Court File No.: 98-CV-158832

ONTARIO
SUPERIOR COURT OF JUSTICE

BETWEEN:

SHEILA WILSON

Plaintiff

- and -

SERVIER CANADA INC., LES LABORATOIRES SERVIER, SERVIER AMERIQUE, INSTITUT DE RECHERCHES INTERNATIONALES SERVIER ("I.R.I.S"), SCIENCE UNION ET CIE, ORIL S.A., SERVIER S.A.S., ARTS ET TECHNIQUES DU PROGRES, BIOLOGIE SERVIER, INSTITUT DE DEVELOPEMENT ET DE RECHERCHE SERVIER, ORIL INDUSTRIE, BIO RECHERCHE SERVIER, INSTITUTO DI RICERCA, IDUX, BIOPHARMA ARTEM, SCIENCE UNION S.A.R.L., LABORATOIRES SERVIER INDUSTRIE, I.R.I.S. ET CIE DEVELOPEMENT, INFORMATION SERVIER, SERVIER MONDE, SERVIER INTERNATIONAL, I.R.I.S. SERVICES S.A.R.L., ADIR, SERVIER R&D BENELUX, DR. JACQUES SERVIER and BIOFARMA S.A.

Defendants

Proceeding under the *Class Proceedings Act, 1992*

AFFIDAVIT OF DR. JOHN GRANTON

I, JOHN GRANTON, of the City of Toronto, in the Province of Ontario, **MAKE OATH AND SAY:**

1. I am a medical doctor licensed to practice medicine in Ontario. I am an Associate Professor of Medicine at the University of Toronto, Director of the Pulmonary Hypertension Programme at the University Health Network, Programme Director

of Critical Care Medicine at the University of Toronto, and consultant in the medical and surgical intensive care units at the University Health Network.

2. I specialize in the treatment of pulmonary disorders and have treated hundreds of patients with Pulmonary Arterial Hypertension ("PAH") and Primary Pulmonary Hypertension ("PPH"), including the Plaintiff, Sheila Wilson and other class members. I have served as an Applicant, Investigator and/or Site Investigator for several clinical trials of therapies for PAH and/or PPH, including trials of Sildenafil, Bosentan and UT-15 performed since 2000. Attached hereto as Exhibit "A" is a true copy of my curriculum vitae which more fully articulates my experience and qualifications.

3. I was retained by counsel for the Plaintiff National Class as an expert witness from the outset of this litigation, as well as throughout the settlement negotiations. As such, I have participated in the drafting of the Medical Conditions List and other portions of the Settlement Agreement relating to the diagnosis of PPH and the appropriate criteria for qualifying for benefits under the Settlement Agreement. As a result, I have knowledge of the facts hereinafter deposed to except where I have been informed of such facts, in which case I have stated the source of such facts and I hereby state that I believe such facts to be true.

4. I swear this affidavit in support of a motion to approve the Settlement Agreement in this action and to comment on matters relating to PPH, including the eligibility criteria for PPH benefits under the Settlement Agreement.

Background

5. PPH is a rare disease with a prevalence of approximately 1-2 per million in the general population. A diagnosis of PPH is made by excluding other known causes of pulmonary arterial hypertension ("PAH"). PAH is characterized by raised pulmonary vascular resistance and elevated artery pressures, resulting in diminished right-heart function due to increased right ventricular afterload and is clinically defined as a mean pulmonary arterial pressure (mPAP) of more than 25mmHg at rest or more than 30mmHg during exercise. Patients suffering from PPH experience progressive elevation of pulmonary artery pressure, which eventually leads to right heart failure and death. Attached hereto as Exhibits "B", "C", and "D" are peer-reviewed articles which reflect these statements.

6. PPH is a disabling disease that detrimentally impacts upon the activities of daily living and eventually destroys the quality of life of the patient. Historically, the mean survival from onset of symptoms until death for PPH patients has been two to three years. Promising but costly new treatments, as well as potential new treatments still under study, have raised hopes of improved mortality and morbidity. However, many patients continue to struggle with and die from PPH despite these advances. For more than 10 percent of PPH patients, lung transplantation still remains the only long-term option. Unfortunately, many patients on the lung transplant waiting list with PAH die before they are transplanted.

