

TOLLING OF THE STATUTE OF LIMITATIONS

A. Discovery Rule Tolling

203. As a result of the acts and omissions of Defendants, Plaintiff and Class members could not have discovered, through the exercise of reasonable due diligence, that exposure to Elmiron was associated with increased risk to vision-threatening retinal changes as set forth above. Thus, the applicable limitations periods did not begin to accrue until Plaintiff and Class members discovered, or through the exercise of reasonable diligence should have discovered, Defendants' wrongful acts and omissions.

B. Fraudulent Concealment Tolling

204. All applicable statutes of limitation have also been tolled by Defendants' knowing and active fraudulent concealment and denial of the vision-threatening retinal changes associated with Elmiron throughout the time period relevant to this action.

205. Defendants are under a continuing duty to disclose the true character, quality and nature of Elmiron to Plaintiff and the Class members. At all relevant times, Defendants nevertheless failed to inform patients and doctors about the vision threatening retinal changes associated with Elmiron, as discussed above.

206. Plaintiff and Class members reasonably relied upon Defendants' knowing, affirmative, or active concealment when they continued to use Elmiron as prescribed.

207. Because Defendants actively concealed the vision-threatening retinal changes associated with Elmiron, they are estopped from relying on any statutes of limitations defense.

C. Estoppel

208. Defendants were and are, under a continuous duty to disclose to Plaintiff and Class members the vision-threatening retinal changes associated with Elmiron. Instead, they actively concealed the true character, quality and nature of Elmiron and knowingly made misrepresentations or omissions about the safety of Elmiron and the vision-threatening retinal changes associated with Elmiron use.

209. Plaintiff and Class members reasonably relied upon Defendants' knowing and affirmative misrepresentations and active concealment of material facts. Therefore, Defendants are estopped from relying on any defense based on statutes of limitations in this action.

CLASS ALLEGATIONS

A. Medical Monitoring Class Definitions

210. Plaintiff brings this action on behalf of himself and all other persons similarly situated pursuant to Rules 23(a), 23(b)(2), 23(b)(3) and 23(c)(4) of the Federal Rules of Civil Procedure, which satisfy the numerosity, commonality, typicality, adequacy, predominance and superiority requirements of those provisions:

> **Class:** All Massachusetts citizens who have been prescribed and have taken Elmiron in Massachusetts and have suffered subcellular changes but have not been diagnosed with Elmiron Maculopathy.

211. Excluded from the Class are Defendants, their members, parents, employees, officers, directors, legal representatives, heirs, successors and wholly or partly owned subsidiaries; affiliated companies or assigns; governmental entities; class counsel and their employees; and the judicial officers and their immediate family members and associated court staff assigned to this case.

212. Plaintiff reserves the right to modify, expand, or amend the definition of the Class following the discovery period and before the Court determines whether class certification is appropriate.

213. Certification for class-wide treatment of the Class's claims is appropriate because the Plaintiff of the Class can prove the elements of their respective claims on a class-wide basis using the same evidence as would be used to prove those elements in an individual action alleging the same claims in the state of Massachusetts.

B. Numerosity of the Class Members

214. This action satisfies the requirements of Fed. R. Civ. P. 23(a)(1). The Class Members of the Class are so numerous that individual joinder of all class members is impracticable. While Plaintiff is informed and believe that there are thousands of patients who have taken or are taking Elmiron in Massachusetts, who would be members of the Class, the

precise number of Class Members is unknown to Plaintiff, but may be ascertained from various sources including prescription records. Class Members may be notified of the pendency of this action by recognized, Court-approved notice dissemination methods, which may include U.S. Mail, electronic mail, internet postings or published notice.

