IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IN RE COPAXONE 40 MG CONSOLIDATED CASES	Civil Action No. 14-1171-GMS (CONSOLIDATED)

FOURTH DECLARATION OF EDWARD J. FOX, M.D., PH.D.

I am the same Edward J. Fox who submitted declarations in this case dated September 11, 2015, October 2, 2015, and December 18, 2015. I submit this declaration to address certain opinions expressed in the Declaration of Samuel J. Pleasure, M.D., dated December 18, 2015 ("Pleasure Dec."), concerning the meaning of two claim terms in U.S. Patent 9,155,776 ("the '776 patent"). I reserve the right to supplement this declaration as appropriate and to respond to any declaration or report submitted on behalf of the Defendants in this action.

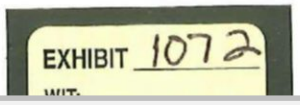
COMPENSATION AND PRIOR TESTIMONY

1. I am being compensated for my time spent working on this case at the rate of $500 per hour.

2. I have not testified as an expert at trial or by deposition in the previous four years.

MATERIALS CONSIDERED

3. I have reviewed the Declaration of Samuel J. Pleasure, M.D. in support of Defendants' Opening Claim Construction Brief Regarding U.S. Patent No. 9,155,776, dated December 18, 2015, including the exhibits attached thereto and defendants' opening claim construction brief. My opinions in this declaration are based on my education and over twenty-three years of experience as a practicing clinician and scientist/researcher. I have also reviewed and considered other documents attached to this declaration as Exhibits A-C.



SUMMARY OF OPINIONS

4. I disagree with Dr. Pleasure's opinion that a person of ordinary skill in the art ("POSA") would have interpreted the claims of the '776 patent in various ways as of the priority date and therefore the severity terms are indefinite.[1] (Pleasure Dec. ¶¶ 26-27 and 30.) In my opinion, a POSA would have readily understood the meaning of the severity terms in view of their plain and ordinary meanings, their use in the patent specification, and the knowledge and practice of a POSA. Thus, as explained in my third declaration, a POSA would have understood the scope of the inventions claimed in the '776 patent with reasonable certainty. A POSA also would have known how to determine whether a reduction in the frequency and severity of injection reactions had occurred through clinical observation and study.

5. I also disagree with Dr. Pleasure's opinion that the constructions of the severity terms should specify that the reduction in severity and/or frequency is limited to an individual patient, as opposed to a patient population. (Pleasure Dec. ¶¶ 25 and 29.) In my opinion, the severity terms do not require construction because, as used in the claims of the '776 patent, they have plain and ordinary meanings that would have been readily understood by a POSA. If it is determined that the terms need to be construed, in my opinion, a POSA would have understood them to encompass a reduction in the frequency and severity of IPIRs and ISRs in a group of patients as well as an individual patient. Dr. Pleasure's proposal to limit the constructions to an individual patient would introduce redundancy because several claims contain the phrase "in the human patient" immediately after the severity terms. In addition, Dr. Pleasure's proposal is inconsistent with how the severity terms are used in the patent specification.

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[1] The disputed claim terms – "reduced severity of injection site reactions" the "reduced frequency and severity of immediate post injection reactions and injection site reactions" – are collectively referred to herein as "the severity terms."

THE SEVERITY TERMS ARE NOT INDEFINITE

6. Dr. Pleasure contends that in 2009 "there was no agreed upon meaning in the art regarding severity." (Pleasure Dec. ¶ 38.) This is simply not true. As explained in my third declaration, in 2009, severity was generally understood to mean the same thing as intensity. Dr. Pleasure acknowledged this in his declaration. (Pleasure Dec. ¶ 28.) This definition is adopted by various literature from the relevant timeframe. For example, several books defined "severity" as "intensity of a specific event, as in mild, moderate or severe."[2] In addition, based on my personal experience treating thousands of patients and participating in more than 60 clinical trials, several of which evaluated the severity of injection reactions associated with Copaxone, in my opinion, POSAs and patients being treated for multiple sclerosis would have understood the meaning of severity as it is used in the claims of the '776 patent. There was no confusion in the art among clinicians or patients about what constituted a more or less severe IPIR or ISR.

