AstraZeneca

Clinical Overview

Drug Substance quetiapine fumarate

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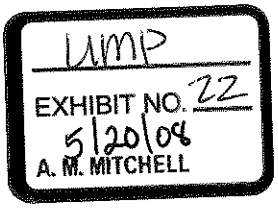

SEROQUEL (quetiapine fumarate)

Clinical Overview:

Glucose dysregulation in patients treated with SEROQUEL (quetiapine)

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this Clinical Overview

Abbreviation or special term	Explanation
ADA	American Diabetes Association
ADR	Adverse drug reaction
AE(s)	Adverse event(s)
$AUC_{0\text{-}2h}$	Area under curve of oral glucose tolerance test
BMI	Body mass index (as kg/m^2)
DKA	Diabetic ketoacidosis
DM	Diabetes mellitus
HbA1c	Glycosylated hemoglobin
$HOMA_R$	Homeostasis model assessment of insulin resistance
NKHHC	Non-ketotic hyperglycemic-hyperosmolar coma
Incidence density	Exposure duration adjusted incidence (per 100 patient years)
OGTT	Oral glucose tolerance test
PLA	Placebo
QTP	Quetiapine
QUICKI	Quantitative insulin sensitivity check index
SERM	Safety evaluation and review meeting
ULN	Upper limit of normal
US	United States

1. INTRODUCTION AND RATIONALE

1.1 Introduction

1.1.1 SEROQUEL

SEROQUEL® (quetiapine fumarate, quetiapine) is an atypical antipsychotic agent, which interacts with a broad range of neurotransmitter receptors. Quetiapine exhibits affinity for brain serotonin ($5HT_2$) and dopamine D_1 and D_2 receptors. Quetiapine also has high affinity at histaminergic and adrenergic α_1 receptors, with a lower affinity at adrenergic α_2 receptors, but no appreciable affinity at cholinergic, muscarinic or benzodiazepine receptors.

SEROQUEL was first approved for marketing in the United Kingdom on 31 July 1997 and was first launched in the United Kingdom on 22 September 1997 for the treatment of psychosis/schizophrenia and is currently approved in 85 countries for this indication. It was first approved for bipolar mania in Mexico in June 2003 and is currently approved in 77 countries for this indication. In October 2006 the United States (US) was the first country to approve SEROQUEL for bipolar depression.

It has been estimated that about 23.2 million patients worldwide (an estimate of almost 14.4 million patients in the US and 8.8 million patients in countries outside the US) have been exposed to SEROQUEL for all time through February 2007 for the US and through 2006 for countries outside the US.

1.2 Glucose dysregulation

1.2.1 Definitions

1.2.1.1 Definitions of diagnostic criteria for diabetes mellitus

The following definitions for glucose dysregulation laboratory values according to the American Diabetes Association (ADA 2004) are used in this document:

- Hyperglycemia: fasting plasma glucose ≥7.0 mmol/L (126 mg/dL) or 2h-glucose ≥11.1 mmol/L (200 mg/dL)
- Impaired fasting glucose: fasting glucose ≥5.6 mmol/L (100 mg/dL) and <7.0 mmol/L (126 mg/dL)
- Impaired glucose intolerance: 2-h glucose ≥7.8 mmol/L (140 mg/dL) and <11.1 mmol/L (200 mg/dL) (oral glucose tolerance test)

1.2.1.2 Definitions of clinically important glucose regulation laboratory values in AstraZeneca clinical trials

In clinical trials, AstraZeneca has used cutoff levels for clinically important blood glucose values identical to the ADA criteria for diagnosis of diabetes mellitus provided directly above in Section 1.2.1.1 for "hyperglycemia", "impaired fasting glucose", and "impaired glucose

tolerance". For HbA1c (which is not considered by the ADA to be a diagnostic criteria for diabetes mellitus), AstraZeneca has used a cutoff level of 7.5% as clinically important.

1.2.2 Prevalence of DM in patients with psychiatric disorders

Several studies have also shown a substantially higher prevalence of diabetes in populations with schizophrenia than in others. In the US, Medicare and Medicaid data from 1991 showed a prevalence rate of diabetes in schizophrenia patients of 12.5% and 11%, respectively (Dixon et al 2000). The prevalence of current diabetes in a cohort of patients being treated for schizophrenia that was part of a Schizophrenia Patient Outcomes Research Team (PORT) study was 11%; 15% of participants reported ever having diabetes (Dixon et al 2000). (Mukherjee et al 1996) found an overall prevalence of known diabetes of 15.8% in a cohort of patients with schizophrenia admitted to a long-term care facility in Italy, which is substantially higher than the estimated 2% to 3% prevalence of diabetes in the general population of Italy (Bruno et al 1992, Verrillo et al 1985). On the other hand, analysis of the National Hospital Discharge Survey from 1979-1989, before the introduction of atypical antipsychotics, found that schizophrenia inpatients and medical inpatients had similar diabetes prevalence rates (Basu and Meltzer 2006).

Schizophrenia is only one of several psychiatric disorders in which there appears to be a relatively high prevalence of abnormal glucose metabolism. Medical records of 254 inpatients aged 50-74 with a diagnosis of an Axis I psychiatric disorder found rates of type 2 diabetes of 50% in schizoaffective patients, 26% in bipolar I patients, 18% in major depression patients, 18% in dementia patients, and 13% in schizophrenia patients (Regenold et al 2002).

Reasons for an increased prevalence of diabetes among patients with schizophrenia remain speculative. The mechanisms behind the association between schizophrenia and diabetes are likely to be multifactorial and to include environmental, genetic, and neuroendocrine factors.

2. NON-CLINICAL STUDIES

There is no evidence from preclinical data that SEROQUEL treatment in humans may be associated with DM. The only salient observation was small changes in glucagon secreting cells (hyperplasia) after 12 months administration of quetiapine in one rat study. These changes were minimal and were not seen in another rat study after two years of quetiapine dosing. No such changes were observed in the pancreatic islets of mice, dogs, or primates in studies of up to one year.

No changes in serum glucose levels and no degenerative pathology that would indicate the induction of a diabetic state were observed in any species throughout the preclinical toxicology program. Thus, the changes observed in the single rat study are considered to be of minimal pathological significance and would not be expected to have any clinical significance in humans.

3. OVERVIEW OF CLINICAL PHARMACOLOGY

Not applicable.

4. OVERVIEW OF EFFICACY

Not applicable

5. OVERVIEW OF SAFETY

5.1 Clinical trials data

Safety data from SEROQUEL clinical trials is transferred to the SEROQUEL clinical trial safety database (Safety 9.1) after a study is completed and the clinical study report has been finalized. Data from Safety 9.1 are presented in Section 5.1.1 for all clinical trials in the database, and in Section 5.1.2 for the subset of placebo-controlled trials in the database. Data from the longer-term bipolar maintenance studies D1447C00126 (hereafter referred to as Study 126) and D1447C00127 (hereafter referred to as Study 127) are not yet available in the Safety 9.1 database, and are presented separately in Section 5.1.3. Data from Study D1441C00125 (hereafter referred to as Study 125), which was designed to evaluate glucose metabolism, is already included in the Safety 9.1 database but is also presented separately in Section 5.1.4 because the methodology of the glucose measurements is particularly relevant to the topic of glucose metabolism.

By convention, adverse event data are presented first, although laboratory data are more meaningful when making a diagnosis of hyperglycemia or DM. The preferred terms included in the search are provided in appendix Table A 1. In addition to terms of hyperglycemia, DM, and DKA; other types of events that may or may or may not be related to diabetes mellitus (eg polydipsia, polyuria, thirst) are provided for completeness.