C. Commonality of Law and Fact

215. This action satisfies the requirements of Fed. R. Civ. P. 23(a)(2) and 23(b)(3) because there are questions of law and fact that are common to all Class Members. These common questions predominate over any questions affecting only individual Class Members. The predominating common or Class-wide fact questions include, without limitation:

a. Whether Elmiron significantly increases the risk of vision threatening retinal changes;

b. Whether Defendants knew or should have known that Elmiron significantly increases the risk of vision threatening retinal changes;

c. Whether Defendants were negligent in selling Elmiron;

d. Whether Defendants were reckless in their testing protocols;

e. Whether Defendants failed to warn consumers regarding the risk of vision threatening retinal changes associated with Elmiron; and

f. Whether Plaintiff and Class Members are entitled to equitable relief, including injunctive relief.

D. Typicality of the Claims

216. This action satisfies the requirements of Fed. R. Civ. P. 23(a)(3) because Plaintiff's claims are typical of the claims of each of the Class Members, as all members of the Class were and are similarly affected and their claims arise from the same wrongful conduct of Defendants. Each member was prescribed and exposed to Elmiron and faces a significantly increased risk of vision-threatening retinal changes. Plaintiff's claims are based upon the same legal theories as

those of the other members of the Class. The relief Plaintiff seeks in this action is typical of the relief sought for the absent Class Members.

E. Adequacy of Representation

217. Plaintiff will fairly and adequately protect the interests of the Class Members. Plaintiff is committed to the vigorous prosecution of this action and there is no hostility or conflict between or among Plaintiff and the unnamed Class Members. Plaintiff anticipates no difficulty in the management of this litigation as a class action.

218. To prosecute this case, Plaintiff has chosen the undersigned law firm, which has substantial experience as class counsel in the prosecution of large and complex class action litigations and have the financial resources to meet the costs associated with the vigorous prosecution of this type of litigation. Furthermore, Plaintiff and his counsel will fairly and adequately protect the interest of all Class Members, and neither Plaintiff, nor his counsel, has any interests that conflict with the interests of other Class Members.

F. Superiority of a Class Action

219. This action satisfies the requirements of Fed. R. Civ. P. 23(b)(3). A class action is superior to other available methods for the fair and efficient adjudication of the rights of the Class Members. The joinder of individual Class Members is impracticable because of the vast number of Class Members who have been prescribed and taken Elmiron.

220. Because this is a claim for equitable relief, the expense and burden of individual litigation would make it difficult or impossible for individual Class Members to redress the wrongs done to each of them individually, such that most or all Class Members would have no rational economic interest in individually controlling the prosecution of specific actions. The burden

imposed on the judicial system by individual litigation and to the Defendants, by even a small fraction of the Class Members, would be enormous.

221. In comparison to piecemeal litigation, class action litigation presents far fewer management difficulties, far better conserves the resources of both the judiciary and the parties and far more effectively protects the rights of each of the Class Members. The benefits to the legitimate interests of the parties, the court and the public resulting from class action litigation substantially outweigh the expenses, burdens, inconsistencies, economic infeasibility and inefficiencies of individualized litigation. Class adjudication is simply superior to other alternatives under Fed. R. Civ. P. 23(b)(3)(D).

222. Plaintiff is unaware of any obstacles likely to be encountered in the management of this action that would preclude its maintenance as a class action. Rule 23 provides the Court with the authority and flexibility to maximize the efficiencies and benefits of the class mechanism and reduce management challenges. The Court may, on motion of Plaintiff or on its own determination, certify classes for claims sharing common legal questions; utilize the provisions of Fed. R. Civ. P. 23(c)(4) to certify particular claims, issues, or common questions of law or of fact for class-wide adjudication; certify and adjudicate bellwether class claims; and utilize Fed. R. Civ. P. 23(c)(5) to divide any Class into subclasses.

Declaratory and Injunctive Relief - Requirements of Fed. R. Civ. P. 23(b)(2)

223. Defendants have acted or failed to act in a manner generally applicable to Plaintiff and the Class Members, thereby making appropriate final injunctive relief or corresponding declaratory relief with respect to the Class.