7. Epidemiological studies have shown that that the typical interval from onset of symptoms to a diagnosis of PPH is usually 2-3 years. However, it should be noted that there are documented cases of very rapid progression, as well as cases involving an extended period of either latency or subclinical progression such that even initial symptoms might not appear for more than 10 years. The overall course of PPH can be highly variable and is often unpredictable.

8. Since the initial symptom of PAH is breathlessness on exertion, which is a symptom of normal living, it is very common for patients and physicians to attribute the onset of these symptoms as being related to either obesity, aging, poor conditioning or misdiagnosis.

9. Although PPH is incurable, current therapies can increase a patient's survival period and include the use of medications such as calcium channel blockers, Bosentan, sildenafil, parenteral, prostacyclin, and lung and heart / lung transplantation.

Association Between PPH and Anorexigens

10. Fenfluramine, an anorexigen, was introduced in Europe and other markets worldwide in the early 1960s and in Canada in the 1970s.

11. The first case report of an association between PPH and the use of fenfluramine was published in the scientific literature in 1981.

12. Some of these later reports related to dexfenfluramine, another anorexigen, which was introduced in Europe in the late 1980s and approved for use in Canada by Federal authorities in January 1997.

13. Both fenfluramine and dexfenfluramine were withdrawn from the Canadian market in September 1997.

14. There are no Canadian case reports in the scientific literature that I am aware of.

15. For ease of reference, the terms fenfluramine and dexfenfluramine will be collectively referred to as "the Products" in the balance of this affidavit.

16. In part as a result of concerns caused by these case reports, a multi-centre case-controlled epidemiologic study of the risk factors associated with PPH was launched in 1992. The Study was led by Dr. Lucien Abenheim, and is known as the International Primary Pulmonary Hypertension Study ("IPPHS").

17. The findings of the IPPHS were published in the *New England Journal of Medicine* ("NEJM") in August of 1996 and included the following:

> We believe that the association between anorexic agents and Primary Pulmonary Hypertension is due to neither bias nor chance. Our findings are consistent with observations in the 1960's of an association of Primary Pulmonary Hypertension with the use of aminorex fumarate and of more recent associations with fenfluramine derivatives, other anorexic agents, or related products. The consistency of our observations with previous findings, the strength of the association, the fact that it increases with longer use, and the fact that it is stronger with recent use than with past use all favor a causal relationship.

Attached hereto as Exhibit "E" is a true copy of this NEJM article.

18. There was an additional report relating to the association between the use of the Products and the development of PPH, entitled "*Anorexigens and Pulmonary Hypertension in the United States – Results of the Surveillance of North American Pulmonary Hypertension (SNAP)*" in Chest in March 2000. Attached hereto as Exhibit "F" is a true copy of the SNAP study summary.

19. In addition, the World Symposium on Primary Pulmonary Hypertension sponsored by the World Health Organization ("WHO") has identified the Products as "definite" risk factors for PPH. According to the Symposium, a "definite" risk factor indicates "an association based on several concordant observations, including a major controlled study or clear epidemic. Definite risk factors are considered to play a causal role in the development of the disease." In my professional opinion, this continues to express the consensus of scientific and medical opinion. Attached hereto at Exhibit "G" is a copy of this WHO document.

20. In my professional opinion there is enough scientific evidence to lead me to believe that there is a causal link between use of the Products and the development of PPH.

21. I am informed by National Class Counsel that the Defendants contend there is no scientific or medical study that has established a causal link between the use of the Products and the development of PPH and that the existence of such a causal

link as well as other legal and factual issues were vigorously contested by the Defendants.

Settlement Negotiations

22. I was consulted extensively in drafting the Medical Conditions List ("MCL"). I participated in multiple meetings, both in person and by conference call, with Class Counsel, *Lieff Cabraser*, defence counsel and the Court-Appointed Monitor with a view to ensuring that the MCL was medically sound.

23. The issues discussed included, but were not limited to, whether there should be a duration of use requirement, whether and what latency issues came into play, how the diagnostic algorithm for PPH should be articulated, as well as issues relating to the diagnosis of PAH, and the circumstances under which individuals suffering from PPH will experience extreme hardship relative to other individuals claiming PPH benefits under this Settlement. I will address each of these issues in turn.