Following the adverse event data, clinically important glucose regulation laboratory data from the trials is presented, including data from Studies 126 and 127. Tables for glucose measurements including mean blood glucose, HbA1c, blood insulin, HOMA-R, and QUICKI are provided in appendix tables for completeness.

Except for Study 125, these studies were not designed to evaluate glucose metabolism. Fasting glucose measurements were requested in all of AstraZeneca's clinical trials starting in July 2004. Even in those studies which required fasting glucose measurements, documented fasting was determined as >8 hours from time of last meal; however, there was still the possibility of caloric intake in the form of liquids or snacks. The American Diabetes Association (ADA) recommends that "in the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day" (ADA 2004). Blood samples in most studies were collected in order to perform routine laboratory tests, and the results were generally not confirmed by repeat testing.

5.1.1 Summary of all clinical trials

Data from all trials are presented to give an overview of the relevant data from all AstraZeneca sponsored trials. These trials include all placebo-controlled, active drug comparator, open label, and open-label extension trials. Since it is a combination of trials of varying designs and comparison groups, the treatment groups are not directly comparable. For comparison to placebo refer to Section 5.1.2, which contains data from only the placebo-controlled trials.

5.1.1.1 Adverse events potentially related to diabetes in all clinical trials in the Safety 9.1 database

Table A 2 shows the AE data from patients in all clinical trials in the Safety 9.1 database that reported events that may be potentially related to DM. Among quetiapine-treated patients, there were 40 reports of hyperglycemia (incidence density of 1.1), 14 reports of DM (incidence density of 0.4) and 2 reports of DKA (incidence density of 0.1).

5.1.1.2 Glucose regulation laboratory data in all clinical trials in the Safety 9.1 database.

Table A 3 shows the mean changes in glucose, HbA_{1c}, insulin, $HOMA_R$, and QUICKI in all clinical trials in the Safety 9.1 database. The mean changes in glucose were 0.20 mmol/L in the quetiapine-treated group and 0.059 mmol/L in the placebo-treated group. Because these data are from a combination of fasting and non-fasting samples, the interpretation of this data is limited. Data for Studies 126 and 127 are not yet available in Safety 9.1, and are provided in detail in Section 5.1.3.

5.1.1.3 Clinically important glucose regulation laboratory data in all clinical trials in the Safety 9.1 database and Studies 126 and 127.

Table 1 displays the number of patients with shifts to clinically important glucose or HbA1c values for all clinical trials in the Safety 9.1 database and also includes the data from Studies 126 and 127 although they are not yet in the database. Across all clinical trials (including Studies 126 and 127), the percentage of quetiapine-treated patients who had a shift to a high blood glucose level was 5.48%.

Table 1 Shift to clinically important lab values at any time (All trials) – including studies 126 and 127

	QTP N=11659		Pla N=2272		Chl N=348		Hal N=1028		Li N=98		Olz N=168		Ri N=888	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Glucose (mmol/L)														
Low[a]	5689	20 (0.35)	1951	10 (0.51)	92	1 (1.1)	228	0 (0)	91	2 (2.2)	168	0 (0)	426	0 (0)
High[b]	5545	304 (5.48)	1898	79 (4.16)	92	0 (0)	220	5 (2.3)	91	1 (1.1)	167	11 (6.6)	418	17 (4.1)
HbA1c (%)														
High[b]	2673	38 (1.42)	1051	6 (0.57)	NA	NA	NA	NA	NA	NA	168	0 (0)	172	0 (0)

a N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
b N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
Chl Chlorpromazine. Hal Haloperidol. Li Lithium. Olz Olanzapine. Pla Placebo. QTP Quetiapine. Ri Risperidone.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.

5.1.1.4 Summary

Across all clinical trials (including Studies 126 and 127), the percentage of quetiapine-treated patients who had a shift to a high blood glucose level was 5.48%.

5.1.2 Summary of all placebo-controlled clinical trials

These trials include both fasting and non-fasting data, and trials where adjunct therapy was given (e.g. quetiapine plus lithium vs placebo plus lithium). Since this combined data represents trials of various sizes and design a direct comparison between placebo and quetiapine cannot necessarily be made.

5.1.2.1 Adverse events potentially associated with diabetes mellitus in all placebo-controlled clinical trials in the Safety 9.1 database

Table 2 below shows the AE data from patients in placebo-controlled trials in the Safety 9.1 database that reported events that may be potentially related to DM. Among quetiapine-treated patients, there were 12 reports of hyperglycemia (incidence density of 3.2), 2 reports of DM (incidence density of 0.5) and no reports of DKA. Ten of these 14 reports of DM or hyperglycemia in quetiapine-treated patients were considered to be not related by the study investigator, and 8 had or were suspected to have a prior history of DM. No information regarding the patients dietary habits or information about conditions (e.g. infections), which could precipitate an exacerbation of DM were provided.

Table 2 Number of patients with adverse events related to diabetes (All placebo-controlled trials in the Safety 9.1 database)

Category of adverse event	Treatment	Patients with event	Total patients[a]	Exposure[b]	Incidence rate[c]	Incidence density[d]
Any[e]	Quetiapine	28 (0)	3437	371.3 (372.9)	0.81 (0.00)	7.5 (0.0)
	Placebo	10 (1)	1592	172.0 (172.9)	0.63 (0.06)	5.8 (0.6)
Diabetic Ketoacidosis	Quetiapine	0 (0)	3437	372.9 (372.9)	0.00 (0.00)	0.0 (0.0)
	Placebo	0 (0)	1592	172.9 (172.9)	0.00 (0.00)	0.0 (0.0)
Polydipsia	Quetiapine	2 (0)	3437	372.8 (372.9)	0.06 (0.00)	0.5 (0.0)
	Placebo	0 (0)	1592	172.9 (172.9)	0.00 (0.00)	0.0 (0.0)
Polyuria	Quetiapine	4 (0)	3437	372.8 (372.9)	0.12 (0.00)	1.1 (0.0)
	Placebo	2 (0)	1592	172.6 (172.9)	0.13 (0.00)	1.2 (0.0)
Thirst	Quetiapine	9 (0)	3437	371.9 (372.9)	0.26 (0.00)	2.4 (0.0)
	Placebo	5 (0)	1592	172.3 (172.9)	0.31 (0.00)	2.9 (0.0)
Hyperglycaemia	Quetiapine	12 (0)	3437	372.6 (372.9)	0.35 (0.00)	3.2 (0.0)
	Placebo	2 (0)	1592	172.8 (172.9)	0.13 (0.00)	1.2 (0.0)
Diabetes mellitus	Quetiapine	2 (0)	3437	372.9 (372.9)	0.06 (0.00)	0.5 (0.0)
	Placebo	1 (1)	1592	172.9 (172.9)	0.06 (0.06)	0.6 (0.6)

Table 2 Number of patients with adverse events related to diabetes (All placebo-controlled trials in the Safety 9.1 database)

Category of adverse event	Treatment	Patients with event	Total patients[a]	Exposure[b]	Incidence rate[c]	Incidence density[d]
Urine glucose abnormalities	Quetiapine	0 (0)	3437	372.9 (372.9)	0.00 (0.00)	0.0 (0.0)
	Placebo	0 (0)	1592	172.9 (172.9)	0.00 (0.00)	0.0 (0.0)

a Patients must have received at least one dose of trial medication.
b Exposure in patient-years, censored at first event.
c 100 x total number of patients with event/total number of patients.
d 100 x total number of patients with event/total patient years of exposure.
e The number of patients with any of the adverse events. Since a patient can have more than one adverse event within the adverse event group, the number does not necessarily equal the sum of the numbers below.
Note: Numbers outside brackets refer to all adverse events and numbers in brackets refer to serious adverse events.
Pgm: Reg-Def\Diabetes Mar 07 SERM\..\AE_pla_ctrl.SAS. Data version: V9.1 User: Malin Dreyer 2007-05-02 20:21.

