CANADA

PROVINCE OF QUEBEC
DISTRICT OF MONTREAL

NO: 500-06-000409-074

(Class Action)
SUPERIOR COURT

D. WOODS

and

R. PEPIN

Petitioners

-vs.-

GLAXOSMITHKLINE INC.

and

GLAXOSMITHKLINE PLC.

Respondents

**RE-AMENDED MOTION TO AUTHORIZE THE BRINGING OF A CLASS ACTION &
TO ASCRIBE THE STATUS OF REPRESENTATIVE
(Art. 1002 C.C.P. and following)**

TO THE HONOURABLE JUSTICE JEAN-PIERRE CHRÉTIEN OF THE SUPERIOR COURT, SITTING IN AND FOR THE DISTRICT OF MONTREAL, YOUR PETITIONERS STATE AS FOLLOWS:

1. Petitioners wish to institute a class action on behalf of the following class, of which they are members, namely:

    - all persons residing in Canada who have taken and/or purchased the drug rosiglitazone (sold under the brand name AVANDIA®, AVANDAMET®, and AVANDARYL®) since March 21st 2000 and their successors, assigns, family members, and dependants or any other group to be determined by the Court.

    Alternately (or as a subclass)

    - all persons residing in Quebec who have taken and/or purchased the drug rosiglitazone (sold under the brand name AVANDIA®,

AVANDAMET®, and AVANDARYL®) since March 21st 2000 and their successors, assigns, family members, and dependants or any other group to be determined by the Court.

Facts that give rise to an individual action of the part of the Petitioners against the Respondents

(2…) *replaced by paragraph 69*

(3…) *replaced by paragraph 70*

(4…) *replaced by paragraph 71*

(5…) *replaced by paragraph 72*

(6…) *replaced by paragraph 73*

(7…) *replaced by paragraph 130*

(8…) *replaced by paragraph 138*

The Respondents

9. Respondent GlaxoSmithKline Plc. is a British pharmaceutical company having its head office at 980 Great West Road, town of Brentford, county of Middlesex, Country of Great Britain, TW8 9GS, the whole as more fully appears from a copy of their website attached hereto as **Exhibit R-2**;

10. Respondent GlaxoSmithKline Plc. does business in Canada and Quebec through GlaxoSmithKline Inc., which has its principal place of business at 6455, Autoroute Trans-Canada, city of Saint-Laurent, Province of Quebec, H4S 1Z1, the whole as more fully appears from a copy of the Quebec Inspector General of Financial Institutions Report attached hereto as **Exhibit R-3**;

10.1 *(11…)* GlaxoSmithKline Inc. is an affiliate of GlaxoSmithKline Plc. and as such they have both, either directly or indirectly, performed any one of the commercial activities of designing, testing, manufacturing, labelling, packaging, assembling, advertising, marketing, promoting, branding, distributing, selling, and/or putting Avandia, Avandamet, and Avandaryl onto the marketplace in Canada and Quebec;

10.2 Given the close ties between the Respondents and considering the preceding, both Respondents are solidarily liable for the acts and omissions of the other. Unless the context indicates otherwise, both Respondents will be referred to as "GlaxoSmithKline" for the purposes hereof;

(11…) *replaced by paragraph 10.1*

(12…) *replaced by paragraph 105*

(13…) *replaced by paragraph 106*

(14…) *replaced by paragraph 107*

(15…) *replaced by paragraph 108*

(16…) *replaced by paragraph 109*

(17…) *replaced by paragraph 112*

(18…) *replaced by paragraph 124*

(19…) *replaced by paragraph 125*

(20…) *replaced by paragraph 126*

(21…)
a) *replaced by paragraph 130*
b) *replaced by paragraph 132*
c) *replaced by paragraph 135*

(22…)
a) *replaced by paragraphs 139a and 139c*
b) *replaced by paragraph 139d*
c) *replaced by paragraphs 139i and 139k*
d) *removed*
e) *replaced by paragraphs 139j, 139l, and 139m*
f) *replaced by paragraph 139n*
g) *replaced by paragraphs 139 u and 139v*

(23…) *replaced by paragraph 154*

(24…) *replaced by paragraph 141*

(25…) *replaced by paragraph 142*

(26…)
a) *replaced by paragraph 151*
b) *replaced by paragraph 152*
c) *replaced by paragraph 153*

(27…)
a) *replaced by paragraph 143*
b) *replaced by paragraph 149*
c) *replaced by paragraph 147*
d) *replaced by paragraph 150*

(28…) *replaced by paragraph 155*

Type 2 Diabetes

28. Type 2 diabetes is a chronic disease that has no cure. It is the most common form of diabetes, afflicting an estimated 2 million Canadians, 18 million Americans and 200 million people worldwide. Each year approximately 60,000 Canadians and 1.2 million Americans are diagnosed with the disease;

29. Diabetes occurs when the body does not produce enough insulin (a hormone needed to convert sugar and other food into energy) or cannot effectively use what it manages to produce. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems including heart disease, kidney damage, loss of limbs, and blindness. The main management objective of diabetes is to lower a patient's blood sugar to a normal level;

30. Patients with type 2 diabetes are at a high risk for fatal and non-fatal macrovascular events. These events are the main reason for their decreased life expectancy, which is about 8 years shorter in a 40 year old patient newly diagnosed with diabetes than in the general population;

31. Diabetes is also the leading cause of death by disease in Canada. The greatest long-term risk in diabetes is cardiovascular disease, being the cause of as much as 80% of mortality;

The Drugs

32. The class of drugs knows as thiazolidinediones (TZDs) are agonists of the peroxisome-proliferation-activated-receptor-gamma (PPAR-*γ*) which regulate transcription of a variety of genes encoding proteins involved in glucose homeostasis and lipid metabolism. Unlike conventional diabetes therapies that work by increasing insulin production, or lowering glucose production in the liver, TZDs help sensitize the fat and muscle cells to the action of the body's own natural insulin;

33. There are currently three (3) types of TZDs, namely:

    a. troglitazone (Rezulin)
    b. pioglitazone (Actos)
    c. rosiglitazone (Avandia)

34. The first from this class of drugs, troglitazone (Rezulin), was introduced in 1997 but withdrawn from the market in March 2000 owing to serious liver toxicity. The two (2) other thiazolidinediones, rosiglitazone (Avandia) and pioglitazone (Actos) remain as the only approved diabetes medicines known as insulin sensitizers;

35. By virtue of their efficacy in achieving glycemic control, pioglitazone and rosiglitazone are both widely used to treat patients with type 2 diabetes mellitus. They are intended to improve cardiovascular risk factors, such as insulin resistance, blood pressure, microalbuminuria and surrogate markers of cardiovascular disease such as serum C-reactive protein and carotid intimal thickness;

36. One difference between these two (2) drugs, is that rosiglitazone increases low density lipoprotein (LDL) cholesterol in contrast to pioglitazone where a decrease is observed;

37. Avandia's active ingredient is rosiglitazone maleate. It is a prescription medicine used for the management of type 2 (adult-onset or non-insulin dependant) diabetes mellitus (high blood sugar). Avandia was approved by the Food and Drug Administration (FDA) on May 25th 1999 and by Health Canada on March 21st 2000;

38. Avandamet combines Avandia with metformin in one single pill. It is also recommended and prescribed to treat type 2 diabetes mellitus. Avandamet was approved by the FDA on October 10th 2002 and by Health Canada on May 13th 2003;

39. Avandaryl combines Avandia with glimepiride in one single pill. It is also recommended and prescribed to treat type 2 diabetes mellitus. Avandaryl was approved by the FDA on November 23rd 2005 and by Health Canada some time after that;

40. Since the drug's approval, more than 7 million people worldwide have taken Avandia, generating sales worth $3 billion annually. In the year 2006, there were approximately 13 million prescriptions of Avandia filled in the United States and approximately 1.2 million prescriptions filled in Canada. The retail value of the prescriptions in Canada for the year 2006 was $156 million. A one-month supply of Avandia costs between $90 and $170;

The Studies

41. The studies that will be reviewed herein are intended to demonstrate that rosiglitazone seriously increases the risk of adverse cardiovascular events as compared to other anti-diabetic drugs (many of which cost less) and placebo. Further, that pioglitazone (the other TZD) has the opposite effect, in that it reduces a patient's overall risk of an adverse cardiovascular event;

42. On May 21st 2007, the New England Journal of Medicine published an article written by Steven Nissen MD and Kathy Wolski MPH entitled "Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from

Cardiovascular Causes", the whole as appears more fully from a copy of said journal article, produced herein as **Exhibit R-4**;

43. The authors set out to study the effect of anti-diabetic therapy on cardiovascular outcomes. To do this, they performed a meta-analysis of 42 trials found in published literature, the website of the FDA, and a clinical-trials registry maintained by GlaxoSmithKline;

