**UNITED STATES DISTRICT COURT**
**MIDDLE DISTRICT OF FLORIDA**
**ORLANDO DIVISION**

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| **In Re:** | § | **Case No. 6:06-md-1769-ACC-DAB** |
| | § | |
| **SEROQUEL PRODUCTS LIABILITY LITIGATION** | § | **ALL CASES** |
| | § | |
| **MDL 1769** | § | |
| | § | |
| **ALL UNNAMED PLAINTIFFS** | § | |
| | § | |
| **v.** | § | **JURY TRIAL DEMANDED** |
| | § | |
| **ASTRAZENECA PHARMACEUTICALS, LP, ASTRAZENECA, LP, ASTRA USA, INC., KBI SUB INC. ASTRAZENECA, AB, ASTRAZENECA, PLC and ASTRAZENECA, UK LIMITED** | § | |

# SEROQUEL MASTER COMPLAINT

## I. INTRODUCTION

1. This Master Complaint is submitted to serve the administrative functions of efficiency and economy and to present certain common facts and claims in the context of this Multidistrict proceeding. This Master Complaint is filed with Plaintiffs' full reservation of their right to amend same in accordance with the rules of procedure or with leave of Court. This Master Complaint does not include claims asserted in putative class actions that have been transferred to this Court under 28 U.S.C. § 1407, nor does it constitute a waiver or dismissal of said actions or the claims asserted therein.

## II. JURISDICTION AND VENUE

2. The Court has jurisdiction over this lawsuit under 28 U.S.C. §1332(a)(1) as the amount in controversy exceeds $75,000, excluding interest and costs. This Federal Court sitting in diversity may exercise personal jurisdiction over Defendants under the Florida long-arm statute, § 48.193(1)(b) & (f)(2), Fla. Stat., which permits jurisdiction over a person to the full extent of the

due process clause of the United States Constitution. Venue is proper in this Court pursuant to the July 6, 2006, Transfer Order of the Judicial Panel on Multidistrict Litigation, under 28 U.S.C. §1391(a)(1) because all Defendants "reside" in this judicial district as that term is defined in 28 U.S.C. §1391(c), under 28 U.S.C. §1391(a)(2) in that a substantial part of the events or omissions giving rise to these claims arose in this judicial district, and/or, under 28 U.S.C. §1391(a)(3) because there is no district in which the action may otherwise be brought and at least one Defendant is subject to personal jurisdiction in this district.

## III. PARTIES

3. Plaintiffs are individuals who ingested Seroquel, suffered injuries as a result thereof and currently reside in, and are citizens of, most or all of the states in the United States.

4. Defendant, AstraZeneca Pharmaceuticals LP, is a Delaware limited partnership doing business in the State of Delaware, and the United States. AstraZeneca Pharmaceuticals LP, is the United States Subsidiary of AstraZeneca PLC, and was created as a result of the union of Zeneca Pharmaceuticals and Astra Pharmaceuticals LP in the U.S. after the 1999 merger. AstraZeneca Pharmaceuticals LP's principal place of business is in Delaware1800 Concord Pike, PO Box 15437,Wilmington, DE 19850. Upon Information and belief AstraZeneca Pharmaceuticals LP's general and limited partners are: AstraZeneca AB, a Swedish corporation with its principal place of business in Sweden; Zeneca Inc., a Delaware corporation with its principal place of business in Delaware; Astra USA Inc., a New York corporation with it's principal place of business in Delaware; and Astra US holdings Corporation, a Delaware corporation with it's principal place of business in Delaware. Therefore AstraZeneca Pharmaceuticals LP is a citizen of Delaware, New York and Sweden.

5. Defendant, AstraZeneca LP, is a Delaware limited partnership doing business in the State of Delaware, and the United States. AstraZeneca LP's principal place of business is in Delaware. Upon information and belief AstraZeneca LP's general partner is AstraZeneca Pharmaceuticals LP, which as stated above is a citizen of Delaware, New York, and Sweden. AstraZeneca LP's

sole limited partner, KBI Sub Inc., is incorporated in the state of Delaware and its principal place of business is in New Jersey. Therefore, AstraZeneca LP is a citizen of Delaware, New York, New Jersey and Sweden.