Count I — Medical Monitoring

224. Plaintiff and the Class incorporate the factual allegations previously set forth as

if fully set forth herein and further allege as follows:

225. Plaintiff and the Medical Monitoring Class assert equitable claims under Massachusetts law for medical monitoring against Defendants arising from the wrongful acts and negligence detailed above and below.

226. At all material times, Defendants had a duty to exercise reasonable care and had the duty of an expert in all aspects of the design, formulation, manufacture, compounding, testing, inspection, packaging, labeling, distribution, marketing, promotion, advertising, sale, warning, post-sale warning, testing and research to assure the safety of the product when used as intended or in a way that Defendants could reasonably have anticipated and to assure that the consuming public—including Plaintiff, the Class and their respective physicians—obtained accurate information and adequate instructions and warnings for the safe use or non-use of Elmiron.

227. At all material times, Defendants had a duty to warn Plaintiff, the Class, their respective physicians and the general public of Elmiron's dangers and serious side effects, including subcellular changes, severe and potentially irreversible vision impairment and damage to the retina including the macula, since it was reasonably foreseeable that an injury would occur due to proper use of Elmiron.

228. At all material times, Defendants failed to exercise reasonable care and the duty of an expert. Defendants knew, or in the exercise of reasonable care should have known, that Elmiron was not, in fact, properly manufactured, designed, compounded, tested, inspected, packaged, labeled, warned about, distributed, marketed, advertised, formulated, promoted, examined, maintained, sold, or prepared.

229. Defendants' myriad failures to act with reasonable care and the duty of an expert include, but are not limited to:

i. Negligent, careless, reckless and grossly negligent research and testing of Elmiron;

ii. Negligent, careless, reckless and grossly negligent design or formulation of Elmiron;

iii. Negligent, careless, reckless and grossly negligent failure to give adequate warnings that would attract the attention of Plaintiff, Class Members, their respective physicians and the general public, of the dangerous, unsafe and deleterious nature of Elmiron and the risks to the eye associated with its use;

iv. Negligent, careless, reckless and grossly negligent failure to provide instructions and warnings for the safe use of Elmiron to avoid injuries to the eye;

v. Negligent, careless, reckless and grossly negligent failure to provide instructions regarding the need for baseline ophthalmological medical monitoring before taking Elmiron;

vi. Negligent, careless, reckless and grossly negligent failure to provide instructions regarding the need for continued ophthalmological medical monitoring while taking Elmiron;

vii. Negligent, careless, reckless and grossly negligent failure to provide instructions regarding the need for ophthalmological medical monitoring after discontinuing Elmiron;

viii. Negligent, careless, reckless and grossly negligent failure to explain the mechanism, mode and types of adverse events associated with Elmiron, including but not limited to the dangers of vision impairment and damage to the retina including the macula, posed by Elmiron;

ix. Negligent representations that Elmiron was safe;

x. Negligent representations that Elmiron was well-tolerated;

xi. Negligent, careless, reckless and grossly negligent failure to issue adequate post-sale warnings that Elmiron is likely to cause serious and potentially irreversible vision impairment and damage to the retina including the macula.

230. As a direct and proximate result of Defendants' wrongful acts and negligence detailed above, Plaintiff and the Class were exposed to Elmiron without knowing of Elmiron's dangerous nature.

231. As a direct and proximate result of Defendants' wrongful acts and negligence detailed above and Plaintiff's and the Class' exposure to Elmiron, Plaintiff and the Class sustained subcellular damages and have a significantly increased risk of suffering serious and potentially irreversible vision impairment and damage to the retina including the macula.

232. The subcellular damages and significantly increased risk of serious and potentially irreversible vision impairment and damage to the retina including the macula makes periodic diagnostic medical examinations—beyond the monitoring normally recommended in the absence of a significantly elevated risk—reasonable and necessary.

233. A medical monitoring program is reasonable and necessary for early detection of subcellular damage and treatment of the aforementioned latent conditions. Research has revealed that the presenting visual symptoms for Elmiron patients are vague and retinal changes on conventional examination are subtle.