44. The results of this study showed that when rosiglitazone was compared with a placebo or with other diabetic regimens, that it was associated with a:

- 43% increase in the risk of myocardial infarction
- 64% increase in the risk of cardiovascular death;

45. They also made the following relevant remarks:

> "The odds ratio for these shorter-term trials was similar to the overall results of the meta-analysis. Thus, in susceptible patients, rosiglitazone therapy may be capable of provoking myocardial infarction or death from cardiovascular causes after relatively short-term exposure.
> …
> The mechanism for the apparent increase in myocardial infarction and death from cardiovascular causes associated with rosiglitazone remains uncertain. One potential contributing factor may be the adverse effect of the drug on serum lipids. The FDA-approved rosiglitazone product label reports a mean increase in low-density lipoprotein (LDL) cholesterol of 18.6% among patients treated for 26 weeks with an 8-mg daily dose, as compared with placebo. In observational studies and lipid-lowering trials, elevated levels of LDL cholesterol were associated with an increase in adverse cardiovascular outcomes. Thus, an increase in LDL cholesterol of the magnitude observed in the rosiglitazone group may have contributed to adverse cardiovascular outcomes, although the rapidity and magnitude of the apparent hazard was not consistent with an effect produced by lipid changes alone.
> …
> The manufacturer's public disclosure of summary results for rosiglitazone clinical trials is not sufficient to enable a robust assessment of cardiovascular risks. The manufacturer has all the source data for completed clinical trials and should make these data available to an external academic coordinating center for systematic analysis. The FDA also has access to study reports and other clinical-trial data not within the public domain."

46. On June 5th 2007, the New England Journal of Medicine published an editorial written by David Nathan MD entitled "Rosiglitazone and

Cardiotoxicity", the whole as appears more fully from a copy of said journal article, produced herein as **Exhibit R-5**;

47. In this editorial, the author advises against the use of the drugs Avandia, Avandamet, and Avandaryl in the following manner:

> "With the continuing uncertainty regarding the safety of treatment with rosiglitazone, what should physicians and patients do? It is important to remember that there are now nine classes of antidiabetic medications available, including several older medications that are relatively efficacious in lowering glycated hemoglobin levels and are less expensive than the thiazolidinediones. Each class has a unique set of side effects and associated adverse events. Controlling glycemia by keeping glycated hemoglobin levels as close to the nondiabetic range as possible has been established as the primary goal of these medications, given the salutary results of intensive therapy as demonstrated in high-quality clinical trials. The results of clinical trials of the effects of glycemic control on microvascular complications in type 1 and type 2 diabetes, combined with the results of studies in animal models, have supported the maintenance of lower glycated hemoglobin levels as advantageous, regardless of the means used to achieve that control. However, now that we are faced with evidence that specific medication regimens used to treat type 2 diabetes may have an adverse macrovascular effect independent of achieved levels of glycated hemoglobin, this premise may be challenged.
> …
> Given the other choices of therapy available, including pioglitazone, which has limited clinical trial data suggesting a protective cardiovascular effect (albeit in a study that has been criticized for its design and its analysis), the answer should be no… Physicians may find it difficult to explain to patients why they are starting treatment with a potentially dangerous drug when other choices with longer and better safety records are available."

48. On August 3rd 2007, the journal Pharmacoepidemiology and Drug Safety published an article by Charles Gerrits PharmD, PhD et als. entitled "A comparison of pioglitazone and rosiglitazone for hospitalization for acute myocardial infarction in type 2 diabetes", the whole as appears more fully from a copy of said journal article, produced herein as **Exhibit R-6**;

49. The results of this study showed that pioglitazone (Actos), in comparison to rosiglitazone (Avandia) was associated with a:

- 22% relative risk reduction of myocardial infarction
- 15% relative risk reduction of the composite endpoint of myocardial infarction or coronary revascularization;

50. They also made the following relevant remarks:

> "Despite the fact that pioglitazone and rosiglitazone have similar glucose-lowering effects, differences in lipid metabolism have been demonstrated. In a direct comparator study in patients with type 2 diabetes, pioglitazone lowered triglycerides, while rosiglitazone increased triglycerides; furthermore, pioglitazone increased HDL cholesterol to a greater extent than rosiglitazone. In addition, favorable changes in LDL particle concentration and particle size have been observed with pioglitazone relative to rosiglitazone."

51. On September 12th 2007, the Journal of the American Medical Association published an article by Michael Lincoff MD et als. entitled "Pioglitazone and Risk of Cardiovascular Events in Patients with Type 2 Diabetes Mellitus", the whole as appears more fully from a copy of said journal article, produced herein as **Exhibit R-7**;

52. The authors' objective was to analyse whether pioglitazone had the same risk of adverse cardiovascular events as rosiglitazone. To accomplish this, they did a meta-analysis of 19 trials. The authors came to the following conclusions:

> "…this meta-analysis demonstrated that therapy with pioglitazone is associated with a significantly lower risk of death, myocardial infarction, or stroke among a broad population of patients with diabetes. The magnitude and direction of this protective effect of pioglitazone was homogeneous across trials of different durations ranging from 4 months to 3.5 years, across studies using a variety of control or concomitant diabetic therapies, and among trials of patients with or without established vascular disease. Consistent with previously observed effects of thiazolidinediones on edema, the incidence of serious heart failure was increased by pioglitazone, although without an associated increase in mortality. These findings suggest that the net clinical cardiovascular benefit with pioglitazone therapy is favorable, with an important reduction in irreversible ischemic events that is not attenuated by the risk of more frequent heart failure complications."

53. On September 12th 2007, the Journal of the American Medical Association published an article written by Sonal Singh MD et als. entitled "Long-term Risk of Cardiovascular Events With Rosiglitazone", the whole as appears more fully from a copy of said journal article, produced herein as **Exhibit R-8**;

54. The authors' objective was to systematically review only the long-term cardiovascular risk of rosiglitazone. They concluded that rosiglitazone significantly increased the risk of myocardial infarction and heart failure without a significant increase in risk of cardiovascular mortality;

55. They also made the following relevant remarks:

> "The current package insert for rosiglitazone is incomplete and outdated.
> …
> Decisions to approve or prescribe a drug should depend on the balance between the beneficial and harmful effects of that drug. The sum of favorable effects should be weighed against the sum of the unfavorable effects. In this review of rosiglitazone, we have summarized its reported adverse effects - an approximate doubling in risk of heart failure and a 42% increase in the risk of MI without any effect on cardiovascular mortality.
> …
> The cardiovascular differences between rosiglitazone and pioglitazone may be partly explained by a difference in effects on lipids and lipoprotein particles and subclass.
> …
> Another recent systematic review reported that older-generation agents (metformin and sulfonylureas) have superior effects on glycemic control, lipids, and other intermediate end points compared with the thiazolidinediones, without these detrimental adverse effects.
>
> Our findings have potential regulatory and clinical implications. These data suggest a reversal of the benefit-to-harm balance for rosiglitazone present at the time of approval. Thus, currently there appear to be much safer treatment alternatives. Regulatory agencies ought to reevaluate whether rosiglitazone should be allowed to remain on the market. Health plans and physicians should not wait for regulatory actions. They should avoid using rosiglitazone in patients with diabetes who are at risk of cardiovascular events, especially since safer treatment alternatives are available."

56. On December 12th 2007, the Journal of the American Medical Association published an article written by Lorraine L. Lipscombe MD, MSc et als. entitled "Thiazolidinediones and Cardiovascular Outcomes in Older Patients with Diabetes", the whole as appears more fully from a copy of said journal article, produced herein as **Exhibit R-9**;

57. The authors' objective was to study the rate of adverse cardiovascular events (in this case congestive heart failure, acute myocardial infarction, and mortality) with regard to older patients with diabetes when taking thiazolidinediones, primarily with rosiglitazone, as compared to other oral hypoglycemic treatments;

58. Most studies up until that point dealt with clinical trial samples and not with real-world populations. Those over the ages of 65 represent more than 40% of the population with diabetes, however, the majority of clinical trials involved

mostly persons 65 and younger. The present study involved patients aged 66 years or older with diabetes in Ontario;

59. The results of this study showed:

- 60% relative increase in heart failure
- 40% relative increase in heart attacks
- 30% relative increase in death;

60. The authors made the following comments:

> "Using population-based health care data, we found that TZD *(thiazolidinediones)* treatment was associated with a significant increase in the risks of CHF *(chronic heart failure)*, AMI *(acute myocardial infarction)*, and all-cause mortality among older persons with diabetes compared with other oral diabetes treatment. Moreover, the incremental risks associated with TZDs persisted even after adjustment for a number of important prognostic factors and were independent of baseline cardiovascular risk or diabetes duration. Treatment with TZDs was also associated with a higher risk of CHF and death regardless of whether it was used as monotherapy or in combination with other oral agents, further enhancing the argument for a causal relationship with these outcomes. Our findings argue against current labeling of TZDs that warns against use only in persons at high risk of CHF, as we did not identify any subgroup of older diabetes patients who may be protected from the adverse effects of TZDs.
> …
> The association between TZD treatment and cardiovascular events appeared to be limited to rosiglitazone. Our findings are consistent with recent studies that showed an increase in AMI risk and possibly death with rosiglitazone… Moreover, in contrast to clinical trial data, which suggest that both pioglitazone and rosiglitazone are associated with an increased risk of CHF, we observed this association only with rosiglitazone.
> …
> In summary, in this population-based study of older community-dwelling patients with diabetes, TZD treatment was associated with a significant increase in the risks of CHF, AMI, and death compared with other oral hypoglycemic agent treatments. These findings provide evidence from a real-world setting and support data from clinical trials that the harms of TZDs may outweigh their benefits, even in patients without obvious baseline cardiovascular disease."