6. Defendant, Astra USA, Inc. is a New York corporation duly organized and existing under the laws of New York, doing business in the State of New York and the United States. Astra USA, Inc.'s principle place of business is in Delaware. Astra USA, Inc. is a limited partner of AstraZeneca Pharmaceuticals LP. Therefore, Defendant, Astra USA Inc. is a citizen of the State of New York and Delaware.

7. Defendant, KBI Sub Inc., is incorporated in the state of Delaware and its principle place of business is in New Jersey. KBI Sub Inc. is AstraZeneca LP's sole limited partner. Therefore, Defendant KBI Sub Inc. is a citizen of the State of Delaware and New Jersey.

8. Defendant AstraZeneca AB, is the general partner of AstraZeneca Pharmaceuticals LP, and is a foreign company with its principal place of business at SE-151 85, Södertälje, Sweden. Lacking an agreed appearance, this Defendant may be served with process via Registered, Return Receipt Requested, International Mail to its principal place of business pursuant to Articles 10(a) and 15 of the Hague Convention on the Service Abroad of Judicial and Extrajudicial Documents in Civil or Commercial Matters.

9. Defendant AstraZeneca PLC, is the ultimate parent company of all Defendants, and is a foreign company with its principal place of business at 15 Stanhope Gate, London, W1K 1LN, England, United Kingdom. Lacking an agreed appearance, this Defendant may be served with process via Registered, Return Receipt Requested, International Mail to its principal place of business pursuant to Articles 10(a) and 15 of the Hague Convention on the Service Abroad of Judicial and Extrajudicial Documents in Civil or Commercial Matters.

10. Defendant AstraZeneca UK Limited is a company incorporated under the laws of England and Wales and has a registered office in London, England. Defendant AstraZeneca UK Limited is the holder of the New Drug Application by which the U.S. Food and Drug Administration first

granted approval for Seroquel. Lacking an agreed appearance, this Defendant may be served with process via Registered, Return Receipt Requested, International Mail to its principal place of business pursuant to Articles 10(a) and 15 of the Hague Convention on the Service Abroad of Judicial and Extrajudicial Documents in Civil or Commercial Matters.

11. AstraZeneca Pharmaceuticals LP, AstraZeneca LP , Astra USA, KBI Sub Inc., AstraZeneca AB, AstraZeneca PLC AND AstraZeneca UK Limited shall be collectively referred to as "AstraZeneca" or the "Seroquel Defendants"). At all times relevant herein, the Seroquel Defendants were in the business of designing, testing, monitoring, manufacturing, labeling, advertising, marketing, promoting, selling and distributing pharmaceuticals, including Seroquel, for use by the mainstream public, including Plaintiffs.

## IV. FACTUAL BACKGROUND

12. Seroquel (chemically referred to by its active ingredient, quetiapine fumarate) is among a group of drugs known as "atypical antipsychotics" or "second generation antipsychotics". Seroquel was initially approved in September 1997 by the U.S. Food and Drug Administration (hereinafter the "FDA"). Both first and second generation antipsychotics are often referred to as *neuroleptic drugs* as they are believed to produce a sedating or tranquilizing effect, decreased delusions, hallucinations and psychomotor agitation. They are also sometimes referred to as *major tranquilizers*.

13. Other second generation antipsychotics include:

- clozapine (Clozaril) - Novartis – approved 9/89;
- risperidone (Risperdal) - Janssen– approved 12/93;
- olanzapine (Zyprexa) - Eli Lilly – approved 9/96;
- ziprasidone (Geodon) – Pfizer – approved 2/01; and
- aripiprazole (Abilify) – Ortho McNeil – approved 11/02.

Accordingly, Seroquel was at least the fourth "me too", "copy cat" atypical antipsychotic on the market.