1. Duration of Use

24. Unlike the Canadian settlement related to Pondimin (an anorexigen containing fenfluramine but manufactured and marketed by a different company), the terms of this settlement do not impose a "duration of use" requirement on a claimant to be eligible to receive benefits under the Settlement Agreement.

25. In the Pondimin settlement, where a patient had ingested the drug for less than a stipulated period of time, they were compensated on a significantly lower scale

than patients who had ingested the drug for a longer period of time. It is my opinion that if it is determined that the drug(s) were ingested and that none of the conditions listed in section 5.2.3 of the MCL were the "principal cause" (as "cause" is interpreted according to the Settlement Agreement and the MCL) of the Product Recipient's PAH, all patients should be treated the same, regardless of duration of use.

26. My clinical treatment of a patient with what is in my professional opinion anorexigen-induced PPH is not contingent upon the number of pills consumed and the clinical course of treatment does not differ on that basis either. In my view, therefore, a duration of use requirement could unfairly undercompensate some claimants.

2. Latency

27. Another issue about which I was consulted is the potential latency period between exposure to the Products and subsequent diagnosis of PPH.

28. The biologic explanation for latency is that PPH is a gradual process that occurs primarily in the endothelial (intimal or inner) and muscular (medial - middle) layers of the arterioles, the tiny blood vessels in the lungs just upstream from where oxygen transfer occurs. The inner layer of these arterioles gradually become fibrotic and thicken, the middle layer thickens and becomes muscular, and this process gradually narrows the internal diameter of the arterial resulting in a condition called pulmonary arteriopathy. In essence, the same amount of blood

that was formerly passing through a large opening must now pass through a small opening – causing an increase in pulmonary artery pressure. The pace of these changes varies between individuals. In addition, some patients or physicians may become aware of functional limitations earlier than others.

29. While data from the IPPHS indicates that the association between diet drugs and PPH may be strongest if the diet drugs were taken within the year prior to diagnosis, patients can present with symptoms more than one year after having stopped taking diet drugs. Data from a PAH center in France has shown "the interval between the onset of drug intake and that of symptoms related to PPH showed marked individual variation, with a mean of 49 ± 68 months, a minimum of 27 days and a maximum of 23 years". Attached hereto at Exhibit "H" is an article reporting these findings (Supplement to CHEST, 114(3): 195S-199S, 1998).

30. As stated above, because the initial symptom of PAH is breathlessness with exercise, which is a symptom of normal living, it is very common for patients and physicians to attribute the onset of these symptoms as being related to obesity, aging or poor conditioning. The time period from the onset of symptoms until diagnosis is, therefore, highly variable and affected by: (a) the patient's recognition that the symptoms cannot be attributed to normalcy, (b) the patient's inclination to seek medical attention, and (c) the physician's understanding of whether the symptoms are indicators of PAH.

31. As a result, the duration of time between the onset of symptoms and diagnosis of PAH in patients in that report averaged 18 ± 18 months, which is similar to the data from the IPPHS where patients had symptoms for a median of 16 months (range 1 to 104 months prior to diagnosis of PPH).

32. Based on this information, in my professional opinion, if one combines the available data on the delay from diet drug exposure to symptom recognition with the delay from symptom onset to the time of the diagnosis of PPH, one finds the average interval between diet drug exposure and diagnosis is a total of 67 months ± 86 months.

33. One of the terms of the Settlement Agreement is a rebuttable presumption that the Product Recipient's condition was not attributable to the Products where they were not diagnosed with PAH within seven years of their first use of the Products. This term takes into account both the data which supports an increased risk of developing PPH with recent use and the fact that the period of time between ingestion of the Products and diagnosis is highly variable. Because this presumption is rebuttable, I find this term to be fair and reasonable.

3. Diagnostic Algorithm

34. I was also involved in drafting a clinically appropriate definition for PAH and diagnostic algorithm for PPH.

(a) Diagnosis of PAH

35. As noted above, PPH is a diagnosis of exclusion. The starting point in the process – after the development of symptoms – is a diagnosis of pulmonary arterial hypertension ("PAH"). Such a diagnosis means that the patient has a mean pulmonary arterial pressure on cardiac catheterization which is greater than 25 mmHg at rest or greater than 30 mmHg with exercise. This position has recently been affirmed by an expert panel of the American College of Chest Physicians ("ACCP"), which published a series of articles on the diagnosis and management of PAH in a supplement to the July, 2004 edition of *Chest*. Attached hereto at Exhibit "I" are copies of these articles.