5.1.2.2 Glucose regulation laboratory data in all placebo-controlled clinical trials in the Safety 9.1 database

Table A 4 shows the mean changes in glucose, HbA_{1c}, insulin, $HOMA_R$, and QUICKI in all subjects in the placebo-controlled trials in the Safety 9.1 database. The mean changes in glucose were 0.15 mmol/L in the quetiapine-treated group and 0.059 mmol/L in the placebo-treated group. Because of the limitations discussed in 5.1, the interpretation of this data is limited.

5.1.2.3 Clinically important glucose regulation data in all clinical trials in the Safety 9.1 database and Studies 126 and 127

Table 3 below shows all patients who had a clinically important glucose value (low or high) at any point during a trial, and includes all data in the Safety 9.1 database and data from Studies 126 and 127.

Table 3 Shift to clinically important lab values at any time (All placebo-controlled trials) – including studies 126 and 127

	QTP N=4083		Pla N=2272	
	N	n (%)	N	n (%)
Glucose (mmol/L)				
Low[a]	3349	11 (0.33)	1951	10 (0.51)
High[b]	3248	167 (5.14)	1898	79 (4.16)
HbA1c (%)				
High[b]	1743	20 (1.15)	1051	6 (0.57)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
Pla Placebo. QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Note: In studies D1444C00004, D1447C00126 and D1447C00127, all patients received QTP prior to the placebo-controlled phase.

Across all placebo-controlled trials (including Studies 126 and 127), the percentage of quetiapine-treated patients who had a shift to a high blood glucose level was 5.1% and 4.2% in placebo. These findings are consistent with the observations in all clinical trials (compare to Section 5.1.1.3).

Table 4 shows the percentage of patients in the subset of trials in the Safety 9.1 database that were short-term (12 weeks duration or less) placebo-controlled SEROQUEL clinical trials who had a fasting blood glucose ≥126 mg/dl or a non fasting blood glucose ≥200 mg/dl.

Table 4 **Shift to clinically important lab values at any time (short-term [12 weeks duration or less] placebo-controlled SEROQUEL clinical trials in the Safety 9.1 database, excluding D1444C00004)**

	QTP N=3342		Pla N=1490	
	N	n (%)	N	n (%)
Glucose (mmol/L)				
Low[a]	2677	10 (0.37)	1264	10 (0.79)
High[b]	2609	92 (3.5)	1241	26 (2.1)
HbA1c (%)				
High[b]	1072	8 (0.75)	352	1 (0.28)

[a] N is the number of patients with normal or high at baseline, n is the number of patients shifting to low at any time.
[b] N is the number of patients with normal or low at baseline, n is the number of patients shifting to high at any time.
Pla Placebo. QTP Quetiapine.
Clinically important limits are: Glucose (mmol/L), Low: <=2.5, High: >=7 for fasting and >=11.1 for non-fasting. HbA1c (%), High: >7.5.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_sha_pla_ctrl_excl04.SAS. Data version: V91 User: Bengt Franzon. 2007-06-12 09:49.

Across all short-term (12 weeks duration or less) placebo-controlled SEROQUEL clinical trials, the percent of patients who had a fasting blood glucose ≥126 mg/dl or a non-fasting blood glucose ≥200 mg/dl was 3.5% in quetiapine and 2.1% for placebo.

5.1.2.4 Summary

Across the placebo-controlled trials including Studies 126 and 127, the percent of patients who had a fasting blood glucose ≥126 mg/dl or a non fasting blood glucose ≥200 mg/dl was 5.1 % in quetiapine and 4.2 % for placebo. These findings are consistent with the observations in all clinical trials, and higher than the short-term placebo-controlled trials (12 weeks duration or less).

5.1.3 Long-term bipolar maintenance studies (Studies 126 and 127)

5.1.3.1 Study design

Studies 126 and 127 were double-blind, randomized, multi-centre, parallel-group Phase III studies comparing efficacy and safety of quetiapine (oral tablets 400 mg to 800 mg daily in divided doses) to placebo when used as adjunct to mood stabilizers (lithium or valproate) in

the maintenance treatment of Bipolar I disorder in adult patients. Study 127 was conducted in North America (US and Canada) and Study 126 in 18 countries.

The studies consisted of enrollment and 2 phases (see Figure A 1 for a diagram of the study design), an initial open-label treatment phase (12-36 weeks) and a subsequent randomized treatment phase (up to 104 weeks). To be eligible for randomization, a patient must have been treated with quetiapine within the range of 400 to 800 mg/day and mood stabilizer (lithium or valproate) for at least 12 weeks during the open-label treatment phase. The primary objective of these studies was to evaluate the efficacy of quetiapine versus placebo when used as adjunct with lithium or valproate in increasing time to recurrence of a mood episode, and patients were discontinued from the study upon recurrence of a mood episode.

The event rate (recurrence of mood episodes) was significantly lower in quetiapine-treated patients, thus the exposure time in the quetiapine treatment group (mean of 213 days, 375 total patient-years for the combined studies) was 40% higher than in the placebo treatment group (mean of 152 days, 282 total patient-years for the combined studies) during the randomized treatment phase; and the median exposure time was 91% higher in the quetapine group than in the placebo group (168 days vs 88 days).

5.1.3.2 Adverse events potentially associated with diabetes mellitus in Studies 126 and 127

Patients with AEs potentially associated with DM are summarized by randomized treatment and by assigned mood stabilizer for the combined studies in Table 5.

There were 3 reports of "Diabetes mellitus" in the quetiapine group compared to one report in the placebo group, all of them in Study 127. Two patients in the quetiapine group had an AE of "Diabetes mellitus, non-insulin-dependent" reported during the randomized treatment phase. There was 1 AE of "Diabetic ketoacidosis" reported in the quetiapine treatment group.

Table 5 **Trials 126 & 127: Adverse events potentially associated with diabetes mellitus (randomized safety population)**

	Randomized treatment		Assigned mood stabilizer			
	QTP&LI/VAL (N=646)	PLA+LI/VAL (N=680)	QTP+LI (N=274)	PLA+LI (N=287)	QTP+VAL (N=372)	PLA+VAL (N=393)
MEDDRA PREFERRED TERM [a]	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
ANY ADVERSE EVENT	20 (3.1)	7 (1.0)	7 (2.6)	3 (1.0)	13 (3.5)	4 (1.0)
HYPERGLYCAEMIA	4 (0.6)	1 (0.1)	1 (0.4)	0	3 (0.8)	1 (0.3)
DIABETES MELLITUS	3 (0.5)	1 (0.1)	3 (1.1)	0	0	1 (0.3)
HYPERINSULINAEMIA	3 (0.5)	1 (0.1)	0	0	3 (0.8)	1 (0.3)
BLOOD GLUCOSE INCREASED	2 (0.3)	0	1 (0.4)	0	1 (0.3)	0
BLOOD INSULIN INCREASED	2 (0.3)	1 (0.1)	1 (0.4)	1 (0.3)	1 (0.3)	0
DIABETES MELLITUS NON-INSULIN-DEPENDENT	2 (0.3)	0	0	0	2 (0.5)	0
INSULIN RESISTANCE	2 (0.3)	0	0	0	2 (0.5)	0
DIABETIC KETOACIDOSIS	1 (0.2)	0	0	0	1 (0.3)	0
HbA1c INCREASED	1 (0.2)	1 (0.1)	0	0	1 (0.3)	1 (0.3)
POLYDIPSIA	1 (0.2)	1 (0.1)	1 (0.4)	0	0	1 (0.3)
THIRST	1 (0.2)	1 (0.1)	0	0	1 (0.3)	1 (0.3)
POLYURIA	0	2 (0.3)	0	2 (0.7)	0	0

a Patients with multiple events falling under the same preferred term are counted only once in that term.
PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group. n Number of patients.
MedDRA Medical Dictionary of Regulatory Activities. 126 D1447C00126. 127 D144700127.
Note: Events emerging during randomized treatment phase by decreasing frequency in the QTP+LI/VAL group.