61. On November 24th 2008, the Archives of Internal Medicine published an article written by Wolfgang Winkelmayer MD, ScD et als. entitled "Comparison of Cardiovascular Outcomes in Elderly Patients with Diabetes who Initiated Rosiglitazone vs Pioglitazone Therapy", the whole as appears

more fully from a copy of said journal article, produced herein as **Exhibit R-10**;

62. The purpose of this study was to evaluate the risks of cardiovascular events between rosiglitazone (Avandia) and pioglitazone (Actos) in elderly patients. The results of this study showed that the following risks were greater with rosiglitazone than with pioglitazone:

    - 15% greater mortality
    - 13% greater risk of congestive heart failure
    - No difference for the rates of myocardial infarction or stroke

63. The authors then go on to state that:

    > "Although caution needs to be applied in drawing any direct inference on the differences in cardiovascular safety between the 2 TZDs from these separate meta-analyses, an impression is left that rosiglitazone therapy may generate undue harm without any additional clinical benefit.
    > …
    > The current study leaves us with an unexpected dilemma. If rosiglitazone use increases all-cause mortality compared with pioglitazone but no differences in diagnosed MI and stroke are observed between these drugs, what is the mechanism for this harmful mortality effect? Because cardiovascular disease represents more than 75% of mortality in patients with diabetes, there must almost certainly be a link. We hypothesize that many of the deaths were due to MI or stroke. These presumably cardiovascular deaths in our cohort of elderly patients may have occurred suddenly or before the diagnosis was established. Thus, our findings suggest a higher cardiovascular case fatality rate for rosiglitazone. Unfortunately, because of the lack of information on cause of death in our cohort, we cannot formally examine this possibility."

64. On December 10th 2008, the Canadian Medical Association Journal published a commentary written by Lorraine L. Lipscombe MD, MSc entitled "Thiazolidinediones: Do harm outweigh benefits?", the whole as appears more fully from a copy of said journal article, produced herein as **Exhibit R-11**;

65. In this journal commentary, the author states that the risks of the drugs Avandia, Avandamet, and Avandaryl outweigh its benefits in the following manner:

    > "Given the growing evidence of harms, do the benefits of thiazolidinedione therapy still outweigh the risks? These drugs may improve glycemic control for patients who have achieved inadequate glycemic control with other hypoglycemic agents, particularly if insulin therapy is a less feasible

option. Moreover, there may be differences between rosiglitazone and pioglitazone with respect to cardiovascular risk. Regardless, both drugs are associated with a higher risk of heart failure and fracture. Therefore, the net benefit of thiazolidinedione therapy is unclear. Given that there are other effective drugs to control glycemia that are associated with fewer adverse events, thiazolidinediones should not be considered appropriate as first-line therapy for type 2 diabetes mellitus. If a patient is unable to take other therapies or if other therapies have failed, there may be a role for thiazolidinediones in carefully selected patients duly informed of the potential adverse effects. Considering that studies of pioglitazone have not shown the possible higher risk of myocardial infarction seen with rosiglitazone, but rather suggest a reduction in ischemic events, pioglitazone may be a safer option."

66.1 On August 18th 2009, the British Medical Journal published an article written by David Juurlink, division head, et als. entitled "Adverse cardiovascular events during treatment with pioglitazone and rosiglitazone: population based cohort study", the whole as appears more fully from a copy of said journal article, produced herein as **Exhibit R-27**;

66.2 The purpose of this study was to compare the risk of acute myocardial infarction, heart failure, and death in patients with type 2 diabetes treated with either rosiglitazone (Avandia) or pioglitazone (Actos). The patients were aged 66 years and older who were started on rosiglitazone or pioglitazone between April 1st 2002 and March 31st 2008. The results of this study showed that the following risks were reduced with pioglitazone as compared to rosiglitazone:

- 23% lower risk of congestive heart failure
- 14% lower risk of death
- No significance difference in risk of heart attack

The authors estimate that these results translate in a given year there would be one additional hospitalization for heart failure per 120 patients treated with Avandia rather than Actos, and one additional death would occur for every 269 patients treated with Avandia rather than Actos;

66.3 The authors then go on to state:

"In terms of absolute risk, we estimate that approximately one additional composite outcome would be expected to occur annually for every 93 patients treated with rosiglitazone rather than pioglitazone.
…
Using the population based healthcare records of approximately 40 000 patients who started treatment with a thiazolidinedione over a six year period, we found considerable differences in the risk of heart failure and

death between users of rosiglitazone and pioglitazone but no significant difference in the risk of myocardial infarction. Our findings suggest clinically important differences in the cardiovascular safety profiles of rosiglitazone and pioglitazone in clinical practice.

Adverse effects of a class of drugs (class effects) are common in clinical medicine, and recent studies highlighting the cardiovascular risks of rosiglitazone have naturally raised questions about the safety of pioglitazone. Consequently, patients and clinicians have been faced with difficult decisions on the use of these drugs, which are often prescribed to patients with type 2 diabetes whose response to other oral agents is suboptimal but who are reluctant to start insulin. Our study provides direct evidence in otherwise comparable patients that pioglitazone is associated with a lower risk of adverse cardiovascular events and death than is rosiglitazone.

Why pioglitazone might be safer than rosiglitazone is not fully understood, but the possibility is supported by converging lines of evidence. Pioglitazone has more favourable effects on serum lipids than does rosiglitazone, and some evidence suggests that it also imparts anti-inflammatory and anti-atherogenic effects. Rosiglitazone is a far more potent agonist of PPARγ than is pioglitazone, and activation of PPARγ in the kidney seems to be an important mechanism of thiazolidinedione induced salt and water retention. These observations may explain the higher risk of heart failure with rosiglitazone, and we speculate that they also underlie the increased risk of death in patients taking the drug. Unlike rosiglitazone, pioglitazone has been found to significantly reduce ischaemic cardiovascular outcomes in a large randomised trial and a corresponding meta-analysis. Furthermore, although observational studies have reached differing conclusions about the relative safety of the thiazolidinediones, no studies have suggested a safety advantage for rosiglitazone.
…
In a large cohort of older patients starting treatment with a thiazolidinedione, we found that pioglitazone was associated with a lower risk of adverse cardiovascular events and death than was rosiglitazone. Given the accumulating evidence of harm with rosiglitazone treatment and the lack of a distinct clinical advantage for the drug over pioglitazone, questioning whether ongoing use of rosiglitazone is justified in any circumstance is reasonable. Pending the availability of additional data on the benefits and harms of these drugs and a clarification of their role in the pharmacotherapy of type 2 diabetes, we believe that clinicians should re-evaluate the appropriateness of new or ongoing treatment with rosiglitazone."