234. Recent scientific publications have also suggested that Elmiron Maculopathy can continue to evolve years after drug cessation.

235. An additional recent scientific article indicates that symptoms of the damage to the retina may not even begin to manifest until months and even years, after a person stops taking Elmiron.

236. Without referral to a specialist with modern imaging instrumentation, Elmiron Maculopathy is likely to remain undetected or misdiagnosed.

237. The cost of the testing required to detect Elmiron Maculopathy is reasonable.

238. Many existing patients likely have been misdiagnosed with similar-appearing conditions.

239. The Emory research team has identified a series of nonstandard tests most suitable for identification of the Elmiron injury: "The fundus findings in [Elmiron]-associated maculopathy… exhibit a distinctive clinical phenotype on multimodal imaging that's best appreciated by using [fundus autofluorescence]."[59] Fundus autofluorescence is necessary to distinguish Elmiron Maculopathy from other maladies.

240. An easily administered, cost effective monitoring program exists. Indeed, an unrelated prescription medication, Hydroxychloroquine, was found to result in similar vision related issues as those associated with Elmiron and an easily administrated and cost-effective screening program has been created to screen and monitor patients for those effects.

241. Plaintiff seeks for the Court to exercise its equitable powers to create, supervise and implement (or cause to be created, supervised and implemented), and for the Court to order Defendants to fund, an appropriate medical monitoring plan that provides routine medical testing, monitoring and study of Plaintiff and the Class, for the remainder of Plaintiff's and each Class Member's life.

242. Plaintiff and the Class seek for such medical monitoring program to institute comprehensive and appropriate diagnostic tests for the early detection and diagnosis of subcellular damage associated with Elmiron Maculopathy, Elmiron Maculopathy and other serious vision threatening retinal changes associated with Elmiron.

243. The medical monitoring program is reasonable and necessary as a result of Plaintiff's and the Class' increased risk of serious vision threatening retinal changes associated with Elmiron.

[59] Hanif and Jain, *supra*.

244. Plaintiff's and the Class' increased risk of subcelluar damage and serious vision threatening retinal changes associated with Elmiron necessitates a more comprehensive medical monitoring program than the ordinary medical screening generally practiced, recommended, or required for the unexposed population, thus the required regimen is different from that recommended in the absence of Plaintiff's and the Class' exposure.

245. The medical monitoring program is reasonably necessary according to contemporary scientific principles, medical literature and expert opinion, as early detection of the vision changes associated with Elmiron improves prognoses and overall treatment. Without the program, the subcelluar damage and serious vision threatening retinal changes associated with Elmiron may go undiagnosed and, as a result, untreated, while those suffering from them can benefit from medical treatment.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff, on behalf of himself and all other similarly situated Class Members, requests that the Court enter judgment against Defendants as follows:

(1) Declare this action to be a proper class action maintainable under Rule 23(b)(2) of the Federal Rules of Civil Procedure and designate and appoint Plaintiff as Class representative and Plaintiff's chosen counsel as Class Counsel;

(2) Enter an injunction against Defendants to require them to implement a medical monitoring program for Plaintiff and Class Members;

(3) Retain jurisdiction over this action to ensure Defendants comply with such a decree;

(4) Declare, in accordance with Massachusetts law, that Plaintiff and Class Members will not be precluded by the rule against splitting claims from bringing claims for whatever physical injuries that are later attributed to Elmiron;

(5) Award Plaintiff and Class Members their reasonable attorneys' fees and costs, as allowed by law; and

(6) Award Plaintiff and Class Members any further and different relief as this case may require or as determined by this Court to be just, equitable and proper under the circumstances.

DEMAND FOR JURY TRIAL

Pursuant to Fed. R. Civ. P. 38(b), Plaintiff demands a jury trial for any and all issues triable by a jury.

Dated: June 11, 2021

Respectfully Submitted,

PARKER WAICHMAN LLP

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