UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF OHIO
WESTERN DIVISION

JANE GRUPPO,	:	**CASE No:**
PLAINTIFF	:	
V.	:	
JANSSEN PHARMACEUTICALS, INC.	:	**COMPLAINT AND JURY DEMAND**
DEFENDANT	:	

JURISDICTION AND VENUE

1. Plaintiff is a resident and citizen of Hamilton County, Ohio.

2. Defendant Janssen Pharmaceuticals, Inc. is a Pennsylvania corporation. Upon information and belief, its principal place of business is in Mercer County, New Jersey.

3. Plaintiff alleges damages in excess of $75,000, exclusive of interest and costs.

4. This Court has jurisdiction pursuant to 28 U.S.C. §1332, as complete diversity exists between Plaintiff and Defendant and the amount in controversy exceeds $75,000.

5. Venue is proper within this district pursuant to 28 U.S.C. §1391, because a substantial part of the events giving rise to this action occurred in this district.

FACTUAL BACKGROUND

Elmiron development, efficacy and safety issues

6. Defendant manufactures, markets and distributes the prescription drug Elmiron, which contains 100 mg. of the active ingredient pentosan polysulfate sodium ["PPS"], sold in capsule form.

7. Elmiron is indicated for the treatment of interstitial cystitis ["IC"], a rare condition characterized by bladder pain and discomfort.

8. Because no cure exists for IC, patients prescribed a drug for treatment of IC symptoms could remain on the drug for decades.

9. The etiology of IC is unknown. Several theories have been suggested, including the theory that a defect in the mucosal (glycosaminoglycan) layer of the bladder leads to irritation of the bladder wall.

10. PPS has the biochemical properties of sulfated glycosaminocglycans, including an affinity for mucosal membranes.

11. The rationale for the use of Elmiron was that PPS would over time lead to a repair of the presumably defective coating of the bladder wall and thereby reduce symptoms of irritation.

12. FDA designated Elmiron as an orphan drug on August 7, 1985, meaning that it was intended for treatment of a rare condition that affects less than 200,000 people in the United States. Orphan drug status provides economic incentives for manufacturers to develop drugs for rare diseases or conditions.

13. The original Sponsor of the New Drug Application ["NDA"] for Elmiron, Baker Norton Pharmaceuticals Inc., filed for marketing approval on June 11, 1991. The Sponsor supported the NDA with limited scientific data, including two efficacy studies.

14. Efficacy Study E-001 presented data from 110 subjects, 54 exposed to Elmiron and 56 to placebo, from investigators at 5 sites. Study E-002 presented data from 148 subjects, 74 in each of the Elmiron and placebo groups, from investigators at 7 sites. Three of the investigators participated in both studies. Thus the total number of patients exposed to Elmiron in these two efficacy studies was 128.

15. FDA rejected Study E-001 as support for the efficacy of Elmiron in treating IC due to its lack of independence from Study E-002 and because it only had positive results for one of six study endpoints. The positive results did not reach statistical significance when analyzed using methodology required for studies reporting multiple endpoints. These positive results were seen at only one site – a site ran by Phillip Hanno, MD.

16. In rejecting study E-001, FDA noted: "The success rate at center 1 [Phillip Hanno, MD] is significantly different than the other sites and is responsible for the overall effect." Hanno reported 8 patients whose overall evaluation was "better" after treatment with Elmiron compared to 7 patients who were "not better," thus indicating a marginally favorable response for Elmiron. None of the other four investigators reported favorable results for Elmiron. In fact, their combined results demonstrated only 7 patients who were "better" versus 32 who were "not better" after Elmiron treatment. Across all five sites, only 15 of 54 subjects in E-001 reported improvement with Elmiron, while 7 of 56 subjects reported improvement on placebo.

17. Study E-002 provided positive results for only 2 of 6 study endpoints. Once again, the FDA Medical Reviewer questioned the data, noting that the data from center 1 appeared to be skewed. This time center 1 was operated by C. Lowell Parsons, MD. The

reviewer again stated: "The success rate at center 1 [C. Lowell Parsons, MD] is significantly different than the other sites and is responsible for the overall effect."

18. The data from Dr. Parsons in Study E-002 was far out of line with the data from any other investigator in either study. In fact, other than the one result from Dr. Hanno in Study E-001 where he reported 8 subjects given Elmiron being "better" and 7 "not better," no other investigator at any site in either study showed more patients "better" than "not better" on Elmiron.

19. Yet in Study E-002, Dr. Parsons reported 10 subjects treated with Elmiron were evaluated as "better" and 5 "not better," while only 2 subjects given placebo were "better" and 12 were "not better." The other six investigators combined reported 14 subjects given Elmiron were "better" and 45 were "not better," and for placebo treatment 10 were "better" compared to 50 "not better." In other words, Parsons reported that 66.6% of the subjects were "better" with Elmiron compared to 14.3% who claimed to be "better" on placebo, while the other six investigators combined reported only 23.7% were "better" after taking Elmiron, compared to 16.6% who claimed to be "better" after given the placebo.

20. An FDA Group Leader, John Kenealy, MD observed:

> "The reviewing statistician has made the important observation that in each of the studies herein presented, elimination of the results from one of the centers all but destroys the statistical significance of the result of that study. The medical review has indicated that **one of these 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." [emphasis added.]

21. After completing its review of the data, FDA issued a Non-Approvable letter on January 27, 1993.

22. In June of 1993, in response to the Non-Approvable letter, Baker Norton submitted a re-analysis of the original two efficacy studies. In this analysis, in response to critique by the FDA, the Sponsor eliminated all data from Dr. Parsons and reanalyzed the data. The FDA reviewer, Dr. Waymack, commented on the Sponsor's submission of the combined data from E-001 and E-002 after excluding all results from Dr. Parsons:

> When this [exclusion of Parson's data] was done, the lowest p value obtained was only .107[1] which was for the Overall Improvement (Investigator Impression.) This raises a number of possible explanations for these significant p value 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.