The Fall Out

66. Not surprisingly, immediately after the publication of Nissen's article (Exhibit R-4), prescriptions of Avandia in the United States dropped by approximately 10% overall and new prescriptions dropped by approximately 40%. Sales of Avandia have continued to plunge steadily ever since. In the United States, GlaxoSmithKline saw a 26% decline in sales during 2007 and reported a 56% decrease in sales for the first quarter of 2008. In terms of sales for Avandia, GlaxoSmithKline saw a decrease from approximately $2.3 billion USD in 2006 to $1.4 billion USD in 2007 and a plummet to $500 million USD in 2008;

67. In 2008, the American Diabetes Association and the European Association for the Study of Diabetes unanimously advised against using rosiglitazone (Avandia) as a treatment for type 2 diabetes;

The United States

68. *(2…)* Following the release of Dr. Nissen's article (Exhibit R-4) and for many months afterwards, several class action and individual actions (over 100) were taken against GlaxoSmithKline in various United States courts. A copy of some of these class action complaints are produced herein as **Exhibits R-1**, **R-1b**, and **R-1c**. These actions have been consolidated into the United States District Court, Eastern District of Pennsylvania before the Honourable Justice Cynthia Rufe in court file number 2:07-md-01871;

69. *(3…)* In general, these actions contend that (…) GlaxoSmithKline continued to market, sell and distribute it's diabetes drug Avandia (rosiglitazone) to unsuspecting diabetics despite having access to results from numerous trials indicating that patients using the drug suffered from a 43% higher risk of a heart attack and a 64% increased risk of cardiovascular death;

70. *(4…)* Also, that GlaxoSmithKline itself did a "meta-analysis" of numerous studies that showed that Avandia was associated with a 31% higher risk of adverse cardiovascular events, such as heart attacks;

71. *(5…)* Despite GlaxoSmithKline's longstanding knowledge of these dangers, Avandia's label only warns about possible heart failure and other heart problems when taken with insulin. Respondents failed to warn and disclose to consumers that Avandia significantly increased the risk of adverse cardiovascular events;

72. *(6…)* Therefore, Avandia users have suffered (…) physical, emotional, and financial injuries or are potentially at risk for such injuries;

The Food and Drug Administration

73. Following the release of Dr. Nissen's article (Exhibit R-4), the FDA made a number of decisions regarding the future of the drugs Avandia, Avandamet, and Avandaryl;

74. On May 21st 2007, the FDA immediately released a Safety Alert to the public to alert them that:

> "Recently, the manufacturer of Avandia provided the FDA with a pooled analysis (meta analysis) of 42 randomized, controlled clinical trials in which Avandia was compared to either placebo or other anti-diabetic therapies in patients with type 2 diabetes. The pooled analysis suggested that patients receiving short-term (most studies were 6-months duration) treatment with Avandia may have a 30-40 percent greater risk of heart attack and other heart-related adverse events than patients treated with placebo or other anti-diabetic therapy. These data, if confirmed, would be of significant concern since patients with diabetes are already at an increased risk of heart disease."

the whole as appears more fully from a copy of said Safety Alert, produced herein as **Exhibit R-12**;

75. Internal discussions within the FDA then took place to decide the future of Avandia, Avandamet, and Avandaryl. The FDA's Drug Safety Office felt that the risks of these drugs outweighed their benefit and recommended their withdrawal from the market. The joint meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee acknowledged the findings that the drugs increase the risk of adverse cardiovascular events, however, they voted in favour of not removing rosiglitazone from the market and instead to change the warning associated with these drugs. The Drug Safety Oversight Board was divided on the issue;

76. The FDA itself finally decided that the risk of adverse cardiovascular events was very serious and needed to be addressed in various labelling changes including the strongest warning available, a "black box" warning. The FDA also reached an agreement with GlaxoSmithKline with regard to long term studies of the drugs and their comparison with other oral anti-diabetic agents such as pioglitazone to determine the drugs' cardiovascular safety;

77. On August 14th 2007, the FDA and GlaxoSmithKline agreed to the wording of their new "black box" warning in the following manner:

WARNING: CONGESTIVE HEART FAILURE
● Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients (see WARNINGS). After initiation of AVANDIA, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of AVANDIA must be considered.
● AVANDIA is not recommended in patients with symptomatic heart failure. Initiation of AVANDIA in patients with established NYHA Class III or IV heart failure is contraindicated.
(See CONTRAINDICATIONS and WARNINGS.)

the whole as appears more fully from a copy of said letter and label, produced herein as **Exhibit R-13**;

78. On November 14th 2007, the FDA and GlaxoSmithKline agreed to the modified wording of the "black box" warning in the following manner:

WARNING: CONGESTIVE HEART FAILURE AND MYOCARDIAL ISCHEMIA
● Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients (5.1). After initiation of AVANDIA, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of AVANDIA must be considered.
● AVANDIA is not recommended in patients with symptomatic heart failure. Initiation of AVANDIA in patients with established NYHA Class III or IV heart failure is contraindicated. (4, 5.1)
● A meta-analysis of 42 clinical studies (mean duration 6 months; 14,237 total patients), most of which compared AVANDIA to placebo, showed AVANDIA to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction. Three other studies (mean duration 41 months; 14,067 patients), comparing AVANDIA to some other approved oral antidiabetic agents or placebo, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive. (5.2)

the whole as appears more fully from a copy of said letter and label, produced herein as **Exhibit R-14**;

79. A copy of Avandia's label just prior to the addition of the "black box" warning is attached hereto as **Exhibit R-15**;

Health Canada

80. Following the release of Dr. Nissen's article (Exhibit R-4), Health Canada made a number of decisions regarding the future of the drugs Avandia, Avandamet, and Avandaryl;

81. On May 30th 2007, GlaxoSmithKline in conjunction with Health Canada released a Public Communication regarding safety information on Avandia, Avandamet, and Avandaryl stating:

> "An article recently published in the New England Journal of Medicine (NEJM) has raised concern about an increased risk of myocardial infarction (heart attack) and cardiovascular death in patients with type 2 diabetes treated with Avandia®. This article was based on a review of 42 clinical studies. The conclusions reached require confirmation. Further investigation of these results is underway and more information will be communicated when available."

the whole as appears more fully from a copy of said Public Communication, produced herein as **Exhibit R-16**;

82. On June 1st 2007, GlaxoSmithKline in conjunction with Health Canada disseminated to health care professionals information regarding the cardiac safety of Avandia, Avandamet, and Avandaryl stating:

> "An article in the New England Journal of Medicine (NEJM) on May 21, 2007, has generated significant public attention on the cardiac safety of Avandia®, Avandamet® and Avandaryl™. The Nissen & Wolski article, based on a meta-analysis of 42 clinical studies, noted a statistically significant increased risk of myocardial infarction (OR 1.43, CI 1.03-1.98, p = 0.03) and a statistically non-significant increase in the risk of cardiovascular death (OR 1.64, CI 0.98-2.74, p = 0.06) associated with the use of rosiglitazone in comparison to the use of a placebo or other anti-diabetic therapies.
>
> The conclusions reached require confirmation. Analysis of all currently available data is ongoing and findings will be communicated when review is complete."

the whole as appears more fully from a copy of said Communiqué, produced herein as **Exhibit R-17**;

83. On November 1st 2007, GlaxoSmithKline in consultation with Health Canada announced to health care professionals that, further to Health Canada's assessment of adverse event reports, published articles and other available information on congestive heart failures, myocardial infarction, and related

events, that there would be important new restrictions on the treatment of type 2 diabetes with rosiglitazone-containing products Avandia, Avandamet, and Avandaryl and that the Canadian Product Monographs would be updated in consequence, the whole as appears more fully from a copy of said Communiqué, produced herein as **Exhibit R-18;**

84. The changes included:

> "• Rosiglitazone (AVANDIA®) is no longer approved as monotherapy for type 2 diabetes, except when metformin use is contraindicated or not tolerated.
>
> • Rosiglitazone is no longer approved for use in combination with a sulfonylurea, except when metformin is contraindicated or not tolerated.
>
> • Treatment with all rosiglitazone products is now contraindicated in patients with any stage of heart failure (i.e., NYHA Class I, II, III or IV)."

85. On November 6th 2007, GlaxoSmithKline in consultation with Health Canada announced to the public that, based on a Health Canada's review of information available on cardiovascular safety, that there would be important new restrictions on which patients with type 2 diabetes can use rosiglitazone containing products and that the consumer section's official Canadian Product Monographs for rosiglitazone-containing products were being updated in consequence, the whole as appears more fully from a copy of said Public Communication, produced herein as **Exhibit R-19;**

86. The changes included:

> "• Rosiglitazone (Avandia®) is no longer approved for use alone to treat type 2 diabetes, except when metformin* use is contraindicated or not tolerated.
>
> • Rosiglitazone is no longer approved for use with a sulfonylurea drug** (such as glyburide), except when metformin is contraindicated or not tolerated.
>
> • Rosiglitazone should not be used if you have heart failure, or have experienced heart failure in the past.
>
> • Patients who are taking rosiglitazone, especially those with underlying heart disease, or those who are at high risk of heart attack or heart failure, should talk to their doctor about the benefits and risks of continuing rosiglitazone therapy."