5.1.3.3 Glucose regulation laboratory data in Studies 126 and 127

Descriptive statistics for change from randomization to end of treatment in glucose regulation laboratory data are summarized by randomized treatment group and assigned mood stabilizer for the combined studies in Table A 5. A larger mean increase (5.00 mg/dL) in glucose levels from randomization to end of treatment was observed in patients treated with quetiapine compared to placebo (-0.05 mg/dL). The difference in median change was smaller (QTP=2.00 mg/dL, PLA=0.00 mg/dL).

The proportion of patients with clinically important glucose regulation laboratory data was higher in the quetiapine treatment group than in patients randomized to placebo treatment (Table 6). At least one glucose value ≥126 mg/dL was observed in 12.2% of quetiapine compared to 8.1% of placebo patients. The corresponding numbers for at least one glucose value ≥200 mg were 2.9% and 0.5% for quetiapine and placebo, respectively. Mean exposure was 213 days for SEROQUEL (646 patients) and 152 days for placebo (680 patients), the exposure adjusted rate of any increased blood glucose level (≥ 126 mg/dl) for patients more than 8 hours since last meal was 18.03 per 100 patient years for SEROQUEL (10.7% of patients) and 9.53 for placebo per 100 patient years (4.6% of patients).

Table 6 Glucose regulation laboratory data, clinically important values at any time (randomized safety population)

	Randomized treatment				Assigned mood stabilizer							
	QTP&LI/VAL N = 646		PLA&LI/VAL N = 680		QTP&LI N = 274		PLA & LI N = 287		QTP & VAL N = 372		PLA &VAL N = 393	
	N[a]	n(%)	N[a]	n(%)	N[a]	n(%)	N[a]	n(%)	N[a]	n(%)	N[a]	n(%)
Glucose (mg/dL)												
≤45	588	1 (0.2)	611	0	252	1 (0.4)	256	0	336	0	355	0
≥126	556	68 (12.2)	581	47 (8.1)	238	28 (11.8)	249	21 (8.4)	318	40 (12.6)	332	26 (7.8)
≥200	587	17 (2.9)	607	3 (0.5)	252	6 (2.4)	256	2 (0.8)	335	11 (3.3)	351	1 (0.3)
HbA1c (%)												
>7.5	576	12 (2.1)	611	5 (0.8)	248	3 (1.2)	253	1 (0.4)	328	9 (2.7)	358	4 (1.1)

a Number of patients at risk i.e. not fulfilling the criteria at randomization.
PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group. n Number of patients. HbA1C Hemoglobin A1c.
126 D1447C00126. 127 D144700127.
Note: Clinically important values emerging during randomized treatment phase.
Note: Percentages are calculated as (n/Na)*100.
Note: Values at any time after randomization.

5.1.3.4 Summary

In these 2 longer-term placebo-controlled clinical trials, mean exposure was 213 days for SEROQUEL (646 patients) and 152 days for placebo (680 patients), the exposure adjusted rate of any increased blood glucose level (≥ 126 mg/dl) for patients more than 8 hours since last meal was 18.03 per 100 patient years for SEROQUEL (10.7% of patients) and 9.53 for placebo per 100 patient years (4.6% of patients). However, given the absence of definitive

diagnostic testing for diabetes within the design of these studies, reliable and accurate determination of incidence and risk for diabetes for patients enrolled in these studies is not possible.

5.1.4 Glucose metabolism study (Study 125)

5.1.4.1 Study design

This was an international, multicentre, randomised, open-label, flexible-dose, comparative, parallel group study evaluating the effect on glucose metabolism of quetiapine (400, 600 or 800 mg/day), olanzapine (10, 15 or 20 mg/day) and risperidone (4, 6 or 8 mg/day) in schizophrenic patients after 24 weeks of treatment.

The primary objective was to compare the safety/tolerability profile of quetiapine and olanzapine on glucose metabolism in schizophrenic patients by evaluating the change from randomisation at Week 24 in Area Under the Curve (AUC) $_{0\text{-}2h}$ of the plasma glucose values following Oral Glucose Tolerance Test (OGTT).

5.1.4.2 Adverse events potentially related to diabetes

In this study there were no DM associated AEs in the quetiapine treatment group.

5.1.4.3 Glucose regulation laboratory data

The LS mean changes in fasting glucose and in 2-hour glucose from randomization at Week 24 are summarized by treatment in Table A 6. Table 7 shows the number of patients with hyperglycaemia and impaired fasting glucose or impaired glucose tolerance at randomization and after 24 weeks treatment.

Table 7 Patients with hyperglycaemia and impaired fasting glucose or impaired glucose tolerance

	Quetiapine N = 115		Olanzapine N = 146		Risperidone N = 134	
	n[a]	n (%)	n[a]	n (%)	n[a]	n (%)
Proportion of patients with hyperglycemia						
Randomization	114	3 (2.6)	145	10 (6.9)	134	7 (5.2)
Week 24	115	5 (4.3)	146	10 (6.8)	133	9 (6.8)
Proportion of patients with fasting glucose ≥7.0 mmol/L						
Randomization	114	2 (1.8)	145	3 (2.1)	134	3 (2.2)
Week 24	115	3 (2.6)	146	5 (3.4)	134	4 (3.0)
Proportion of patients with 2h-glucose ≥11.1 mmol/L						
Randomization	114	1 (0.9)	145	8 (5.5)	134	5 (3.7)
Week 24	115	2 (1.7)	146	8 (5.5)	134	7 (5.2)
Proportion of patients with impaired fasting glucose or impaired glucose tolerance						
Randomization	114	30 (26.3)	145	29 (20.0)	134	43 (32.1)

Table 7 Patients with hyperglycaemia and impaired fasting glucose or impaired glucose tolerance

	Quetiapine N = 115 n[a] n (%)	Olanzapine N = 146 n[a] n (%)	Risperidone N = 134 n[a] n (%)
Week 24	115 37 (32.2)	146 43 (29.5)	133 54 (40.6)

a Number of patients with non-missing value.
SOURCE DOCUMENT: GLUC_03.SAS GENERATED: 17:48:05 04APR2006 DB version prod: 13.