23. In other words, after excluding Dr. Parsons' data, the results from Study E-002 were far from statistically significant, which raised the serious possibility that Dr. Parsons had engaged in conduct that biased the results in favor of Elmiron.

24. FDA rejected the re-analysis of Study E-001 and E-002 in a second Non-Approvable letter for Elmiron dated October 28, 1994.

25. In rejecting the Sponsor's re-analysis and discussing the need for more data, Dr. Waymack concluded with the recommendation: "I strongly believe that any future pivotal trials should not include Dr. Parsons. This would eliminate the fear of the investigator specific effect, if efficacy were determined by the future trials."

26. U.S. Patent records indicate that Dr. C. Lowell Parsons is the inventor of the patent for sodium pentosanpolysulfate (i.e. PPS or Elmiron), which he filed on July 31, 1989. The Patent Application includes the following use: "the treatment of interstitial

[1] Note that statistical significance requires results of 0.05 or lower, thus the results without Parsons' data provide absolutely no proof of efficacy.

cystitis by the oral administration of sodium pentosanpolysulfate at high dosages on the order of 200 mg. per day or more."

27. In addition to being the inventor who submitted the Patent Application for Elmiron, Dr. Parsons apparently filed the Investigational New Drug Application for Elmiron to treat IC.

28. In an internal FDA document, Dr. Wiley A. Chambers asks, "Why is there not complete information on the CL Parson and SG Mulhollands published study? This study should either be completely reported in the NDA or in **Parson's IND**?" [emphasis added.]

29. As Dr. Waymack summarized:

> Two pivotal well controlled trials had been performed and submitted to support the NDA. These two studies were however flawed in that they had multiple investigators involved in both pivotal trials. The studies were also flawed in that six different efficacy endpoints were chosen, and those that demonstrated statistically significant improvement in one of the trials, failed to demonstrate improvement in the other. Additionally, there was no Bonferroni correction made to compensate for the fact that six different endpoints had been chosen. Finally it 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. These points are discussed in greater detail in prior reviews. (emphasis added.)

30. In response to the second non-approvable letter from FDA, the Sponsor Baker Norton then conducted a retrospective analysis of patients enrolled in an Open Label Compassionate Use Study.

31. Baker Norton submitted its retrospective review of the uncontrolled Compassionate Use Study to FDA in lieu of another efficacy study. The study design (no comparison group) prevented a statistical analysis, but based on drop out rates, it was

estimated that Elmiron was effective in only a 25% subgroup of the enrolled cases, since everyone else (i.e. 75%) has discontinued the drug.

32. However, because no control group existed, no comparison could be made to determine whether or to what extent the patients who remained enrolled in the study were reporting favorable results due to Elmiron, or due to a placebo effect. In particular, because the underlying condition of IC can vary over time, the entire effect could simply indicate the natural course of the disease.

33. The Sponsor contended that the Compassionate Use Study demonstrated efficacy for a sub-group of individuals within those suffering from the rare condition of IC and that the NDA should be approved because of Elmiron's orphan drug status.

34. FDA eventually approved Elmiron for treatment of IC on September 26, 1996.

35. FDA also required as a condition of approval that the Sponsor conduct Phase IV (post-marketing) studies to address unresolved bioavailability and drug metabolism issues, and to evaluate efficacy and long term safety.

36. In 1997, the year following NDA approval, Alza Pharmaceuticals acquired Elmiron from Baker Norton.

37. In approximately 2001, Johnson & Johnson acquired Alza. Johnson & Johnson's wholly owned subsidiary, Ortho McNeil Pharmaceutical, Inc., became the Elmiron NDA Sponsor, marketer, promoter and the licensee for the Elmiron trademark.

38. In approximately 2008, Ortho McNeil Pharmaceutical, Inc. merged with Janssen, and became known as Ortho-McNeil-Janssen Pharmaceuticals, Inc., a subsidiary of Johnson & Johnson. Ortho-McNeil-Janssen Pharmaceuticals continued as the NDA Sponsor, marketer, promoter and licensee of the trademark for Elmiron.

39. In approximately 2011, Ortho-McNeil-Janssen Pharmaceuticals, Inc. changed its name to Janssen Pharmaceuticals, Inc.

40. Defendant Janssen Pharmaceuticals, wholly owned subsidiary of Johnson & Johnson, remains the NDA Sponsor, marketer, promoter and licensee of the trademark for Elmiron, which it now holds from Teva Branded Pharmaceutical Products R&D, Inc.

41. On July 9, 2004, Johnson & Johnson Pharmaceutical Research & Development, L.L.C. first posted on www.clinicaltrials.gov the protocol for a study entitled: "Effectiveness and Safety Study of Pentosan Polysulfate Sodium for the Treatment of Interstitial Cystitis."

42. The post indicated that the study was a Phase IV study which had begun in September 2003 to compare efficacy of Elmiron for IC in three groups: patients taking 100 mg. of Elmiron once a day, patients taking 100 mg. of Elmiron three times a day, and patients taking placebo.

43. Therefore six years elapsed between the commitment to perform a Phase IV study and the initiation of the efficacy study.

44. The study was financially supported by Janssen Research and Development and resulted in a published article entitled "*Pentosan Polysulfate Sodium Sodium for the Treatment of Interstitial Cystitis/Bladder Pain Syndrome: Insights from a Randomized, Double-Blind, Placebo Controlled Study*," Nickel et al, Journal of Urology: Vol. 193, 857-862 (March 2015.)