87. Essentially, Health Canada has withdrawn approval of rosiglitazone for most previous indications. Health Canada has withdrawn approval of Avandia as a stand-alone therapy, except for patients who can't tolerate older diabetes drugs. As well, Health Canada has said that Avandia should be used only in combination with certain other drugs for hard-to-control blood sugar and not for diabetics with current or past heart failure;

Defendants' Prior Knowledge

88. The same day that Nissen's article (Exhibit R-4) was release (May 21st 2007), GlaxoSmithKline attempted to refute the findings that their drugs were harmful in an effort to not lose their market share. In their press release they state:

> "GSK strongly disagrees with the conclusions reached in the NEJM article, which is based on incomplete evidence and a methodology that the author admits has significant limitations."

the whole as appears more fully from a copy of said Press Release, produced herein as **Exhibit R-20;**

89. Despite these remarks, GlaxoSmithKline performed its own meta-analyses regarding the safety of Avandia in the years 2005 (study number ZM2005/00181/01) and 2006 (study number HM2006/00497/00 / WEUSRTP866) and found hazard ratios similar to Nissen (Exhibit R-4). More specifically, GlaxoSmithKline found an excess risk of ischemic cardiovascular events associated with the use of Avandia of 29% and 31% respectively;

90. On June 6th 2007, Moncef Slaoui PhD, chairman of research and development of GlaxoSmithKline testified before the United States House Committee on Oversight and Government reform, the whole as appears more fully from a copy of said statement, produced herein as **Exhibit R-21**;

91. Dr. Slaoui had the following comments to make regarding GlaxoSmithKline's previous studies into Avandia:

> "In September, 2005, results from the first meta-analysis became available. This meta-analysis, which pooled data from 37 clinical trials completed prior to September, 2004, compared 6976 patients on Avandia® and 4610 patients on other treatment regimens including no treatment, metformin, sulfonylureas, and insulin. This analysis showed an overall incidence of ischemic cardiovascular events of 2.24% in Avandia® patients versus 1.71% in the pooled comparison group. This equates to a non-statistically significant estimate of excess risk of ischemic cardiovascular events of 29% associated with the use of Avandia®. The data from this first meta-analysis were officially communicated to the FDA in October, 2005, as well as to the independent Data Safety Monitoring

Boards of the various ongoing clinical trials with Avandia®. This potential excess cardiovascular risk prompted GSK to perform a second meta-analysis as well as a separate epidemiologic study, called the Balanced Cohort Study, and both studies were initiated in January, 2006.

The second meta-analysis, that was initiated in January, 2006, was conducted in order to include 5 studies that had finished between September, 2004, and August, 2005. This second analysis included a total of 42 separate randomized clinical trials that compared 8,604 patients on Avandia® and 5,633 patients on other treatment programs. The results were reviewed in March, 2006. The overall incidence of cardiovascular events was 1.99% in Avandia® patients versus 1.51% in the pooled comparison group, with a hazard ratio of 1.31. This equates to a statistically significant excess risk of ischemic events of 31% associated with the use of Avandia®. This hazard ratio is in the same direction as the NEJM article's meta-analysis.";

92. On January 14th 2009, the Wall Street Journal published a newspaper article entitled "Glaxo's Emails on Avandia Reveal Concern", the whole as appears more fully from a copy of said newspaper article, produced herein as **Exhibit R-22**;

93. In this article, it was revealed that GlaxoSmithKline obtained an early copy of Dr. Nissen's journal article (Exhibit R-4) before it was to be published in the New England Journal of Medicine. The Wall Street Journal makes the following remark with regard to this situation:

> « The study by Dr. Nissen for the New England Journal was supposed to be kept under wraps until its release on May 21, but Glaxo obtained a copy on May 3 from a doctor, Steven Haffner of the University of Texas, who was reviewing it for the medical journal. Dr. Haffner had been a Glaxo consultant on Avandia since 2000 and received $433,000 from Glaxo between 2000 and August 2007. He confirms giving Glaxo the study, though he says doing so was a "terrible mistake." »

94. In consequence, GlaxoSmithKline was able to review the journal article before it was published and comment on it. The Wall Street Journal makes the following remarks with regard to this situation:

> « "The numbers are the numbers, the analysis is very similar to our own," wrote the company's consultant in an email days before the study was published in the New England Journal of Medicine. He added that Glaxo couldn't "undermine" the figures but might find a way to explain them. »
> …
> « In a May 8, 2007, email, Moncef Slaoui, the director of Glaxo research, told several executive: "FDA, Nissen and GSK all come to comparable

conclusions regarding increased risk for ischemic events, ranging from 30% to 43%!" »

95. Since that time, it has been reported that GlaxoSmithKline has, on at least two (2) separate occasions, successfully suppressed and concealed from the public, the medical community, and government regulatory bodies, the true nature and extent of the risks associated with rosiglitazone;

96. In November 2007, the ranking member of the United States Senate Committee on Finance, Senator Chuck Grassley, released a report entitled "The Intimidation of Dr. John Buse and the Diabetes Drug Avandia", which was based on an intensive review of documents provided by GlaxoSmithKline, the whole as appears more fully from a copy of said report, produced herein as **Exhibit R-23**;

97. Dr. John Buse was the 2009 president of medicine and science of the American Diabetes Association (ADA). He is a diabetes expert and head of endocrinology at the University of North Carolina, Chapel Hill. In the year 1999, he was involved as an investigator in a rosiglitazone study and later gave a number of speeches at scientific meetings where he opined that rosiglitazone may carry adverse cardiovascular risks;

98. The report goes on to state:

« However, internal company documents seem to contradict that claim and reveal what appears to be an orchestrated plan to stifle the opinion of Dr. John Buse, a professor of medicine at the University of North Carolina who specializes in diabetes.

In particular, GSK's attempt at intimidation appears to have been triggered by speeches that Dr. Buse gave at scientific meetings in 1999. During those meetings, Dr. Buse suggested that, aside from its benefit of controlling glucose levels in diabetics, Avandia may carry cardiovascular risks.

The effect of silencing this criticism is, in our opinion, extremely serious. At a July 30, 2007, safety panel on Avandia, FDA scientists presented an analysis estimating that Avandia caused approximately 83,000 excess heart attacks since coming on the market.

Had GSK considered Avandia's increased cardiovascular risk more seriously when the issue was first raised in 1999 by Dr. Buse, instead of trying to smother an independent medical opinion, some of these heart attacks may have been avoided.

According to documents provided to the Committee by, among others,

GSK, and the University of North Carolina, it is apparent that the original allegations, regarding Dr. Buse and GSK's attempts at silencing him are true; according to relevant emails, GSK executives labeled Dr. Buse a "renegade" and silenced his concerns about Avandia by complaining to his superiors and threatening a lawsuit.

Even more troubling, documents reveal that plans to silence Dr. Buse involved discussions by executives at the highest levels of GSK, including then and current CEO Jean-Pierre Garnier. Also, GSK prepared and required Dr. Buse to sign a letter claiming that he was no longer worried about cardiovascular risks associated with Avandia. After Dr. Buse signed the letter, GSK officials began referring to it as Dr. Buse's "retraction letter." Documents show that GSK intended to use this "retraction letter" to gain favor with a financial consulting company that was, among other things, evaluating GSK's products for investors. After cutting short Dr. Buse's criticism, GSK executives then sought to bring Dr. Buse back into GSK's favor.

While publicly silent subsequent to signing the "retraction letter," Dr. Buse still remained troubled about Avandia and its possible risks. Years later, he wrote a private email to a colleague detailing the incident with GSK:

> [T]he company's leadership contact[ed] my chairman and a short and ugly set of interchanges occurred over a period of about a week ending in my having to sign some legal document in which I agreed not to discuss this issue further in public.

Dr. Buse ended the email, "I was certainly intimidated by them…. It makes me embarrassed to have caved in several years ago." »

99. On November 18th 2008, the Wall Street Journal published a newspaper article entitled "Doctors Claim Glaxo Dismissed Worries on Avandia", in which the situation of congestive heart failure caused by Avandia was brought to the attention of GlaxoSmithKline in the year 2000 by a Dr. Mary Money of Hagerstown, Maryland, the whole as appears more fully from a copy of said newspaper article, produced herein as **Exhibit R-24**;

100. The Wall Street Journal makes the following remarks with regard to this situation:

« Dr. Money talked recently about a patient who came to her in 1999 with congestive heart failure. "That fall, I had a woman patient with massive fluid overload and such shortness of breath that she had to sit up at night," she said.

The patient had begun taking Avandia two weeks earlier, and an echocardiogram showed high pressure in the arteries of the lungs. Dr. Money said she took the patient off the drug, and within a few days the symptoms almost disappeared.

In the next few months, Dr. Money and the head of the hospital's diabetes center, Stephen Lippman, found other patients who had similar symptoms.

Dr. Money alerted SmithKline Beecham, the name of the drug maker before a 2001 merger. The company met with her and Dr. Lippman at Washington County Hospital in Hagerstown in April 2000.

The two doctors presented data on 85 of their patients who had used Avandia, according to documents from the meeting. More than half of the patients had significant edema, or swelling, and about half of that group also had high pulmonary pressure and shortness of breath. Three had been hospitalized for congestive heart failure.

The meeting was a waste of time, Dr. Money said. "They came to tell us how wrong we were, not to listen," she said.

Meanwhile, a company consultant who called into the meeting from the University of Pennsylvania dismissed the Hagerstown doctors' echocardiograms as too poor to show anything useful.