5.1.4.4 Summary

In a 24 week trial (active-controlled, 115 patients treated with SEROQUEL) designed to evaluate glycemic status with oral glucose tolerance testing of all patients, at week 24 the incidence of a post-glucose challenge glucose ≥200 mg/dl was 1.7% and the incidence of a fasting blood glucose level ≥ 126 mg/dl was 2.6%. These percentages fall within the common category (≥1% - <10 %)

The study results suggest that there were differential effects between the investigational products in how the patients in the respective treatment group responded to stress condition provided by glucose load (OGTT). At Week 24, there was a statistically significant difference between the quetiapine and olanzapine groups in post-load glucose levels as measured by the $AUC_{0\text{-}2h}$ of plasma glucose values, with the quetiapine group showing smaller mean increase from baseline (randomization) than the olanzapine group.

5.2 Post-marketing data

5.2.1 Search strategy

A search of the safety database on 01 March 2007 was performed to identify completed adverse event reports (from sources other than AstraZeneca sponsored studies) of glucose dysregulation (including DM, DKA, diabetic coma, and/or exacerbation of DM) associated with the use of SEROQUEL.

5.2.2 Search results

5.2.2.1 Overview of post-marketing data

A total of 1679 reports were identified from the safety database search on 01 March 2007, summarized in Table A 7. These 1679 reports contained 2305 MedDRA preferred terms, shown in Table A 8.

Assessment of causality was not possible in these cases because of incomplete clinical information, unclear temporal sequence of exposure and outcome, confounding by concomitant medications for which DM or related events have been reported, risk factors for DM (e.g. obesity or family history of DM), documented dietary non-compliance, and/or alternative explanations.

5.2.3 Summary of post-marketing data

Considering an estimated exposure of approximately 23.2 million patients worldwide (an estimate of almost 14.4 million patients in the US and 8.8 million patients outside the US) for all time through February 2007 for the US and through 2006 for countries outside the US, it was determined that there are very rare reports of the events described in Table A 8 on SEROQUEL therapy (1676/23,200,000=0.007%) and that these reports disclose no new safety information about the use of SEROQUEL.

5.3 Literature search

5.3.1 Search strategy

A search of the scientific/medical literature through 27 February 2007 for SEROQUEL, to obtain information on or about glucose dysregulation, was performed utilizing AstraZeneca's in house database for indexing biomedical literature, which searches over 14,000 journals daily. Additional articles were found through other channels (reference lists, tables of contents of relevant journals, information from colleagues). Articles included contain an explicit statistical comparison of the prevalence or incidence of diabetes in patients prescribed quetiapine versus either conventional antipsychotics (an individual conventional antipsychotic or conventional antipsychotics as a group) or no exposure to antipsychotics.

5.3.2 Summary of literature review

The various data sources and analytic techniques used, each with its own strengths and weaknesses, as well as the complication of operationalizing exposure and new-onset diabetes, have contributed to an array of results ranging from a statistically significant decreased risk to a statistically significant increased risk for quetiapine. Limitations in these studies included in appropriate comparison groups, lack of information on major known risk factors for diabetes (e.g. obesity, elevated insulin, family history, physical activity, comorbidities, co-prescriptions), the potential for confounding by indication, lack of systematic screening for diabetes in the subject population, and questionable generalizability due to restrictive inclusion criteria. In sum, the epidemiology literature has been inconsistent and inconclusive with regard to quetiapine and diabetes. Inherent methodological issues contribute to the challenges of studying this complex question.

5.4 Discussion

The incidence of increases in blood glucose to hyperglycaemic levels is common (≥1% - <10 %) in clinical trials, whether placebo-controlled or not. The design of the clinical trials did not allow definitive diagnosis of diabetes due to the combination of fasting and non-fasting glucose sampling, the inability to confirm fasting status, and the lack of confirmation by repeat testing in the clinical trials.

The post-marketing reports are confounded or had limited information and did not establish a causal relationship to diabetes. The reporting rate in the post-marketing data is very rare (0.007%). The epidemiology literature gives conflicting results about hyperglycemia and therefore is inconclusive.

- Based on these considerations, AstraZeneca believes that the US Prescribing Information should be updated to reflect the latest available information.

6. BENEFITS AND RISK CONCLUSIONS

It is the opinion of AstraZeneca that the present safety information with the above-mentioned changes accurately reflects the known safety profile for SEROQUEL. Overall, SEROQUEL is safe and well tolerated. The benefit-risk profile is considered positive.

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8. APPENDIX

Table A 1 Preferred terms used in adverse event search

Category	MedDRA preferred terms
DKA	Diabetic ketoacidosis, Diabetic ketoacidotic hyperglycaemic coma
Diabetic coma	Diabetic hyperglycaemic coma, Diabetic coma, diabetic hyperosmolar coma, Hyperglycaemic hyperosmolar nonketotic syndrome
Gestational diabetes	Diabetes complicating pregnancy, gestational diabetes, glycosuria during pregnancy, glucose tolerance impaired in pregnancy
Polydipsia	Polydipsia
Polyuria	Polyuria
Thirst	Thirst
Hyperglycemia	Blood glucose fluctuation, Blood glucose increased, Glycosylated haemoglobin increased, Impaired fasting glucose, Hyperglycaemia
Impaired glucose tolerance	Glucose tolerance test decreased, Glucose tolerance impaired, Glucose tolerance test abnormal
Insulin resistance	Insulin resistance, Insulin resistance syndrome, Insulin tolerance test abnormal
Diabetes mellitus[a]	Increased insulin requirement, Insulin resistant diabetes, Insulin-requiring Type II Diabetes mellitus, Diabetes mellitus, Diabetes mellitus inadequate control, Diabetes mellitus insulin-dependent, Diabetes mellitus non-insulin dependent, Diabetes with hyperosmolarity, Dawn phenomenon, Somogyi phenomenon, Latent autoimmune diabetes in adults
Diabetic complications	Diabetic complications
Blood ketone abnormalities	Blood ketone body present, Blood ketone body increased
Blood insulin abnormalities	Anti-insulin antibody increased, Anti-insulin antibody positive, Blood insulin abnormal, Blood insulin decreased, Blood insulin increased, Blood insulin C-peptide abnormal, Blood insulin C-peptide decreased, Blood insulin C-peptide increased, Blood proinsulin abnormal, Blood proinsulin decreased, Blood proinsulin increased, Hyperinsulinaemia, Hyperinsulinism, Impaired insulin secretion
Urine glucose abnormalities	Glucose urine present, Glucose urine, Urine glucose abnormality

[a] These terms may describe new onset or an exacerbation of pre-existing DM.

Table A 2 Number of patients with adverse events related to diabetes (All trials in Safety 9.1)

Category of adverse event	Treatment	Patients with event	Total patients[a]	Exposure[b]	Incidence rate[c]	Incidence density[d]
Any[e]	Quetiapine	100 (10)	11013	3460.3 (3490.5)	0.91 (0.09)	2.9 (0.3)
	Placebo	10 (1)	1592	172.0 (172.9)	0.63 (0.06)	5.8 (0.6)
	Chlorpromazine	3 (0)	348	47.2 (47.6)	0.86 (0.00)	6.4 (0.0)

Table A 2 Number of patients with adverse events related to diabetes (All trials in Safety 9.1)