45. As such, it took 18 years for the results of the required Phase IV efficacy study to be completed and published in a medical journal.

46. The primary endpoint for the study was for a responder to achieve a 30% or greater reduction in score - based upon an established interstitial cystitis symptom index - after 24 weeks treatment with Elmiron.

47. After over 50% of the planned number of patients completed the study, it was stopped because an interim analysis indicated that Elmiron provided no more symptom relief than placebo. In fact, it provided less relief than placebo for the subgroup of patients identified as suffering from IC.

48. Specifically, in the combined group of IC and Bladder Pain Syndrome cases, 40.7% of patients in the placebo group reported relief in symptoms, compared to 39.8% in the 100 mg. Elmiron group, and 42.6% in the 300 mg. Elmiron group. Thus no statistical difference existed between the three groups in regard to relief of symptoms.

49. In a subgroup of patients who met a strict clinical definition of IC (as opposed to bladder pain syndrome), 50.6% of the patients in the placebo group reported relief of symptoms, compared to 30.3% in the 100 mg. Elmiron group and 34.5% in the 300 mg. Elmiron group. This result indicates that Placebo provided an improvement in symptoms compared to either dose of Elmiron, which was likely statistically significant.

50. In short, Defendant's own Phase IV efficacy study establishes that Elmiron does not work. It did not provide improvement in symptoms of IC or bladder pain syndrome and in fact was less beneficial than Placebo for patients with IC.

51. No data other than that submitted by the drug's "champion," Dr. Parsons, in Study E-002 [i.e. 10 "better" versus 5 "not better"] provides evidence that Elmiron provides a statistically significant relief of symptoms of IC.

52. Another post marketing efficacy study reached the same conclusion: Elmiron does not work.

53. In this study by G.R. Sant, et al, "A Pilot Clinical Trial of Oral Pentosan Polysulfate and Oral Hydroxyzine in Patients with Interstitial Cystitis," Journal of Neurology (2003), Vol. 170, 810-815, the authors compared PPS, Hydroxyzine and placebo. The authors stated: "The low global response rates for PPS and hydroxyzine suggest that neither provided benefit for the majority of patients with IC." They concluded: "In this pilot study neither PPS nor hydroxyzine improved the global response assessment sufficiently to initiate a larger clinical trial of these agents."

54. Janssen acknowledged in the Nickel 2015 Journal of Urology article that its study and the Sant 2003 study were "negative" studies, which it contrasted with "[e]arly studies demonstrating PPS efficacy compared to placebo enrolled patients with the more traditional diagnosis of IC." However these two "early" studies cited by Janssen are the published versions of E-001 and E-002, which Janssen knew as the NDA holder for Elmiron were highly flawed, non-significant and/or contained suspect, biased data.

55. Prior to the submission of the Elmiron NDA, published medical literature indicated that Elmiron did not provide relief to symptoms of IC. In the study by Holm-Bentzen, et al, "A Prospective Double-Blind Clinically Controlled Multicenter Trial of Sodium Pentosanpolysulfate in the Treatment of Interstitial Cystitis and Related Painful Bladder Disease," Journal of Urology (1987) Vol. 138, 503-507, in which subjects were given 400 mg. of PPS a day, the authors stated: "We conclude that no statistically or clinically significant effect of sodium pentosanpolysulfate was found compared to placebo in patients with painful bladder disease."

56. Further, the authors debunked the biological mechanism theory advanced by Dr. Parsons as the basis for the treatment. "In 1977 Parsons and associates proposed the theory that the mucous layer coating the urothelium [of the bladder] had an important

barrier function. ... However, recently it has been shown that in patients with interstitial cystitis the mucous surface layer is identical morphologically to that of controls..." Id. at 503, citing Dixon, et al, "Electron microscopic investigation of the bladder utothelium and glycocalyx in patients with interstitial cystitis," Journal of Urology (1986), Vol. 135: 621.

57. Based upon a detailed review of the data, the authors stated: "we find a placebo effect of approximately 50 percent versus a drug effect of approximately 60 per cent," which the authors rejected as "of no clinical importance." (*Id*. at 506-507.)

58. Thus Janssen has been aware for decades that Elmiron was not proven effective in the treatment of IC. Besides the single set of data from Parsons' investigatory site in Study E-002, no researcher had ever found evidence of a statistically significant effect in a prospective, placebo-controlled, double-blind efficacy study. Even the proposed mechanism had been refuted as far back as 1986.

59. The policy against administrating drugs with no proven benefit is that it exposes patients to potentially harmful drug effects for no reason, and may deter the administration of alternative effective remedies.

60. Serious adverse events have been reported with Elmiron.

61. In the Compassionate Use study 33 patients of 2499 reported serious adverse events in the first three months of use, and 211 dropped out in the first three months due to adverse events.

62. The serious adverse events reported in the first three months included optic neuritis; bilateral retinopathy; blurred vision with left central optic vein occlusion; and filmy sensation over left eye.

63. Among adverse events leading to discontinuation in the Compassionate Use Study was a case of atrophic bilateral macular degeneration, which the investigator determined had a "probable" relationship to the use of Elmiron.

64. Other adverse events relating to vision which led to discontinuation in the Compassionate Use Study included: Amblyopia, Blurred Vision; Double Vision, Lacrimation Photo Sensitive, and Visual Field Defect.

65. In total, reported eye disorders among persons exposed to Elmiron in the Compassionate Use Study included: 6 amblyopia, 6 conjunctivitis, 2 eye disorder, 2 eye hemorrhage, 2 keratoconjunctivitis, 1 cataract unspecified, 1 eye pain, 1 optic atrophy, 1 (or 2) optic neuritis, 1 retinal artery occlusion, 1 retinal hemorrhage, 1 retinal vein thrombosis, and 1 visual field defect.