"They suggested we were country bumpkins, and practically said, 'Don't worry your pretty heads. We have smarter people than you looking at this, and there's no problem,'" recalled Dr. Lippman, a physician who also holds a doctorate in molecular biology.

A GlaxoSmithKline spokeswoman, Mary Ann Rhyne, said Dr. Money's theories were "unsubstantiated" and she was misinterpreting journal articles to support her case.

The next month, two SmithKline executives wrote to the hospital's chief of staff, calling on him to stop Dr. Money from talking about her concerns to other hospital doctors.

"[W]e respectfully ask that your hospital not involve itself in the dissemination of information which has not been substantially verified, and that you take immediate steps to stop the dissemination of this unsubstantiated information to your medical staff," said the letter, signed by two SmithKline executives, which was viewed by The Wall Street Journal. »

Respondents' Liability

101. Although the drugs Avandia, Avandamet, and Avandaryl are marketed and sold to reduce diabetic patients' risk of adverse cardiovascular events, they actually increase it;

102. A reasonably prudent drug manufacturer, seller, or distributor in GlaxoSmithKline's position would have withdrawn the drugs Avandia, Avandamet, and Avandaryl from the market, never placed it on the market to begin with, or adequately warned of the risks associated with its use;

103. GlaxoSmithKline failed to exercise reasonable care and/or were negligent in the design, manufacture, testing, processing, marketing, advertising, labelling, assembling, branding, distribution, and/or sale of Avandia, Avandamet, and Avandaryl in one or more of the following respects:

    a. they knew, or should have known, that the drugs Avandia, Avandamet, and Avandaryl increased the risk of adverse cardiovascular events and/or carried the risk of serious, life-threatening side effects;

    b. they failed to ensure that the drugs Avandia, Avandamet, and Avandaryl were not dangerous to consumers and that the drugs were fit for their intended purpose and of merchantable quality;

    c. they failed to conduct appropriate testing to determine whether and to what extent the ingestion of Avandia, Avandamet, and Avandaryl poses serious health risks, including adverse cardiovascular events;

    d. they failed to adequately test the products prior to placing them on the market;

    e. they failed to adequately test the drugs Avandia, Avandamet, and Avandaryl in manner that would fully disclose the various side effects and the magnitude of the risks associated with its use;

    f. they failed to use care in designing, developing and manufacturing their products so as to avoid posing unnecessary health risks to users of such products;

    g. they failed to conduct adequate pre-clinical and clinical testing, post-marketing surveillance and follow-up studies to determine the safety of the drugs;

h. they failed to advise that the consumption of the drugs Avandia, Avandamet, and Avandaryl could result is severe and disabling side effects, including but not limited to, heart injury, heart attacks and death;

i. they failed to advise the medical and scientific communities of the potential to increase the risk for severe and disabling side effects, including but not limited to, heart injury, heart attacks and death;

j. they failed to provide timely and/or adequate warnings about the increased potential health risks associated with the use of the drugs Avandia, Avandamet, and Avandaryl;

k. they failed to provide the class members and their physicians with adequate warnings of inherent risks associated with Avandia, Avandamet, and Avandaryl;

l. they failed to provide the class members and their physicians with adequate information and warnings respecting the correct usage of Avandia, Avandamet, and Avandaryl

m. they failed to provide adequate updated and current information to class members and their physicians respecting the risks of Avandia, Avandamet, and Avandaryl as such information became available;

n. they failed to provide prompt warnings of potential hazards of Avandia, Avandamet, and Avandaryl in the products' monograph and in the products' labelling;

o. they failed to warn that class members and their physicians that the risks associated with Avandia, Avandamet, and Avandaryl would exceed the risks of other available diabetes medications;

p. they failed to warn the class members and their physicians about the need for comprehensive regular medical monitoring to ensure early discovery of potentially fatal cardiovascular events;

q. after receiving actual or constructive notice of problems with Avandia, Avandamet, and Avandaryl, they failed to issue adequate warnings, publicize the problem and otherwise act properly and in a timely manner to alert the public, the class members and their physicians, of the drugs' inherent dangers;

r. they failed to establish any adequate procedures to educate their sales representatives and prescribing physicians respecting the risks associated with the drugs;

s. they falsely stated and/or implied that Avandia, Avandamet, and Avandaryl were safe and fit for its intended purpose when they knew or ought to have known that these representations were false;

t. they misstated the state of research, opinion and medical literature pertaining to the purported benefits of Avandia, Avandamet, and Avandaryl and their associated risks;

u. they disregarded reports of symptoms of adverse cardiovascular events among patients who participated in clinical trials of Avandia, Avandamet, and Avandaryl;

v. they failed to accurately and promptly disclose to Health Canada information relating to increased cardiovascular risks associated with Avandia, Avandamet, and Avandaryl and to modify Avandia, Avandamet, and Avandaryl product monograph and product labelling accordingly in a timely manner or at all;

w. they failed to monitor and to initiate a timely review, evaluation and investigation of reports of adverse cardiovascular events associated with Avandia, Avandamet, and Avandaryl in Canada and around the world;

x. they failed to properly investigate cases of adverse cardiovascular events caused by Avandia, Avandamet, and Avandaryl;

y. they deprived patients of a chance for safe, effective and/or successful treatment at a lower cost;

z. in all of the circumstances of this case, they applied callous and reckless disregard for the health and safety of their consumers;

Petitioners Situations

D. WOODS

104. *(12…)* Petitioner WOODS is a 63 year old woman who had been taking Avandia since (…) 2006 to reduce her blood-sugar level, the whole as appears more fully from a copy of an extract of her pharmacy record, produced herein as **Exhibit R-25**;

105. *(13…)* At no time was Petitioner made aware by the Respondents of the true risks associated with taking Avandia, more specifically that it causes or exacerbates the risk of adverse cardiovascular events;

106. *(14…)* Since taking Avandia, she now suffers from heart palpitations and shortness of breath; she is constantly winded, even while performing minor strenuous activities (i.e. walking up the stairs, etc…);

107. *(15…)* In the year 2007, she discovered that Avandia increases her risk of adverse cardiovascular events and has abandoned taking said drug, opting instead to take Metformin;

108. *(16…)* Petitioner would not have taken Avandia if the Respondents had properly disclosed the risks and benefits of taking this medication;

109. Petitioner is at risk of developing more pronounced health problems in the near future;

110. Petitioner's damages are a direct and proximate result of her use of the drug Avandia and Respondents' negligence and/or a lack of adequate warnings;

111. *(17…)* In consequence of the foregoing, Petitioner is justified in claiming damages;

R. PEPIN

112. Petitioner PEPIN is a 54 year old man who began taking Avandia on or about June 2005 to reduce his blood-sugar level, the whole as appears more fully from a copy of a pharmacy receipt, produced herein as **Exhibit R-26**;

113. At no time was Petitioner made aware by the Respondents of the true risks associated with taking Avandia, more specifically that it causes or exacerbates the risk of adverse cardiovascular events;

114. In December 2005, Petitioner began to suffer from major fluid retention; he gained approximately 50 pounds within this period;

115. At the end of December 2005, Petitioner was prescribed a diuretic to reduce the fluid retention, which did not work;

116. In January 2006, Petitioner's situation was so grave that was forced to go to the emergency room, where he was informed that he was suffering from congestive heart failure and kidney problems;

117. Petitioner has undergone aggressive dobutamine treatments at the coronary care unit until finally his kidneys have completely failed him; Petitioner is now on dialysis treatments and is waiting a transplant; Petitioner now suffers from class 2 heart failure;

118. Petitioner abandoned the drug Avandia and now uses Metformin; nevertheless, he is no longer able to work;

119. Petitioner would not have taken Avandia if the Respondents had properly disclosed the risks and benefits of taking this medication;

120. Petitioner is at risk of developing more pronounced health problems in the near future;

121. Petitioner's damages are a direct and proximate result of his use of the drug Avandia and Respondents' negligence and/or a lack of adequate warnings;

122. In consequence of the foregoing, Petitioner is justified in claiming damages;

Facts giving rise to an individual action by each of the members of the class

123. *(18…)* Every member of the class has either ingested and/or purchased Avandia, Avandamet, and/or Avandaryl or is the successor, family member, assign, and/or dependant of a person who purchased and/or ingested one of the aforementioned drugs;

124. *(19…)* The class members' damages would not have occurred but for the acts and/or omissions of the Respondents in failing to ensure that the drugs Avandia, Avandamet, and Avandaryl were safe for use or, in the alternative, for failing to provide adequate warning of the risks associated with using Avandia, Avandamet, and Avandaryl to class members and to their physicians;