Category of adverse event	Treatment	Patients with event	Total patients[a]	Exposure[b]	Incidence rate[c]	Incidence density[d]
	Haloperidol	3 (0)	1028	179.6 (180.4)	0.29 (0.00)	1.7 (0.0)
	Lithium	5 (0)	98	17.1 (17.7)	5.10 (0.00)	29.3 (0.0)
	Mosapramine	1 (0)	90	10.4 (10.4)	1.11 (0.00)	9.6 (0.0)
	Olanzapine	0 (0)	168	71.2 (71.2)	0.00 (0.00)	0.0 (0.0)
	Risperidone	8 (0)	888	178.2 (179.1)	0.90 (0.00)	4.5 (0.0)
Diabetic Ketoacidosis	Quetiapine	2 (2)	11013	3492.0 (3492.0)	0.02 (0.02)	0.1 (0.1)
	Placebo	0 (0)	1592	172.9 (172.9)	0.00 (0.00)	0.0 (0.0)
	Chlorpromazine	0 (0)	348	47.6 (47.6)	0.00 (0.00)	0.0 (0.0)
	Haloperidol	0 (0)	1028	180.4 (180.4)	0.00 (0.00)	0.0 (0.0)
	Lithium	0 (0)	98	17.7 (17.7)	0.00 (0.00)	0.0 (0.0)
	Mosapramine	0 (0)	90	10.4 (10.4)	0.00 (0.00)	0.0 (0.0)
	Olanzapine	0 (0)	168	71.2 (71.2)	0.00 (0.00)	0.0 (0.0)
	Risperidone	0 (0)	888	179.1 (179.1)	0.00 (0.00)	0.0 (0.0)
Polydipsia	Quetiapine	14 (0)	11013	3483.5 (3492.6)	0.13 (0.00)	0.4 (0.0)
	Placebo	0 (0)	1592	172.9 (172.9)	0.00 (0.00)	0.0 (0.0)
	Chlorpromazine	2 (0)	348	47.3 (47.6)	0.57 (0.00)	4.2 (0.0)
	Haloperidol	0 (0)	1028	180.4 (180.4)	0.00 (0.00)	0.0 (0.0)
	Lithium	1 (0)	98	17.6 (17.7)	1.02 (0.00)	5.7 (0.0)
	Mosapramine	1 (0)	90	10.4 (10.4)	1.11 (0.00)	9.6 (0.0)
	Olanzapine	0 (0)	168	71.2 (71.2)	0.00 (0.00)	0.0 (0.0)
	Risperidone	2 (0)	888	178.8 (179.1)	0.23 (0.00)	1.1 (0.0)
Polyuria	Quetiapine	9 (0)	11013	3491.5 (3492.6)	0.08 (0.00)	0.3 (0.0)
	Placebo	2 (0)	1592	172.6 (172.9)	0.13 (0.00)	1.2 (0.0)
	Chlorpromazine	1 (0)	348	47.5 (47.6)	0.29 (0.00)	2.1 (0.0)
	Haloperidol	2 (0)	1028	179.6 (180.4)	0.19 (0.00)	1.1 (0.0)
	Lithium	1 (0)	98	17.5 (17.7)	1.02 (0.00)	5.7 (0.0)
	Mosapramine	0 (0)	90	10.4 (10.4)	0.00 (0.00)	0.0 (0.0)
	Olanzapine	0 (0)	168	71.2 (71.2)	0.00 (0.00)	0.0 (0.0)
	Risperidone	1 (0)	888	179.1 (179.1)	0.11 (0.00)	0.6 (0.0)
Thirst	Quetiapine	24 (0)	11013	3487.5 (3492.6)	0.22 (0.00)	0.7 (0.0)
	Placebo	5 (0)	1592	172.3 (172.9)	0.31 (0.00)	2.9 (0.0)
	Chlorpromazine	0 (0)	348	47.6 (47.6)	0.00 (0.00)	0.0 (0.0)
	Haloperidol	0 (0)	1028	180.4 (180.4)	0.00 (0.00)	0.0 (0.0)
	Lithium	2 (0)	98	17.4 (17.7)	2.04 (0.00)	11.5 (0.0)
	Mosapramine	0 (0)	90	10.4 (10.4)	0.00 (0.00)	0.0 (0.0)

Table A 2 Number of patients with adverse events related to diabetes (All trials in Safety 9.1)

Category of adverse event	Treatment	Patients with event	Total patients[a]	Exposure[b]	Incidence rate[c]	Incidence density[d]
	Olanzapine	0 (0)	168	71.2 (71.2)	0.00 (0.00)	0.0 (0.0)
	Risperidone	2 (0)	888	178.8 (179.1)	0.23 (0.00)	1.1 (0.0)
Hyperglycaemia	Quetiapine	40 (5)	11013	3482.8 (3492.5)	0.36 (0.05)	1.1 (0.1)
	Placebo	2 (0)	1592	172.8 (172.9)	0.13 (0.00)	1.2 (0.0)
	Chlorpromazine	0 (0)	348	47.6 (47.6)	0.00 (0.00)	0.0 (0.0)
	Haloperidol	0 (0)	1028	180.4 (180.4)	0.00 (0.00)	0.0 (0.0)
	Lithium	0 (0)	98	17.7 (17.7)	0.00 (0.00)	0.0 (0.0)
	Mosapramine	0 (0)	90	10.4 (10.4)	0.00 (0.00)	0.0 (0.0)
	Olanzapine	0 (0)	168	71.2 (71.2)	0.00 (0.00)	0.0 (0.0)
	Risperidone	2 (0)	888	179.0 (179.1)	0.23 (0.00)	1.1 (0.0)
Diabetes mellitus	Quetiapine	14 (4)	11013	3486.7 (3491.1)	0.13 (0.04)	0.4 (0.1)
	Placebo	1 (1)	1592	172.9 (172.9)	0.06 (0.06)	0.6 (0.6)
	Chlorpromazine	0 (0)	348	47.6 (47.6)	0.00 (0.00)	0.0 (0.0)
	Haloperidol	1 (0)	1028	180.4 (180.4)	0.10 (0.00)	0.6 (0.0)
	Lithium	1 (0)	98	17.7 (17.7)	1.02 (0.00)	5.6 (0.0)
	Mosapramine	0 (0)	90	10.4 (10.4)	0.00 (0.00)	0.0 (0.0)
	Olanzapine	0 (0)	168	71.2 (71.2)	0.00 (0.00)	0.0 (0.0)
	Risperidone	2 (0)	888	178.9 (179.1)	0.23 (0.00)	1.1 (0.0)
Urine glucose abnormalities	Quetiapine	7 (0)	11013	3489.8 (3492.6)	0.06 (0.00)	0.2 (0.0)
	Placebo	0 (0)	1592	172.9 (172.9)	0.00 (0.00)	0.0 (0.0)
	Chlorpromazine	0 (0)	348	47.6 (47.6)	0.00 (0.00)	0.0 (0.0)
	Haloperidol	0 (0)	1028	180.4 (180.4)	0.00 (0.00)	0.0 (0.0)
	Lithium	0 (0)	98	17.7 (17.7)	0.00 (0.00)	0.0 (0.0)
	Mosapramine	0 (0)	90	10.4 (10.4)	0.00 (0.00)	0.0 (0.0)
	Olanzapine	0 (0)	168	71.2 (71.2)	0.00 (0.00)	0.0 (0.0)
	Risperidone	0 (0)	888	179.1 (179.1)	0.00 (0.00)	0.0 (0.0)

a Patients must have received at least one dose of trial medication.
b Exposure in patient-years, censored at first event.
c 100 x total number of patients with event/total number of patients.
d 100 x total number of patients with event/total patient years of exposure.
e The number of patients with any of the adverse events. Since a patient can have more than one adverse event within the adverse event group, the number does not necessarily equal the sum of the numbers below.
Note: Numbers outside brackets refer to all adverse events and numbers in brackets refer to serious adverse events.
Pgm: Reg-Def\Diabetes Mar 07 SERM\..\AE_all_trials.SAS. Data version: V9.1 User: Malin Dreyer 2007-05-02 20:19.