66. Prior to the marketing of Elmiron in the United States, a subcutaneous or intramuscular injectable form of PPS called Hemoclar was marketed in France from 1961 through 1994 for use as a low molecular weight heparin, and was also formulated for sublingual use to treat hyperlipoproteinemia.

67. Hemoclar was withdrawn from the market in France in 1994 due to safety concerns.

68. Safety issues with Hemoclar centered on bleeding and blood clotting abnormalities, as well as delayed immuno-allergic thrombocytopenia associated with hemorrhage or thrombosis (heparin induced thrombocytopenia.)

69. Although the anticoagulant properties of Elmiron are estimated to be 15% of those of heparin, reports of aneurysm, stroke and thrombocytopenia are included among the adverse events reported in the clinical trials for Elmiron.

70. Post marketing adverse events continued to include patients with serious eye problems. From January 1997 through October 2008, 65 reports of vision problems, eye pain and serious vision disorders were submitted for Elmiron. The adverse event reports included 4 reports of blindness, 8 reports of macular degeneration or maculopathy, 12 reporting impaired vision and 10 with blurred or halo vision. In addition, 7 reported eye pain, 4 eye or retinal hemorrhage, and 4 others reported retinal disorder, retinopathy, retinal vascular thrombosis or retinal injury.

71. Similarly, in the Janssen study by Nickel, et al, published in 2015, even though only 240 subjects were administered either 100 mg. or 300 mg. of Elmiron, and even though 42% of the Elmiron subjects dropped before completing the planned 4 months of use, adverse event reports included 1 patient with macular degeneration, and 4 patients with blurred vision or reduced visual acuity.

72. In November of 2018, Pearce, et al published "Pigmentary Maculopathy Associated with Chronic Exposure to Pentosan Polysulfate Sodium, American Academy of Opthalmology (2018), Vol. 25, No. 11, 1793-1802.

73. Pearce describes six adult patients who had been prescribed Elmiron and had been evaluated by the study authors for vision problems. The authors reported a unique pigmentary maculopathy (i.e. a disease of the macula, or center, of the retina) among patients with long term exposure to Elmiron. The patients were all prescribed 300 mg. or more Elmiron a day, with a mean length of exposure of 15 years.

74. The findings on examination included paracentral hyperpigmentation at the level of the retinal pigment epithelium, along with vitelliform-like deposits. Two of the patients had paracentral retinal pigment epithelium and others had generalized retinal pigment epithelium abnormalities. The authors noted that the findings resembled those

seen with macular degeneration and other macular diseases, and warned that physicians should be aware of the relationship to PPS in order to avoid a mistaken diagnosis.

75. The Elmiron patients diagnosed with the unusual maculopathy reported difficulty in reading and prolonged dark adaptation as the principal symptoms of their eye disorder.

76. In 2019 researchers from Emory University, along with the University of Michigan and the Oregon Health and Science University, authored a multi-institutional case series of 35 patients with maculopathy after long term use of Elmiron. Their ocular findings among patients exposed to Elmiron included hyperpigmented macular spots, interspersed pale yellow deposits, retinal pigment epithelium elevation or thickening, and a symmetric, confluent pattern of hyperautoflourescent and hypoautoflourescent spots in the fovea of the eyes extending to the retinal periphery. Hanif, et al, "Phenotypic Spectrum of Pentosan Polysulfate Sodium-Associated Maculopathy, A Multicenter Study, JAMA (2019) Opthalmology Vol. 137, Number 11, 1275-1282, at 1275.

77. The Elmiron-exposed subjects in the Emory multicenter study who exhibited these findings reported visual symptoms including metamorphopsia (i.e. straight lines appear curved), blurred vision, and prolonged dark adaptation.

78. The authors concluded: "These findings suggest that PPS-associated maculopathy is a vision-threatening condition that can manifest in the setting of long-term exposure to the drug." Id. at 1275.

79. In December 2019 a third article on Elmiron related eye damage was published in the medical literature. Wang, et al authored, "Pentosan-associated maculopathy: prevalence, screening guidelines, and spectrum of findings based on

prospective multimodal analysis," Canadian Journal of Ophthalmology (2020) Vol , No. 55, 116-125.

80. The authors identified Elmiron users from review of electronic medical records from the University of California Los Angeles. 50 Elmiron patients agreed to participate in the study; 10 of the 50 patients (20%) were diagnosed with PPS associated maculopathy. The most common symptoms was night blindness, although visual distortion and blurry vision were also reported.

81. The authors reported that there was a highly significant association between the duration of use of Elmiron: 19.2 years in the affected group compared to 6.6 years in the unaffected group. Further the daily dose in the affected group (444.8 mg) was significantly higher than in the unaffected group (301.8 mg). Similarly, the mean cumulative dose was significantly higher in those suffering vision damage from Elmiron (3375.4 g. v. 691.7 g.).

82. The findings on evaluation of the patients in the affected group were similar to those previously reported by the Emory researchers.

> A well-circumscribed region of speckled hyper- and hypoautofluoresence was centered around the macula, often with extension around the optic disc and even into the periphery. A peripapillary halo of hypoautofluorescence was noted in all affected eyes. The hyperautofluorescent lesions corresponded with focal areas of hyperpigmentation on the color fundus photography and focal areas of hyper-reflective RPE thickening with cross-sectional and en face OCT. . ." In regard to exposure to higher dosages of PPS, they authors identified: "A more widespread pattern of autofluorescent alterations or even a sever pattern of diffuse chorioretinal atrophy were appreciated with more significant toxic exposures.