125. *(20…)* In consequence of the foregoing, each member of the class is justified in claiming at least one or more of the following as damages:

    a. physical and mental injuries, including pain, suffering, anxiety, fear, loss of quality and enjoyment of life, increased risk of health problems, and reduction of life expectancy;

    b. out-of-pocket expenses incurred or to be incurred, including those connected with hospital stays, medical treatment, life care, medications, medical monitoring services, and the diagnosis and treatment of Avandia, Avandamet, and Avandaryl side effect services;

    c. loss of income and loss of future income;

    d. refund of the purchase price of Avandia, Avandamet, and Avandaryl or alternately, the incremental costs of Avandia, Avandamet, and

Avandaryl as paid for by class members and/or by the *Régie de l'assurance maladie du Québec*, the Ontario Health Insurance Plan, and other provincial health insurers;

e. disgorgement of all profits earned by the Respondents from the sale of the drugs Avandia, Avandamet, and Avandaryl;

f. punitive damages;

126. As a direct result of the Respondents' conduct, the patients' family members, and dependants have, had, and/or will suffer damages and loss, including:

a. out of pocket expenses, including paying or providing nursing, housekeeping and other services;

b. loss of income and loss of future income;

c. loss of support, guidance, care, consortium, and companionship that they might reasonably have expected to receive if the injuries had not occurred;

127. Some of the expenses related to the medical treatment that the class members have undergone or will undergo, will have been borne by the various provincial health insurers, including the *Régie de l'assurance maladie du Québec* and the Ontario Health Insurance Plan. As a result of the Respondent's conduct, these various provincial health insurers have suffered and will continue to suffer damages for which they are entitled to be compensated by virtue of their right of subrogation in respect to all past and future insured services. These subrogated interests are asserted by the Petitioners and the class members;

128. All of these damages to the class members are a direct and proximate result of the use of Avandia, Avandamet, and Avandaryl and Respondents' negligence and/or a lack of adequate warnings;

The composition of the class renders the application of articles 59 or 67 C.C.P. difficult or impractical

129. *(7…, 21a…)* Rosiglitazone has been sold in Quebec and Canada since March 21st 2000, whether in the form of Avandia, Avandamet, or Avandaryl. Petitioners are unaware of the specific number of persons who took and/or purchased these drugs, however, based on the Respondents' sales figures and the number of prescriptions issued, it is safe to estimate that it is in the tens of thousands (if not hundreds of thousands);

130. Class members are numerous and are scattered across the entire province and country;

131. *(21b…)* Petitioners have no way of knowing the names and addresses of potential class members due to the confidential nature of medical and pharmacy records;

132. In addition, given the costs and risks inherent in an action before the courts, many people will hesitate to institute an individual action against the Respondents. Even if the class members themselves could afford such individual litigation, the court system could not as it would be overloaded. Further, individual litigation of the factual and legal issues raised by the conduct of Respondents would increase delay and expense to all parties and to the court system;

133. Also, a multitude of actions instituted in different jurisdictions, both territorial (different provinces) and judicial districts (same province), risks having contradictory judgements on questions of fact and law that are similar or related to all members of the class;

134. *(21c…)* These facts demonstrate that it would be impractical, if not impossible, to contact each and every member of the class to obtain mandates and to join them in one action;

135. In these circumstances, a class action is the only appropriate procedure for all of the members of the class to effectively pursue their respective rights and have access to justice;

The questions of fact and law which are identical, similar, or related with respect to each of the class members with regard to the Respondents and that which the Petitioners wish to have adjudicated upon by this class action

136. Individual questions, if any, pale by comparison to the numerous common questions that predominate;

137. *(8…)* The damages sustained by the class members flow, in each instance, from a common nucleus of operative facts, namely, Respondents' misconduct;

138. The recourses of the members raise identical, similar or related questions of fact or law, namely:

    a. *(22a…)* Do Avandia, Avandamet, and Avandaryl cause, exacerbate, or contribute to adverse cardiovascular events, including but not limited

to, chest pain, acute myocardial infarction, chronic heart failure, ischemic heart disease, angina, stroke and death?

b. Were the Respondents negligent and/or did they fail in their duty of safety, duty of care, and/or duty to inform imposed upon them as manufacturers, distributers and/or sellers of Avandia, Avandamet, and Avandaryl?

c. *(22a…)* Were Avandia, Avandamet, and Avandaryl created and designed with defects that increase a patient's risk of adverse cardiovascular events?

d. *(22b…)* Do Avandia, Avandamet, and Avandaryl increase a patient's risk of adverse cardiovascular events as a result of their defects?

e. Are Avandia, Avandamet, and Avandaryl unfit for the purpose for which they were intended?

f. Do Avandia, Avandamet, and Avandaryl possess a superior efficacy over other treatments of type 2 diabetes available on the market?

g. Do the risks associated with the use of Avandia, Avandamet, and Avandaryl outweigh their utility/benefits?

h. Did the Respondents know or should have known about the risks associated with the use of Avandia, Avandamet, and Avandaryl?

i. *(22c…)* Did the Respondents knowingly, recklessly or negligently breach a duty to warn class members and/or their physicians of the risks of harm from the use/ingestion of Avandia, Avandamet, and Avandaryl?

j. *(22e…)* Did the Respondents knowingly, recklessly or negligently misrepresent to class members and/or their physicians the risks of harm from the use/ingestion of Avandia, Avandamet, and Avandaryl?

k. *(22c…)* Did the Respondents' knowingly fail to disclose and warn of Avandia, Avandamet, and Avandaryl's defects?

l. *(22e…)* Did the Respondents adequately and sufficiently warn the members and/or their physicians of the class about the risks associated with the use of Avandia, Avandamet, and Avandaryl?

m. *(22e…)* Should Avandia, Avandamet, and Avandaryl have been sold with more appropriate warnings?

n. *(22f…)* Did the Respondents engage in false advertising when it represented, through advertisements, promotions and other representations, that Avandia, Avandamet, and Avandaryl were safe or omitted to disclose material facts regarding Avandia, Avandamet, and Avandaryl's safety?

o. Did the Respondents fail in their duty to inform class members and/or their physicians about the importance of a follow-up program for patients taking Avandia, Avandamet, and Avandaryl so as to prevent the consequences that could result?

p. Were the members of the class prejudiced by taking Avandia, Avandamet, and Avandaryl instead of other anti-diabetic therapies, which have similar benefits but do not pose an increased risk of adverse cardiovascular events and/or reduce such risk?

q. In the affirmative to any of the above questions, did Respondents conduct engage their solidary liability toward the members of the class?

r. If the responsibility of the Respondents is established, what is the nature and the extent of damages and other remedies to which the members of the class can claim from the Respondents?

s. Are members of the class entitled to bodily, moral, and material damages?

t. Are members of the class entitled to recover the medical costs incurred in the screening, diagnosis and treatment of medical conditions caused by taking Avandia, Avandamet, and Avandaryl?

u. *(22g…)* Are the members of the class entitled to recover as damages an amount equal to the purchase price of Avandia, Avandamet, and Avandaryl or any part of the purchase price?

v. *(22g…)* Should Defendants be ordered to disgorge (…) all or part of its ill-gotten profits received from the sale of Avandia, Avandamet, and Avandaryl (…)?

w. Are members of the class entitled to aggravated or punitive damages?

The questions of fact and law which are particular to each member of the class

139. To identify the physical, economic, and moral damages suffered by each of the members of the class and to determine the quantum;

The nature of the action that the Petitioners wish to exercise for the benefit of the class

140. *(24…)* The action that Petitioners wish to institute on behalf of the members of the class is an action in damages for the product liability of a drug manufacturer-distributer-seller;

141. *(25…)* The conclusions that Petitioners wish to introduce by way of a motion to institute proceedings are:

GRANT (…) the class action of Petitioners and each of the members of the class that they represent;

DECLARE the Defendants solidarily liable for the damages suffered by the Petitioners and each of the members of the class that they represent;

CONDEMN the Defendants to pay to each member of the class a sum to be determined in compensation of the damages suffered, and ORDER collective recovery of these sums;

CONDEMN the Defendants to reimburse to each of the members of the class, the purchase price of the product, and ORDER collective recovery of these sums;

CONDEMN the Defendants to pay to each of the members of the class, punitive damages, and ORDER collective recovery of these sums;

RESERVE the right of each of the members of the class to claim future damages related to the use of Avandia, Avandamet, and Avandaryl;

CONDEMN the Defendants to pay interest and additional indemnity on the above sums according to law from the date of service of the motion to authorize a class action;

ORDER the Defendants to deposit in the office of this court the totality of the sums which forms part of the collective recovery, with interest and costs;

ORDER that the claims of individual class members be the object of collective liquidation if the proof permits and alternately, by individual liquidation;

CONDEMN the Defendants to an amount sufficient to compensate the various provincial health insurers for the medical treatments and expenses that the class members have undergone and will continue to undergo in the future, and ORDER the Defendants to deposit in the office of this court these

sums so as to establish a fund to be administered as this Honourable Court deems fit;