36. In addition, a further diagnostic basis was added for patients who had recorded a peak systolic pulmonary pressure of greater than 60 mmHg estimated during Doppler trans-thoracic echocardiogram. This was added in order to avoid excluding the legitimate claims of patients for whom a cardiac catheterization was medically contraindicated. In my professional opinion, this alternative definition is medically appropriate and clinically sound.

(b) Exclusion of Potential Alternative Causes of PAH

37. For the purposes of this Settlement Agreement, we developed an algorithm that operationally incorporated accepted potential alternative causes of PAH.

(i) Potential Alternative Causes of PAH

38. This diagnostic algorithm includes medical conditions and factors that have some association with the development of PAH.

39. In my professional opinion, based on the relevant scientific literature and based on my personal clinical experience, this list is medically sound.

(ii) Process to Exclude Potential Alternative Causes

40. Under the Settlement Agreement, Claims Adjudicators will be required to determine whether Claimants are entitled to PPH benefits. First, the Claims Adjudicator will confirm whether a Product Recipient meets one of the definitions for a diagnosis of PAH discussed above.

41. After confirmation of a diagnosis of PAH, the Claims Adjudicator must determine whether any of the listed potential alternative cause(s) is/are the principal cause of the Product Recipient's PAH.

42. To streamline this analysis, the Medical Conditions List defines circumstances under which the listed conditions generally will not cause PAH and therefore will not bar compensation under this Settlement. Section 5.2.3 of the Medical Conditions List stipulates that if a Product Recipient's medical records reflect clinical findings that fall within the specifically defined parameters for the listed potential alternative causes, the listed potential alternative cause(s) will not be considered to be the principal cause (within the meaning of the Settlement

Agreement and Medical Conditions List) of the Product Recipient's PAH. If none of the potential alternative causes can be considered as the principal cause (within the meaning of the Settlement Agreement and Medical Conditions List) of the Product Recipient's PAH based on the parameters set forth in section 5.2.3, the claim will be approved.

43. If evidence of one or more of the listed potential alternative causes exists and cannot be ruled out as the principal cause (within the meaning of the Settlement Agreement and Medical Conditions List) of the Product Recipient's PAH by reference to the parameters set forth in section 5.2.3, the Claims Adjudicator must assess whether or not the alternative cause is the principal cause (within the meaning of the Settlement Agreement and Medical Conditions List) of the Product Recipient's PAH. Where the Claims Adjudicator determines that none of the potential alternative causes for the PAH is the principal cause (within the meaning of the Settlement Agreement and Medical Conditions List) of the Product Recipient's PAH, the claim will be approved.

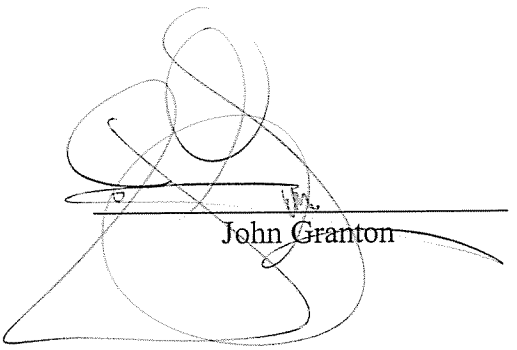
44. It is my professional opinion, based on my review of the applicable scientific literature and my personal clinical experience, that this diagnostic algorithm is medically sound and will advance the goal of providing benefits to legitimate claimants.

Conclusion

45. Based on my understanding of the relevant scientific literature, as well as my personal clinical experience in treating patients with PAH, it is my professional opinion that the approach taken in the MCL for defining the diagnostic and other criteria for qualification for PPH benefits under the Settlement Agreement is fair and reasonable and reflects parameters which are medically appropriate and generally accepted in the medical community.

46. I swear this affidavit in support of a motion for approval of the Settlement Agreement reached between the parties hereto and for no other purpose.

SWORN BEFORE ME at the City of Toronto, in the Province of Ontario, this 24th day of September, 2004.



John Granton

A Commissioner for Taking Affidavits

SUSAN ALLISON PHILLIPS, a Commissioner, etc., City of Toronto, for Rochon/Genova, Barristers and Solicitors. Expires November 27, 2005.