83. The authors concluded "The prevalence of toxicity within this study cohort was noted to be 20%, which is remarkable" and warned that "PPS can lead to vision-alerting changes in the macula."

84. Throughout this time, and until June 16, 2020, the **WARNINGS** section of the Elmiron prescribing information was quite succinct. Until June 16, 2020, under **WARNINGS**, Defendant Janssen simply said "None."

85. Finally, in June of 2020, after Elmiron had been on the market for 24 years, Defendant Janssen revised the Warnings section of the label. Instead of saying "None," Defendant added a paragraph to the Warnings entitled **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 mot 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 te 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 imagine) 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.

86. While advising doctors and patients to re-evaluate the risks and benefits of continuing Elmiron treatment if vision problems develop, Defendant wholly failed to reveal that multiple studies, including Janssen's own Phase IV trial, indicated that Elmiron provides no more relief than a placebo. Therefore Janssen has encouraged a false analysis to proceed, where physicians and patients assume that some benefit actually does exist to prescribing Elmiron which may justify the risk of vision damage.

87. The assumption by the medical community that Elmiron actually works is apparent in the 2019 article conducted at UCLA with Wang as lead author. The authors state:

> The symptoms of IC can be especially burdensome, and discontinuation of PPS due to the risk of progressive vision loss must be weighted against the benefits of symptom relief, especially when alternative treatments have already been exhausted. Ophthalmologists should manage PPS-associated maculopathy on a case-by-case basis and approach the subject of PPS discontinuation with caution as patients may become distressed and distraught by the recommendation to discontinue PPS therapy. Open communication with the patient and his or her urologist prescribing the drug is essential.

88. Defendant's warning remains inadequate as it fails to dispel the belief that Elmiron provides a clinical benefit which must be balanced against the actual risk of significant harm.

89. Defendant "recommends" in the Elmiron label a dose of 300 mg. a day, but provides no instruction or warning against prescribing higher doses.

90. Defendant provides no instruction to stop the use of Elmiron if adverse events occur.

Plaintiff Jane Gruppo's Use and Injuries from Elmiron

91. Plaintiff Jane Gruppo began treatment with Elmiron approximately fifteen to twenty years ago.

92. After more than a decade of treatment with Elmiron, Plaintiff began to experience serious symptoms which can now be recognized as evidence of Elmiron toxicity.

93. Plaintiff suffered deterioration in her vision, which was originally diagnosed as maculopthy in 2015.

94. Plaintiff's physician noted "lattice degeneration, pattern dystrophy" but was unable to determine the cause, suggesting acute macular degeneration, Stargardt's or Dominant Drusen diseases as possibilities.

95. Plaintiff's physicians were not aware in 2015 that Elmiron use could cause eye damage.

96. In 2017, Plaintiff's physician ordered genetic testing in an attempt to diagnose her eye condition. The tests were negative.

97. By March of 2020, after medical literature reports of serious eye damage among patients exposed long term to Elmiron, Plaintiff's physicians diagnosed her with bilateral neovascular acute macular degeneration with active choroidal neovascularization, stable pattern dystrophy, stable lattice degeneration and dry eye syndrome, likely due to her Elmiron exposure.

98. Plaintiff's physicians discontinued her Elmiron prescription in 2020.

FIRST CAUSE OF ACTION

Strict Products Liability
Design Defect
O.R.C. § 2307.75

99. Plaintiff hereby incorporates by reference, as if fully set forth herein, each and every allegation set forth in the preceding paragraphs and further alleges as follows.

100. Defendant is the manufacturer, designer, marketer, distributor and seller of Elmiron.

101. The Elmiron manufactured, designed, marketed, distributed and sold by Defendant was expected to and did reach the consumer, Plaintiff Jane Gruppo, without any alterations or changes.

102. The Elmiron manufactured, designed, marketed, distributed and sold by Defendant was defective in design or formulation, because when it left the hands of the Defendant, the foreseeable risks of the product exceeded the benefits associated with its design or formulation.

103. In particular, with the exception of reports from a single investigation site involving 15 people treated with Elmiron (which was overseen by the inventor of Elmiron,) no report from any prospective, placebo-controlled, double-blind studies supports the claim that Elmiron is more effective than a placebo to a statistically significant degree.

104. Based on the lack of utility, any use of Elmiron to treat patients confers the risk of adverse effects for no benefit.

105. The foreseeable risks of Elmiron include serious damage to the eye, initially described as atrophic bilateral macular degeneration, amblyopia, blurred vision, double vision, lacrimation, photo sensitivity and visual field defect.

106. An Elmiron specific eye injury has been identified in the medical literature, described as PPS-associated maculopathy or macular toxicity, which was reasonably foreseeable based upon the experience in the initial trials. In fact, bilateral macular degeneration was identified as probably related to Elmiron therapy in the initial studies on Elmiron.

107. The maculopathy caused by Elmiron has similarities to macular degeneration, and is characterized by blurred vision, distorted vision, difficulty reading, night blindness and/or prolonged dark adaptation.

108. The prognosis for patients who suffer maculopathy due to Elmiron use is unknown.

109. Other treatments are available for IC, ranging from changes in diet, stress management and bladder training, to invasive surgical procedures. Several drugs are considered viable options, including amitriptyline, cimetidine, hydroxyzine, cyclosporine A, gabapentinoids, and quercetin.

110. As a treatment for intersititial cystitis or painful bladder syndrome, Elmiron is rated as a "D" by the Canadian Urology Association, while all other medical therapies score a B or C.

111. Further, since placebo was shown to be more efficacious in Janssen's own Phase IV study, a sugar pill would be a better option than Elmiron.