CONDEMN the Defendants to bear the costs of the present action including expert and notice fees;

RENDER any other order that this Honourable court shall determine and that is in the interest of the members of the class;

The Petitioners request that they be attributed the status of representatives of the Class

142. *(27a…)* Petitioners are members of the class;

143. Petitioners are ready and available to manage and direct the present action in the interest of the members of the class that they wish to represent and are determined to lead the present dossier until a final resolution of the matter, the whole for the benefit of the class, as well as, to dedicate the time necessary for the present action before the Courts of Quebec and the *Fonds d'aide aux recours collectifs*, as the case may be, and to collaborate with their attorneys;

144. Petitioners have the capacity and interest to fairly and adequately protect and represent the interest of the members of the class;

145. Petitioners have given the mandate to their attorneys to obtain all relevant information with respect to the present action and intend to keep informed of all developments;

146. *(27c…)* Petitioners, with the assistance of their attorneys, are ready and available to dedicate the time necessary for this action and to collaborate with other members of the class and to keep them informed;

147. Petitioners are in good faith and have instituted this action for the sole goal of having their rights, as well as the rights of other class members, recognized and protecting so that they may be compensated for the damages that they have suffered as a consequence of the Respondents' actions;

148. (27b…) Petitioners understand the nature of the action;

149. (27d…) Petitioners' interests are not antagonistic to those of other members of the class;

The Petitioners suggest that this class action be exercised before the Superior Court of justice in the district of Montreal

150. *(26a…)* A great number of the members of the class reside in the judicial district of Montreal and in the appeal district of Montreal;

151. *(26b…)* Respondent GlaxoSmithKline Inc. has its principal place of business in the judicial district of Montreal;

152. *(26c…)* The Petitioners' attorneys practice their profession in the judicial district of Montreal;

153. *(23…)* The interests of justice favour that this motion be granted in accordance with its conclusions;

154. *(28…)* The present motion is well founded in fact and in law.

FOR THESE REASONS, MAY IT PLEASE THE COURT:

GRANT the present motion;

AUTHORIZE the bringing of a class action in the form of a motion to institute proceedings in damages for the product liability of a drug manufacturer-distributer-seller;

ASCRIBE the Petitioners the status of representative of the persons included in the class herein described as:

- all persons residing in Canada who have taken and/or purchased the drug rosiglitazone (sold under the brand name AVANDIA®, AVANDAMET®, and AVANDARYL®) since March 21st 2000 and their successors, assigns, family members, and dependants or any other group to be determined by the Court.

Alternately (or as a subclass)

- all persons residing in Quebec who have taken and/or purchased the drug rosiglitazone (sold under the brand name AVANDIA®, AVANDAMET®, and AVANDARYL®) since March 21st 2000 and their successors, assigns, family members, and dependants or any other group to be determined by the Court.

IDENTIFY the principle questions of fact and law to be treated collectively as the following:

a. Do Avandia, Avandamet, and Avandaryl cause, exacerbate, or contribute to adverse cardiovascular events, including but not limited to, chest pain, acute myocardial infarction, chronic heart failure, ischemic heart disease, angina, stroke and death?

b. Were the Respondents negligent and/or did they fail in their duty of safety, duty of care, and/or duty to inform imposed upon them as manufacturers, distributers and/or sellers of Avandia, Avandamet, and Avandaryl?

c. Were Avandia, Avandamet, and Avandaryl created and designed with defects that increase a patient's risk of adverse cardiovascular events?

d. Do Avandia, Avandamet, and Avandaryl increase a patient's risk of adverse cardiovascular events as a result of their defects?

e. Are Avandia, Avandamet, and Avandaryl unfit for the purpose for which they were intended?

f. Do Avandia, Avandamet, and Avandaryl possess a superior efficacy over other treatments of type 2 diabetes available on the market?

g. Do the risks associated with the use of Avandia, Avandamet, and Avandaryl outweigh their utility/benefits?

h. Did the Respondents know or should have known about the risks associated with the use of Avandia, Avandamet, and Avandaryl?

i. Did the Respondents knowingly, recklessly or negligently breach a duty to warn class members and/or their physicians of the risks of harm from the use/ingestion of Avandia, Avandamet, and Avandaryl?

j. Did the Respondents knowingly, recklessly or negligently misrepresent to class members and/or their physicians the risks of harm from the use/ingestion of Avandia, Avandamet, and Avandaryl?

k. Did the Respondents' knowingly fail to disclose and warn of Avandia, Avandamet, and Avandaryl's defects?

l. Did the Respondents adequately and sufficiently warn the members and/or their physicians of the class about the risks associated with the use of Avandia, Avandamet, and Avandaryl?

m. Should Avandia, Avandamet, and Avandaryl have been sold with more appropriate warnings?

n. Did the Respondents engage in false advertising when it represented, through advertisements, promotions and other representations, that Avandia, Avandamet, and Avandaryl were safe or omitted to disclose material facts regarding Avandia, Avandamet, and Avandaryl's safety?

o. Did the Respondents fail in their duty to inform class members and/or their physicians about the importance of a follow-up program for patients taking Avandia, Avandamet, and Avandaryl so as to prevent the consequences that could result?

p. Were the members of the class prejudiced by taking Avandia, Avandamet, and Avandaryl instead of other anti-diabetic therapies, which have similar benefits but do not pose an increased risk of adverse cardiovascular events and/or reduce such risk?

q. In the affirmative to any of the above questions, did Respondents conduct engage their solidary liability toward the members of the class?

r. If the responsibility of the Respondents is established, what is the nature and the extent of damages and other remedies to which the members of the class can claim from the Respondents?

s. Are members of the class entitled to bodily, moral, and material damages?

t. Are members of the class entitled to recover the medical costs incurred in the screening, diagnosis and treatment of medical conditions caused by taking Avandia, Avandamet, and Avandaryl?

u. Are the members of the class entitled to recover as damages an amount equal to the purchase price of Avandia, Avandamet, and Avandaryl or any part of the purchase price?

v. Should Defendants be ordered to disgorge (…) all or part of its ill-gotten profits received from the sale of Avandia, Avandamet, and Avandaryl (…)?

w. Are members of the class entitled to aggravated or punitive damages?

IDENTIFY the conclusions sought by the class action to be instituted as being the following:

GRANT (…) the class action of Petitioners and each of the members of the class that they represent;

DECLARE the Defendants solidarily liable for the damages suffered by the Petitioners and each of the members of the class that they represent;

CONDEMN the Defendants to pay to each member of the class a sum to be determined in compensation of the damages suffered, and ORDER collective recovery of these sums;

CONDEMN the Defendants to reimburse to each of the members of the class, the purchase price of the product, and ORDER collective recovery of these sums;

CONDEMN the Defendants to pay to each of the members of the class, punitive damages, and ORDER collective recovery of these sums;

RESERVE the right of each of the members of the class to claim future damages related to the use of Avandia, Avandamet, and Avandaryl;

CONDEMN the Defendants to pay interest and additional indemnity on the above sums according to law from the date of service of the motion to authorize a class action;

ORDER the Defendants to deposit in the office of this court the totality of the sums which forms part of the collective recovery, with interest and costs;

ORDER that the claims of individual class members be the object of collective liquidation if the proof permits and alternately, by individual liquidation;

CONDEMN the Defendants to an amount sufficient to compensate the various provincial health insurers for the medical treatments and expenses that the class members have undergone and will continue to undergo in the future, and ORDER the Defendants to deposit in the office of this court these sums so as to establish a fund to be administered as this Honourable Court deems fit;

CONDEMN the Defendants to bear the costs of the present action including expert and notice fees;

RENDER any other order that this Honourable court shall determine and that is in the interest of the members of the class;

DECLARE that all members of the class that have not requested their exclusion (…), be bound by any judgement to be rendered on the class action to be instituted in the manner provided for by the law;

FIX the delay of exclusion at thirty (30) days from the date of the publication of the notice to the members, date upon which the members of the class that have

not exercised their means of exclusion will be bound by any judgement to be rendered herein;

ORDER the publication of a notice to the members of the group in accordance with article 1006 C.C.P. within sixty (60) days from the judgement to be rendered herein in LA PRESSE, the GLOBE AND MAIL, and the NATIONAL POST;

ORDER that said notice be available on the Respondent GlaxoSmithKline Inc.'s website with a link stating "Notice to Avandia, Avandamet, and Avandaryl users";

RENDER any other order that this Honourable court shall determine and that is in the interest of the members of the class;

THE WHOLE with costs including publications fees.

Montreal, August 28, 2009

(s) Jeff Orenstein

_____

COMSUMER LAW GROUP INC.
Per: Me Jeff Orenstein
Attorneys for the Petitioners