14. "First generation", "conventional" or "typical antipsychotics" (another subclass of neuroleptic drugs) include chlorpromazine (Thorazine), fluphenazine (Prolixin), haloperidol (Haldol, Halperon), mesoridazine (Serentil), perphenazine (Trilafon), thioridazine, and trifluoperazine (Stelazine). They also produce significant extrapyramidal symptoms such as dystonic reactions, Parkinsonism, akathisia (restlessness and agitation), and tardive dyskinesia. Further, they have been associated to a lesser degree than the second generation drugs with the development of metabolic side effects like diabetes.

15. The initial indication for Seroquel approved by the FDA was solely for treatment of adults with schizophrenia, a relatively rare condition that affects less than one percent of the population of the United States.

16. The pharmacologic action of Seroquel is thought to be dependent on its ability to block or moderate the level of dopamine, a chemical found in the brain that in excessive amounts is believed to cause abnormal thinking and hallucinations. Likewise, all neuroleptic drugs act as inhibitors of the dopamine-2 (D2) receptor. First generation antipsychotics bind tightly to the receptor to produce a prolonged duration of effect but also increased side effects. Second generation antipsychotics, it was originally theorized, would bind more loosely producing fewer side effects.

17. Medical literature dating back to the 1950s, demonstrated that conventional antipsychotics had the potential to cause diabetes, diabetes-related injuries (e.g. severe weight gain, hyperglycemia, diabetic ketoacidosis), pancreatitis, cardiovascular complications, and other severe adverse effects. The medical reports describe cases of sudden onset hyperglycemia after the initiation of chlorpromazine treatment which resolved upon withdrawal of the drug. Additionally, patients with existing diabetes had a notable worsening of symptoms with antipsychotic treatment. Hiles, BW, *Hyperglycemia and Glycosuria Following Chlorpromazine Therapy*. JAMA 1956;162:1651.

18. In another 1950's study, all patients were given a measured dose of glucose (assimilating the same amount of food intake), however, the group that was pretreated with a conventional antipsychotic (chlorpromazine) showed a markedly slower drop in blood sugar levels in three hours of blood tests thereafter. Charatan, FBF, *The effect of Chlorpromazine ("Largactil") on Glucose Tolerance*, J. Ment. Sci. 1956;101:351-3. Because of these studies and significant other medical evidence, since 1979 the use of conventional antipsychotics has been listed as a diabetic risk factor by the National Diabetes Data Group. National Diabetes Data Group; *Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance.* Diabetes 1979; 28:1039-57.

19. AstraZeneca's own pre-clinical studies regarding Seroquel confirmed the propensity of its atypical antipsychotic to cause diabetes and related life threatening and deadly conditions - just like conventional antipsychotics.

20. Shortly after AstraZeneca's September, 1997, approval and sales of Seroquel began, reports of U.S. consumers using Seroquel suffering from hyperglycemia, acute weight gain, diabetes mellitus, pancreatitis, and other severe diseases and conditions associated began to surface. AstraZeneca knew, or was reckless in not knowing, of these reports.

21. Based on decades old confirmation of the association between conventional antipsychotics and diabetes and its lethal side effects, AstraZeneca, a manufacturer of an atypical antipsychotic, had every reason to be vigilant in identifying a signal and an association that atypicals would result in diabetes just like conventional antipsychotics. AstraZeneca was aware of studies and journal articles in 1998 and 1999 confirming the link between atypicals, new onset diabetes and permanent hyperglycemia-related adverse events. Wirshing, DA, *Novel Antipsychotics and new onset diabetes*. Biol. Psychiatry, 1998:15;44:778-83; Allison, DB, *Antipsychotic-Induced Weight Gain: A Comprehensive Research Synthesis*. Am. J. Psychiatry, 1989:156:1686-96. Despite this

knowledge, AstraZeneca never attempted to provide an adequate warning label – at least to Americans - until they were ultimately forced to do so by the FDA.

22. Seroquel's worldwide sales in 1998, its first full year on the market, were a modest $63 million. According to AstraZeneca's 2005 Annual Report, worldwide Seroquel sales exceeded $2.76 billion. Restated, sales increased 4,280% in seven years.