112. The Elmiron manufactured, designed, marketed, distributed and sold by Defendant was defective in design or formulation, because when it left the hands of the Defendant, it was more dangerous than an ordinary consumer would expect.

113. No ordinary consumer, including Plaintiff, would accept the risks of Elmiron, including but not limited to significant eye damage, in particular for a drug that provides no or minimal measurable benefit.

114. The Elmiron manufactured, designed, marketed, distributed and sold by Defendant was not unavoidably unsafe, because Defendant could have marketed placebo and gotten the same or better results.

115. Based upon the foregoing, the Elmiron manufactured, designed, marketed, distributed and sold by Defendant was defective in design pursuant to O.R.C. § 2307.75 at the time it left the Defendant's control.

116. Plaintiff consumed Elmiron in its defective condition, unaware that it was a defective product.

117. As a direct and proximate result of the defective design of Elmiron consumed by Plaintiff, Plaintiff suffered damages, including but not limited to personal injury, bodily harm, emotional distress, pain and suffering, permanent physical injury, permanent and substantial physical deformity of her eyes, loss of enjoyment of life, economic and non-economic damages, and will continue to suffer such injuries, distress, pain and suffering, harm, damages, and economic loss in the future.

118. Defendant' conduct as alleged in this Complaint shows that Defendant acted maliciously, with aggravated or egregious fraud, and/or intentionally disregarded Plaintiffs' rights, so as to warrant the imposition of punitive damages.

SECOND CAUSE OF ACTION

Strict Products Liability
Defect Due To Inadequate Warning
O.R.C. § 2307.76

119. Plaintiff hereby incorporates by reference, as if fully set forth herein, each and every allegation set forth in the preceding paragraphs and further alleges as follows.

120. Defendant is the manufacturer, designer, marketer, distributor, and seller of Elmiron.

121. The Elmiron manufactured, designed, marketed, distributed and sold by Defendant was defective due to inadequate warning or instruction pursuant to O.R.C. §2307.76, because at the time it left the control of Defendant and was supplied to Plaintiff, Defendant knew or should have known that their product was unreasonably dangerous as confirmed by the published literature and its own internal data which indicated that it lacked efficacy, and because Elmiron substantially and significantly increases the risk of serious adverse effects including vision damage.

122. Despite the fact that Defendant knew or should have known about the increased risk of serious adverse effects with Elmiron, Defendant failed to exercise reasonable care to adequately warn of the increased risk and dubious efficacy.

123. The Elmiron manufactured and supplied by Defendant was defective due to inadequate warning or instruction pursuant to O.R.C. §2307.76, because at the time it left the control of Defendant and was supplied to Plaintiff, Defendant knew or should have known that its product was unreasonably dangerous, as confirmed by the extensive body of published literature and its own internal data, in that higher doses and long term use of Elmiron substantially and significantly increased the risk of serious adverse effects, including serious eye damage, compared to lower doses or short term use.

124. Despite the fact that Defendant knew or should have known about the increased risk with higher doses and long term use of Elmiron as compared to lower doses for shorter time frames (such as doses of 300 mg. for less than six years,) Defendant failed to exercise reasonable care to adequately warn of the increased risk with higher exposure to Elmiron. In fact, Defendant made no reference in the Elmiron product label to the risk of long term use or higher doses.

125. Rather than providing a warning containing accurate information about the risks and benefits of Elmiron, Defendant's one word statement in the Warnings section of the Elmiron prescribing information was "None."

126. The Elmiron manufactured and supplied by Defendant was defective due to inadequate warning or instruction pursuant to O.R.C. §2307.76, because at the time it left the control of Defendant and was supplied to Plaintiff, Defendant knew or should have known that their product was unreasonably dangerous, as confirmed by the published literature and its own internal data, because ingestion of Elmiron substantially and

significantly increases the risk of serious adverse effects compared to dubious proof of efficacy.

127. The Elmiron manufactured and supplied by Defendant was also defective pursuant to O.R.C. 2307.76 due to inadequate post-marketing warning or instruction, because after Defendant knew or should have known of the extremely questionable efficacy of the drug and the substantially increased risks as described above, Defendant failed to provide adequate and/or timely post-market warnings to consumers and/or their health care providers, and failed to revise the Elmiron label to warn of the serious and substantially increased risk of serious adverse effects caused by Elmiron as compared to its very questionable efficacy.

128. Defendant also failed to issue adequate and/or timely post-market warnings that higher levels of exposure in terms of dosage or length of time significantly increased the risk of serious eye damage.

129. The significantly increased risk of harm from Elmiron and/or its lack of efficacy are properties of Elmiron that are not an open and obvious danger or a matter of common knowledge.

130. Plaintiff was prescribed and ingested Elmiron for many years based upon the Defendant's representations to Plaintiff and her physician that the drug was safe and effective for the treatment of IC.

131. Had Plaintiff and/or her physicians been aware of the serious safety risks of Elmiron and/or its questionable benefits, Plaintiff would not have taken Elmiron.

132. As a direct and proximate result of Elmiron's inadequate warnings and instructions, Plaintiff suffered damages, including but not limited to personal injury, bodily harm, emotional distress, pain and suffering, permanent physical injury, permanent and

substantial physical deformity of her eyes, loss of enjoyment of life, economic and non-economic damages, and will continue to suffer such injuries, distress, pain and suffering, harm, damages, and economic loss in the future.

133. Defendant's conduct as alleged in this Complaint shows that Defendant acted maliciously, with aggravated or egregious fraud, and/or intentionally disregarded Plaintiff's rights, so as to warrant the imposition of punitive damages.