Table A 3 Mean (SD) change from baseline to end of treatment (All trials in Safety 9.1)

		QTP N=11013	Pla N=1592	Chl N=348	Hal N=1028	Li N=98	Olz N=168	Ri N=888
Glucose (mmol/L)								
Patients[a]		5125	1342	92	228	91	168	426
Baseline	Mean (SD)	5.42 (1.45)	5.36 (1.36)	5.55 (1.11)	6.07 (2.15)	5.33 (1.21)	5.13 (0.82)	5.42 (1.56)
Last value	Mean (SD)	5.62 (1.83)	5.42 (1.42)	5.45 (1.21)	6.19 (2.15)	5.49 (1.81)	5.27 (0.62)	5.62 (1.60)
Change	Mean (SD)	0.20 (1.62)	0.059 (1.46)	-0.10 (1.41)	0.11 (1.83)	0.16 (1.73)	0.14 (0.80)	0.20 (1.47)
	Median	0.10	0	0	0.10	0	0.30	0.20
	Range	-9.83 to 29.67	-12.60 to 13.72	-4.50 to 3.80	-5.90 to 10.20	-5.40 to 5.83	-5.70 to 1.90	-7.83 to 14.83
HbA1c (%)								
Patients[a]		2111	443				168	172
Baseline	Mean (SD)	5.39 (0.53)	5.32 (0.50)				5.33 (0.40)	5.35 (0.44)
Last value	Mean (SD)	5.45 (0.61)	5.33 (0.50)				5.34 (0.43)	5.34 (0.46)
Change	Mean (SD)	0.055 (0.33)	0.012 (0.28)				0.0036 (0.34)	-0.013 (0.30)
	Median	0	0				0	0
	Range	-1.90 to 4.50	-1.70 to 1.10				-1.00 to 1.40	-0.90 to 1.00
Insulin (pmol/L)								
Patients[a]		2526	689				141	140
Baseline	Mean (SD)	104.48 (146.57)	93.23 (150.83)				242.30 (238.10)	224.27 (215.81)
Last value	Mean (SD)	131.27 (199.50)	104.76 (138.38)				305.13 (371.28)	254.09 (230.86)
Change	Mean (SD)	26.78 (195.95)	11.53 (182.41)				62.83 (350.06)	29.81 (244.84)
	Median	6.95	6.95				18.96	20.45
	Range	-1965 to 2730	-1875 to 1820				-1124 to 2822	-645.75 to 1492

Table A 3 Mean (SD) change from baseline to end of treatment (All trials in Safety 9.1)

		QTP N=11013	Pla N=1592	Chl N=348	Hal N=1028	Li N=98	Olz N=168	Ri N=888
HOMAR								
Patients[a]		2265	640				130	134
Baseline	Mean (SD)	3.35 (5.51)	3.42 (9.23)				1.46 (1.02)	1.62 (2.30)
Last value	Mean (SD)	4.61 (9.38)	3.79 (6.66)				1.78 (1.51)	1.69 (1.40)
Change	Mean (SD)	1.26 (9.50)	0.37 (10.83)				0.32 (1.42)	0.072 (2.32)
	Median	0.21	0.18				0.15	0.11
	Range	-87.09 to 163.49	-137.15 to 87.11				-3.14 to 8.12	-22.57 to 10.63
QUICKI								
Patients[a]		2265	640				130	134
Baseline	Mean (SD)	0.3226 (0.0766)	0.3046 (0.0906)				0.3763 (0.0394)	0.3729 (0.0374)
Last value	Mean (SD)	0.3161 (0.0781)	0.2994 (0.0919)				0.3692 (0.0440)	0.3673 (0.0364)
Change	Mean (SD)	-0.0064 (0.0410)	-0.0052 (0.0382)				-0.0071 (0.0445)	-0.0056 (0.0322)
	Median	-0.0060	-0.0040				-0.0074	-0.0056
	Range	-0.2105 to 0.1807	-0.1830 to 0.1800				-0.1117 to 0.2593	-0.0896 to 0.0888

a Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Chl Chlorpromazine. Hal Haloperidol. Li Lithium. Olz Olanzapine. Pla Placebo. QTP Quetiapine. Ri Risperidone.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_chg_all_trials.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 12:22.

Table A 4 **Mean (SD) change from baseline to end of treatment (All placebo-controlled trials in Safety 9.1)**

		QTP N=3437	Pla N=1592
Glucose (mmol/L)			
Patients[a]		2763	1342
Baseline	Mean (SD)	5.33 (1.39)	5.36 (1.36)
Last value	Mean (SD)	5.49 (1.65)	5.42 (1.42)
Change	Mean (SD)	0.15 (1.47)	0.059 (1.46)
	Median	0.100	0
	Range	-9.83 to 15.72	-12.60 to 13.72
HbA1c (%)			
Patients[a]		1173	443
Baseline	Mean (SD)	5.39 (0.53)	5.32 (0.50)
Last value	Mean (SD)	5.45 (0.61)	5.33 (0.50)
Change	Mean (SD)	0.056 (0.32)	0.012 (0.28)
	Median	0	0
	Range	-1.40 to 4.50	-1.70 to 1.10
Insulin (pmol/L)			
Patients[a]		1713	689
Baseline	Mean (SD)	95.11 (126.81)	93.23 (150.83)
Last value	Mean (SD)	131.99 (200.57)	104.76 (138.38)
Change	Mean (SD)	36.89 (197.65)	11.53 (182.41)
	Median	7.00	6.95
	Range	-1479 to 2299	-1875 to 1820
$HOMA_R$			
Patients[a]		1566	640
Baseline	Mean (SD)	3.32 (5.54)	3.42 (9.23)
Last value	Mean (SD)	4.93 (9.61)	3.79 (6.66)
Change	Mean (SD)	1.61 (9.83)	0.37 (10.83)
	Median	0.29	0.18
	Range	-87.09 to 127.84	-137.15 to 87.11
QUICKI			
Patients[a]		1566	640
Baseline	Mean (SD)	0.3123 (0.0855)	0.3046 (0.0906)
Last value	Mean (SD)	0.3039 (0.0864)	0.2994 (0.0919)
Change	Mean (SD)	-0.0084 (0.0408)	-0.0052 (0.0382)

Table A 4 Mean (SD) change from baseline to end of treatment (All placebo-controlled trials in Safety 9.1)

		QTP N=3437	Pla N=1592
	Median	-0.0090	-0.0040
	Range	-0.2105 to 0.1800	-0.1830 to 0.1800

a Patients who have received at least one dose of trial medication, have a value at baseline and at least one value post baseline.
Pla Placebo. QTP Quetiapine.
Pgm: Reg-Def\Diabetes Mar 07 SERM\LAB_chg_pla_ctrl.SAS. Data version: V91 User: Bengt Franzon. 2007-05-03 12:38.