23. Critical to this blockbuster success was AstraZeneca's aggressive marketing of Seroquel, which consisted chiefly of overstating the drug's uses and benefits (including massive off-label promotion), while understating and consciously concealing its life-threatening side effects. Seroquel, upon information and belief, was promoted, off-label for the treatment of depression, anxiety, childhood Tourette's Syndrome, autism, obsessive compulsive disorder (OCD), alcoholism, treatment of tardive dyskinesia, treatment-resistant major depressive disorder, Parkinson's disease symptoms and/or insomnia. As part of the aggressive marketing of Seroquel, sales representatives actively detailed and promoted the drugs to physicians, pharmacists and other health care providers by understating, denying and or trivializing risks, overstating benefits, promoting indications outside of the label, and generally diluting the import of the label with aggressive promotion techniques to gain market share.

24. Shortly after Seroquel's product launch and first widespread usage, the number of adverse event reports involving diabetes-related illnesses associated with Seroquel, spiked. These promotional efforts were made, while fraudulently, willfully and wantonly withholding important safety information from the physicians, the FDA, and the public, specifically, that AstraZeneca was aware of numerous reports of diabetes associated with the use of these drugs, well beyond the background rate and well beyond the rate for other antipsychotic agents.

25. In December 2000, an article published in the *British Medical Journal* concluded that "[t]here is no clear evidence that [Risperdal or other atypical anti-psychotics like Seroquel] are more effective or are better tolerated than conventional antipsychotics [including Haldol and

Thorazine]". Geddes, J, et al., *Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis*. Br. Med. J., 2002; 321:1371-76.

26. By July 2001, Defendant AstraZeneca had received at least 46 reports of diabetes mellitus in patients taking Seroquel, including reports in the medical literature, and including at least 21 cases of ketoacidosis or acidosis and 11 deaths, and, by the end of 2003, AstraZeneca had received at least 23 more. Most cases appeared within 6 months of initiating Seroquel therapy.

27. Upon information and belief, prior to and during the time most Plaintiffs ingested Seroquel, the Japanese label for Seroquel provided a detailed warning regarding the risks of diabetes associated with Seroquel, and specifically informed physicians regarding the necessity of medical monitoring of patients on Seroquel. At the time the Plaintiff ingested Seroquel, Defendant AstraZeneca had not adopted this safer, more accurate label for the U.S. distribution of Seroquel.

28. Upon information and belief, prior to and during the time of use of Seroquel by most Plaintiffs, the Japanese label warned specifically of the diabetes risk, prominently in the beginning of the package label stating:

    a. Quetiapine fumarate is contraindicated for use in patients with diabetes or a history of diabetes.

    b. Quetiapine fumarate should be used with caution in patients with risk factors for diabetes, including hyperglycemia, obesity or a family history of diabetes.

    c. Patients receiving quetiapine fumarate should be carefully monitored for symptoms of hyperglycemia, and the drug should be discontinued if such symptoms occur. The symptoms of severe hyperglycemia include weakness, excessive eating, excessive thirst, and excessive urination.

    d. Physicians should educate patients and their family members about the risk of serious hyperglycemia associated with quetiapine fumarate and how to identify the symptoms of hyperglycemia. In April 2002, the Japanese Health & Welfare Ministry issued emergency safety information regarding the risk of diabetes, diabetic ketoacidosis, and hyperosmolar coma for patients prescribed Seroquel. On information and belief, prior to that time, Defendant AstraZeneca was involved in discussions with the Japanese agency regarding labeling changes for Seroquel and other atypicals.

29. While warning of the association of Seroquel with diabetes, glucose dysregulation, ketoacidosis, weight gain and the need for medical monitoring in Japan, AstraZeneca failed to provide the same or similar warnings to the public and prescribing physicians in the United States.

30. In April 2002, the British Medicines Control Agency warned about the risk of diabetes for patients prescribed the atypical antipsychotic Zyprexa in its newsletter *Current Problems in Pharmacovigilance*. This newsletter reported forty (40) reports of diabetes, hyperglycemia, diabetic ketoacidosis, diabetic coma, and one death among users of Zyprexa. Subsequently, the British government required Lilly to warn consumers about the risk of diabetes and diabetic ketoacidosis, and further required Lilly to instruct patients who were using Zyprexa to monitor their blood sugar levels. AstraZeneca knew or should have known that these dangerous side effects were common to all drugs of the class known as atypical antipsychotics.