7. I also disagree with Dr. Pleasure's opinion that "there is no established or agreed-upon way to measure severity (or a reduction thereof)." (Pleasure Dec. ¶¶ 26, 30, 38.) In 2009, there was a well-established and widely-used scale for grading the severity of injection reactions called Common Terminology Criteria for Adverse Events ("CTCAE") published by the National Institutes of Health of the U.S. Department of Health and Human Services (attached hereto as Exhibit C). These criteria were commonly used by clinicians to grade and evaluate the severity of various adverse events, including injection reactions. The CTCAE provides Grades 1 through

[2] *See, e.g.*, Cobert et al., "Practical Drug Safety from A to Z," page 328 (2009) ("The term 'severe' is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction) . . ." (attached hereto as Exhibit A); "A Practical Handbook on the Pharmacovigilance of Antiretroviral Medicines," published by World Health Organization, page 132 (2009) (In the English language, "severe" is used to describe the intensity (severity) of a specific event (as in mild, moderate or severe) . . ." (attached hereto as Exhibit B).

5 with unique clinical descriptions of severity for each adverse event based on the following general guidelines:

Grade 1	Mild; asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

With regard to injection reactions, Grades 4 and 5 are typically not used because such adverse events almost never lead to life-threatening consequences or death.

8. In my opinion, a POSA interpreting the claims of the '776 patent would have used the criteria set forth in the CTCAE, or a similar set of criteria, to determine whether the claimed dosing regimen reduced the severity of injection reactions relative to the 20 mg daily regimen. In particular, a clinician or patient evaluating the severity of one or more injection reactions observed in a patient would grade each reaction as mild, moderate, or severe. A POSA would have known how to aggregate the severity grades observed in a group of patients and/or multiple injection reactions in the same patient to compare them to determine how they compared to the 20 mg daily regimen. Regardless of whether a POSA used the exact criteria set forth in the CTCAE or a slight variation, in my opinion, there would not have been an appreciable difference in the results and Dr. Pleasure does not contend otherwise. Indeed, Dr. Pleasure's declaration provides no evidence that using slightly different methods of evaluating severity of injection reactions would lead to appreciably different results.

9. As an example, starting in July 2009, just one month before the priority date of the '776 patent, I participated as a primary investigator in a study comparing, among other things, the severity of injection reactions in two different dosing regimens: once-daily administration of injections of GA 20 mg/1 mL (Copaxone® marketed formulation) and once-daily administration of injections of GA 20 mg/0.5 mL (reduced volume formulation). In this study known as SONG (Study of New Glatiramer Acetate Formulation), using a Visual Analog Scale (VAS), patients recorded in daily diaries the severity of injection pain immediately and 5 minutes post-injection, and the presence and severity of injection reactions (swelling, redness, itching, lump) within 5 minutes and 24 hours post-injection. The degree of injection reaction severity was rated 0-3, with 0 = none, 1 = mild, 2 = moderate, and 3 = severe. In my opinion, a POSA evaluating severity of the methods claimed in the '776 patent would have used a scale like this or something similar. Regardless of which grading scale was used, the overall results would have been roughly the same. Accordingly, a POSA would have understood the scope of the invention described in the claims of the '776 patent with reasonable certainty.

10. Dr. Pleasure also contends that "severity . . . can be subjective (and some reactions are more amendable to objective measurement than others); . . . even a single person can have a variety of reactions (at the same time); and . . . a certain category of reaction may be inherently more or less severe than another category of reaction." (Pleasure Dec. ¶¶ 26, 30, 34-37.) I do not disagree with the premise of these generalizations. However, there is no evidence that, even if these statements are true, using one grading scale to evaluate severity of injection reactions would lead to a different answer to the overall question compared to a slightly different scale. As explained above, in my opinion, a POSA would have readily understood the meaning of the severity terms in view of their plain and ordinary meanings, there was a well-established scale for grading the severity of injection reactions, there is no evidence that using any method

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