THIRD CAUSE OF ACTION

Strict Products Liability
Nonconformance with Representations
O.R.C. § 2307.77

134. Plaintiff hereby incorporates by reference, as if fully set forth herein, each and every allegation set forth in the preceding paragraphs and further alleges as follows.

135. Defendant is the manufacturer, designer, marketer, distributor and seller of Elmiron.

136. At the time Defendant manufactured, designed, marketed, distributed and sold Elmiron to Plaintiff, Defendant represented to consumers and the medical community through the product label that the benefits of Elmiron in treating IC outweighed the risk of treatment.

137. Specifically, Defendant represented that Elmiron was "indicated for the relief of bladder pain or discomfort associated with interstitial cystitis."

138. By definition, products indicated for treatment of a specific condition are considered to be both safe and effective for that use.

139. Defendant also advised in its product labeling that Elmiron "must be taken continuously for relief as prescribed."

140. However, as described herein, Elmiron failed to conform to these representations and instead is completely unacceptable for use to treat IC, because it lacks utility and causes serious adverse effects, including but not limited to vision loss, thus rendering it both ineffective and unsafe.

141. No treatment at all (i.e. placebo treatment) for IC is safer and just as effective, if not more effective, than Elmiron. Other treatments, such as pain relievers, also provide equivalent or greater efficacy in relieving symptoms of IC than Elmiron.

142. The failure of Elmiron to conform to the representations made by Defendant in the product labeling render the product defective pursuant to O.R.C. § 2307.77.

143. Plaintiff and/or her physicians relied to Plaintiff's detriment upon the representations made by Defendant in Elmiron's labeling concerning the safety and efficacy of Elmiron. As a direct and proximate result of Plaintiff's use of defective Elmiron, which failed to conform to manufacturer representations as described above, Plaintiff suffered damages, including but not limited to personal injury, bodily harm, emotional distress, pain and suffering, permanent physical injury, permanent and substantial physical deformity of her eyes, loss of enjoyment of life, economic and non-economic damages, and will continue to suffer such injuries, distress, pain and suffering, harm, damages, and economic loss in the future.

144. Defendant's conduct as alleged in this Complaint shows that Defendant acted maliciously, with aggravated or egregious fraud, and/or intentionally disregarded Plaintiff's rights, so as to warrant the imposition of punitive damages.

FOURTH CAUSE OF ACTION

Negligent Misrepresentation and Fraud

145. Plaintiff incorporates by reference, as if fully set forth herein, each and every allegation set forth in the preceding paragraphs and further alleges as follows.

146. Defendant manufactures, designs, markets, labels, distributes and sells Elmiron.

147. Defendant had a duty to provide truthful information about its prescription drug Elmiron to consumers and their physicians, including Plaintiff, and a duty not to deceive them.

148. Defendant is responsible for the accuracy and truthfulness of its product labeling at all times.

149. Defendant had the duty to provide accurate prescribing information regarding Elmiron to patients and/or their physicians, including Plaintiff, which included adding or strengthening any contraindication, warnings, precautions, or adverse reactions provided in the product label. *See* 21 C.F.R. §314.70(c)(6)(iii)(A).

150. Defendant had the duty to delete false, misleading, or unsupported indications for use or claims for effectiveness from the label for Elmiron. *See* 21 C.F.R. §314.70(c)(6)(iii)(D).

151. Defendant made representations to Plaintiff and her physician regarding the character and/or quality of Elmiron for guidance in their decision to select Elmiron for Plaintiff's use.

152. Plaintiff and her physicians justifiably relied upon the representations made by Defendant concerning Elmiron in its product labeling.

153. Specifically, Defendant represented that its product was safe and effective as it was indicated for the treatment of IC and instructed patients, including Plaintiff, that Elmiron "must be taken continuously for relief as prescribed."

154. Defendant also represented that patients in its clinical trial who received Elmiron reported a statistically significant improvement in bladder pain. These statistics, however, represented only a single data point from among multiple analysis in the study which were contradicted by other findings.

155. Defendant also knew that the data from this study was suspect based upon 1) the input from Dr. Parsons, who had a financial interest in the outcome and who provided outlier results completely opposite to those of all the other investigators, 2) the fact that multiple analysis were conducted without performing the Bonferroni statistical correction, and 3) the fact that results from the self-assessment of change in pain scores at three months for patients treated with Elmiron (66%) versus placebo (52%) was not significantly different.

156. Defendant's characterizations of the data from Study E-002 as described above contained material misrepresentations and omissions.

157. Defendant also represented that: "In preliminary clinical models, pentosan polysulfate sodium adhered to the bladder wall mucosal membrane. The drug may act as a buffer to control cell permeability preventing irritating solutes in the urine from reaching the cells."

158. However, Defendant knew or should have known that this statement was false. Prior studies had already established that "the mucous surface layer is identical morphologically to that of controls…" thus completely debunking this theoretical method of action.

159. The dearth of data supporting a mechanism of action reinforced the statistical data demonstrating that Elmiron was not effective, but Defendant continued to make false representations as to efficacy of Elmiron for treatment of IC.

160. Defendant also knew that multiple patients in its clinical trials reported serious vision problems after exposure to Elmiron.

161. Defendant provided no Warning of any kind in its labeling for Elmiron about vision problems, or any problems. The only word provided by Defendant under Warnings was “None.”

162. Defendant knew or should have known that its statement providing no warnings of serious side effects Elmiron was false or misleading, in that Elmiron posed a serious risk of eye damage and other adverse effects.

163. Defendant failed to exercise reasonable care to determine the risks of Elmiron, or in fact deliberately misconstrued the safety profile of Elmiron, and provided inaccurate, misleading or false safety information to Plaintiff and her physician.