31. In September, 2002 a population of over 20,000 neuroleptic drug users from the U.K. General Practice Research database were followed (19,102 using atypicals and 958,453 using conventional). 424 cases of new onset diabetes were identified and matched to 1,522 controls (about 4 per case) by age, gender, general practice and index date. The adjusted OR for current use of any antipsychotic was 1.7 (95% CI = 1.3-2.3) and for current use of atypical antipsychotic was 4.7 (95% CI = 1.5-14.9). Kornegay CJ, Vasilakis-Scarmozza C, Jick H; *Incident Diabetes Associated with Antipsychotic use in the United Kingdom General Practice Research Database.* J Clin Psychiatry 2002; 63:758-62.

32. On September 11, 2003, the FDA informed all manufacturers of atypical antipsychotic drugs, including AstraZeneca, that due to an increasing prevalence of diabetes-related illnesses associated with this class of drugs, all labeling must bear the following language in the Warnings section:

> Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in

> patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiologic studies suggest an increased risk of treatment emergent hyperglycemia-related adverse events in patients treated with atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.
>
> Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

33. Despite the FDA action, AstraZeneca waited until January 30, 2004 to send out a "Dear Doctor" letter attempting to advise treating physicians of the new warnings. On April 22, 2004 AstraZeneca was forced to send out a revised "Dear Doctor" letter due to the fact that the first one was misleading, as it potentially downplayed the need to continually monitor a patient's blood sugar levels while on the drug. This critical information did not make it into the *Physicians' Desk Reference* until the 2005 edition.

34. Seroquel may be the least potent atypical antipsychotic – from an efficacy standpoint but not a risk standpoint – in the atypical subclass. Seroquel likely requires more milligrams to be effective than more potent drugs like risperidone or ziprasidone. Seroquel is available in 25mg, 100mg, 200mg, and 300mg dosages. The total daily dose for the first four days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). From Day 4 onwards, the dose is often titrated to an effective dose in the range of 300-450 mg/day or less. That is,

Seroquel is usually given once daily, with the dose often adjusted upward until an optimal dose is found.

35. In a case-control study of 13,611 inpatients in facilities operated by the New York State Office of Mental Hygiene, rates of diabetes were compared in patients taking first and second generation antipsychotics. New cases of diabetes were identified by a new prescription for an anti-diabetic medication. 8,461 patients met the inclusion criteria of being hospitalized for more than 60 days and not using antidiabetic medications in the past. 1,539 of these patients received a prescription for antidiabetic medication for a prevalence rate of 11.31%. Of these, 181 were new prescriptions. Eight controls were matched to each case by year, length of observation period, race, age, and diagnosis for a total of 1,448 controls. Of the 24 cases and 112 controls who took Seroquel, the odds ratio (OR) of developing diabetes was 3.09 (95% Cl = 1.59-6.03) compared to taking a first generation antipsychotic. There was also a statistically significant elevation in risk for those patients taking more than one second generation antipsychotic (OR = 2.86, 95% CI = 1.57-5.2). 42 of the 181 cases of treatment emergent diabetes developed in the group taking more than one second generation antipsychotic. 20 of those 42 cases of new onset diabetes (47%) were taking Seroquel as one of two atypicals. Citrome L, Jaffe A, Levine J, Allingham B, Robinson J; *Relationship between antipsychotic medication treatment and new cases of diabetes among psychiatric inpatients*. Psychiatric Services 2004; 55:1006-13.

36. The marketing and promotion efforts of AstraZeneca, through its advertisers and sales force, overstated the benefits of Seroquel and minimized, downplayed and concealed the risks associated with this drug. Despite the fact that AstraZeneca knew or should have known that Seroquel was associated with the aforesaid adverse effects, including diabetes mellitus, it recklessly, negligently, and with willful and wanton indifference to the health and safety of consumers, failed to include any warning regarding hyperglycemia, diabetes mellitus, or related conditions until on or after January 2004.