164. Defendant had a duty to disclose to Plaintiff, her physician, and the public that Elmiron was not safe due to its toxic effects on the eye, and/or that serious issues existed concerning its efficacy.

165. Defendant also had a duty to disclose the dose relationship between Elmiron and adverse effects, and in particular that long term use and higher doses increased the risk of macular toxicity or eye damage.

166. Defendant did not disclose any of the above information to Plaintiff.

167. Plaintiff and her physicians justifiably relied to her detriment upon Defendant’s misrepresentations and/or omissions concerning the serious risks posed by Elmiron in the product’s labeling, advertisements and promotions.

168. Plaintiff and her physician justifiably relied to her detriment upon Defendant's representations that Elmiron was a safe and effective method of treating IC which must be taken continually to obtain relief.

169. In its 2015 study, Defendant stated: "Results 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." Yet Defendant continued to market the drug for treatment of IC and claimed "we do not believe that this study can be used to justify abandoning one of the few medications with significant clinical trial and experience support for treating IC/BPS…"

170. Defendant took no action to revise its label to reveal the lack of efficacy of Elmiron after it published the Nickel article in 2015, nor did Defendant remove Elmiron from the market.

171. Defendant did not disclose in the Elmiron label that it stopped its Phase IV study due to Elmiron's lack of efficacy, or that Study E-002 contained suspect data, questionable statistics and presented selective results.

172. Had Plaintiff or her physician known of Defendant's misrepresentation and/or concealment of the true facts concerning the lack of safety and lack of efficacy of Elmiron as described herein, Plaintiff would not have been prescribed or taken Elmiron.

173. As a direct and proximate result of Defendant's negligent and/or intentional misrepresentations, Plaintiff ingested Elmiron and suffered damages, including but not limited to personal injury, bodily harm, emotional distress, pain and suffering, permanent physical injury, permanent and substantial physical deformity of her eyes, loss of

enjoyment of life, economic and non-economic damages, and will continue to suffer such injuries, distress, pain and suffering, harm, damages, and economic loss in the future.

174. Defendant charged consumers, including Plaintiff, approximately $500 to $1000 per month for Elmiron. Plaintiff acted in justifiable reliance upon Defendant's representations that Elmiron was a safe and effective treatment for IC, and was misled and defrauded into paying for Elmiron treatment for over 15 years, thereby entitling Plaintiff to recoup the costs of Elmiron from Defendant.

175. Defendant's conduct as alleged in this Complaint shows that Defendant acted maliciously, with aggravated or egregious fraud, and/or intentionally disregarded Plaintiff's rights, so as to warrant the imposition of punitive damages.

FIFTH CAUSE OF ACTION

Breach of Express Warranty

176. Plaintiffs incorporate by reference, as if fully set forth herein, each and every allegation set forth in the preceding paragraphs and further allege as follows.

177. Defendant expressly warranted that Elmiron is indicated to treat the pain or discomfort of IC and must be taken continuously for relief as prescribed.

178. The Elmiron manufactured and sold by Defendant did not conform to this express representation because Elmiron provides no relief to the majority of patients, is less efficacious than placebo in Defendant's own study, and exposed patients to the risk of serious injury.

179. As a direct and proximate result of Defendant's breach of warranty, Plaintiff ingested Elmiron and suffered economic loss, including but not limited to the amount that Plaintiff was charged for treatment with Elmiron, at a cost of approximately $500 to $1000 per month for a period of about 15 years.

SIXTH CAUSE OF ACTION

Unjust Enrichment

180. Plaintiff incorporates by reference, as if fully set forth herein, each and every allegation set forth in the preceding paragraphs and further alleges as follows.

181. As the intended and expected result of their conscious wrongdoing, Defendant has profited and benefited from Plaintiff's long term use and purchase of Elmiron, as well as from other consumers' use and purchase of Elmiron.

182. Defendant has voluntarily accepted and retained those profits and benefits, derived from Plaintiff and other consumers, with full knowledge and awareness that, as a result of Defendant's fraud and other conscious and intentional wrongdoing, Plaintiff and other consumers were not receiving a product of the quality, nature, or fitness that had been represented by Defendant, or that, as a reasonable consumer, they expected to receive.

183. By virtue of the conscious wrongdoing alleged above, Defendant has been unjustly enriched at the expense of Plaintiff and other consumers, and Plaintiff is entitled in equity to, and hereby seeks, the disgorgement and restitution of Defendant's wrongful profits, revenues, and benefits to the extent and in the amount deemed appropriate by the Court; and such other relief as the Court deems just and proper to remedy Defendant's unjust enrichment.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff demands judgment against the Defendant on each of the above-referenced claims and Causes of Action and further demands as follows:

1. Compensatory damages in excess of the $75,000 jurisdictional amount, including but not limited to compensation for injury, pain, suffering, mental anguish,

emotional distress, loss of enjoyment of life, permanent physical injury, permanent and substantial physical deformity of her eyes, and other non-economic damages in an amount to be determined at trial of this action;

2. Economic damages in the form of reimbursement for costs of Elmiron, medical expenses, out-of-pocket expenses, lost earnings, and other economic damages in an amount to be determined at trial of this action;

3. Punitive Damages

4. Disgorgement of profits;

5. Attorneys' fees, expenses, and costs of this action; and

6. Such further relief as this Honorable Court deems necessary, just, and proper.

DEMAND FOR JURY TRIAL

Plaintiff hereby demands trial by jury as to all issues which can be so tried.

_/s/ Janet G. Abaray_____
Janet G. Abaray (0002943)

RESPECTFULLY SUBMITTED,

/s/ Janet G. Abaray
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