Figure A 1 **Study design diagram for Studies 126 and 127**

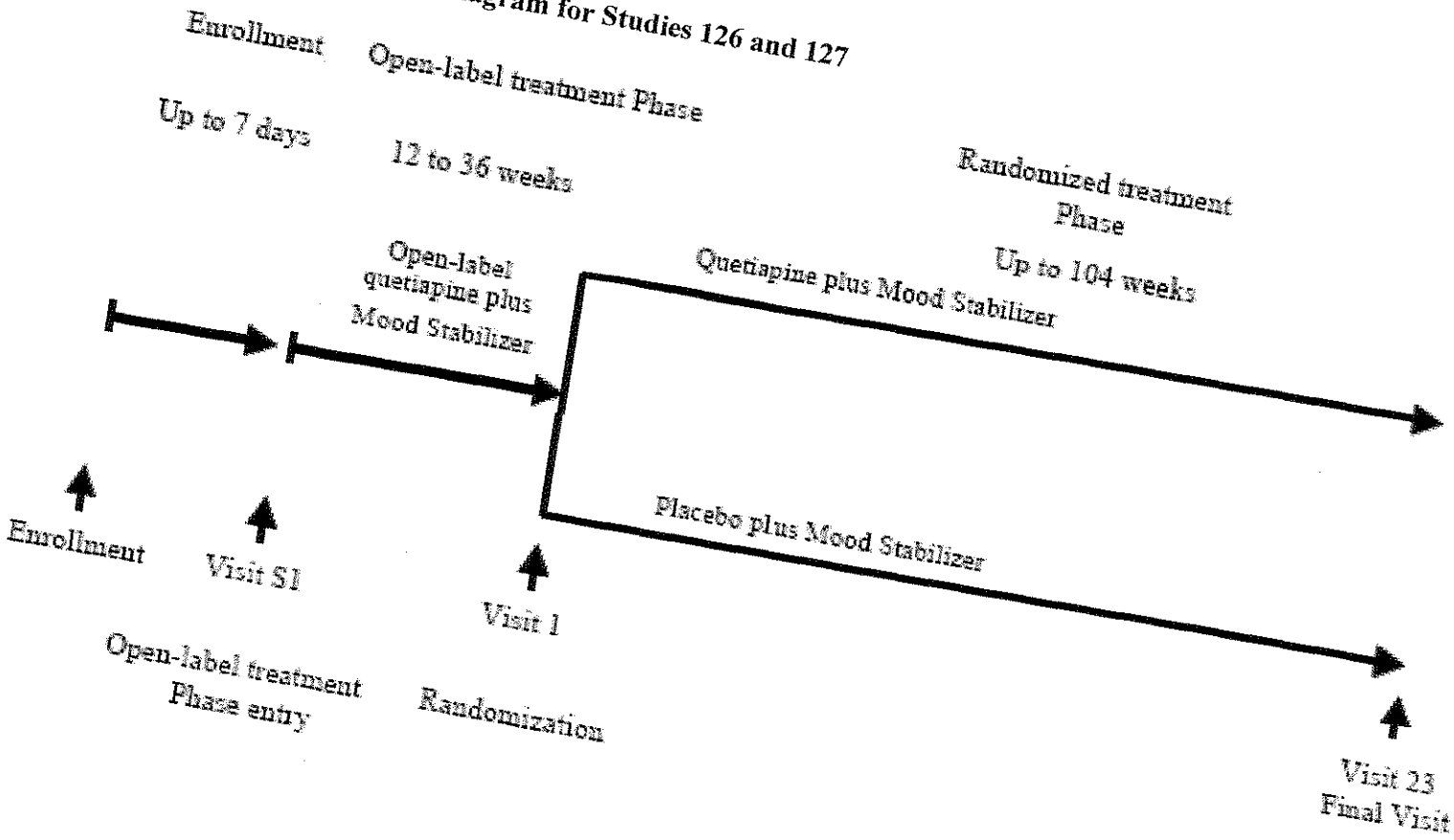

Table A 5 **Trials 126 & 127: Glucose regulation laboratory data, change from randomization to end of treatment (randomized safety population)**

		Randomized treatment		Assigned mood stabilizer			
		QTP & LI/VAL N = 646	PLA & LI/VAL N = 680	QTP &LI N = 274	PLA &LI N = 287	QTP &VAL N = 372	PLA &VAL N = 393
Glucose (mg/dL)							
N [a]		588	611	252	256	336	355
Randomization	Mean(SD)	93.78(19.970)	94.61(20.084)	94.83(18.630)	94.04(14.478)	92.99(20.911)	95.02(23.317)
End of treatment	Mean(SD)	98.78(41.837)	94.55(18.876)	100.10(28.883)	95.29(18.424)	97.78(49.393)	94.02(19.204)
Change	Mean(SD)	5.00(39.900)	-0.05(19.409)	5.27(26.412)	1.26(15.708)	4.79(47.611)	-1.00(21.662)
	Median	2.00	0.00	3.00	0.50	2.00	0.00
	Min to Max	-132.00 to 776.00	-121.00 to 87.00	-84.00 to 287.00	-52.00 to 75.00	-132.00 to 776.00	-121.00 to 87.00
HbAIC (%)							
N [a]		585	618	251	253	334	365
Randomization	Mean(SD)	5.41(0.643)	5.39(0.592)	5.26(0.536)	5.21(0.480)	5.52(0.693)	5.51(0.631)
End of treatment	Mean(SD)	5.59(0.723)	5.42(0.567)	5.43(0.639)	5.26(0.445)	5.71(0.760)	5.54(0.614)
Change	Mean(SD)	0.18(0.460)	0.04(0.346)	0.18(0.331)	0.05(0.304)	0.19(0.537)	0.03(0.373)
	Median	0.10	0.00	0.20	0.00	0.10	0.00
	Min to Max	-2.60 to 3.80	-2.80 to 2.30	-0.90 to 2.00	-2.10 to 1.40	-2.60 to 3.80	-2.80 to 2.30
Insulin (pmol/L)							
N [a]		501	531	211	214	290	317
Randomization	Mean(SD)	132.94(151.842)	135.13(154.995)	121.00(122.661)	121.78(134.202)	141.62(169.636)	144.14(167.185)
End of treatment	Mean(SD)	158.64(175.733)	145.91(202.396)	154.85(145.578)	143.45(157.738)	161.40(194.965)	147.56(227.876)
Change	Mean(SD)	25.70(161.479)	10.78(214.550)	33.85(149.963)	21.67(171.618)	19.77(169.376)	3.42(239.203)
	Median	7.00	0.00	14.00	7.00	0.00	0.00
	Min to Max	-882.00 to 799.00	-945.00 to 2125.00	-771.00 to 660.00	-945.00 to 1049.00	-882.00 to 799.00	-944.00 to 2125.00

Table A 5 Trials 126 & 127: Glucose regulation laboratory data, change from randomization to end of treatment (randomized safety population)

		Randomized treatment		Assigned mood stabilizer			
		QTP & LI/VAL N = 646	PLA & LI/VAL N = 680	QTP &LI N = 274	PLA &LI N = 287	QTP &VAL N = 372	PLA &VAL N = 393
HOMA-R							
N [a]		505	523	215	214	290	309
Randomization	Mean(SD)	4.87(7.590)	4.93(7.509)	4.42(5.661)	4.30(6.051)	5.21(8.744)	5.37(8.353)
End of treatment	Mean(SD)	6.00(8.890)	5.56(9.756)	5.97(9.552)	5.30(7.187)	6.02(8.382)	5.74(11.203)
Change	Mean(SD)	1.13(8.929)	0.63(10.800)	1.55(9.843)	1.00(8.089)	0.81(8.190)	0.37(12.340)
	Median	0.23	0.04	0.47	0.08	0.19	0.00
	Min to Max	-50.60 to 103.32	-85.08 to 86.29	-41.47 to 103.32	-57.69 to 52.79	-50.60 to 33.99	-85.08 to 86.29
QUICKI							
N [a]		505	523	215	214	290	309
Randomization	Mean(SD)	0.3305(0.0425)	0.3299(0.0426)	0.3328(0.0434)	0.3337(0.0424)	0.3287(0.0419)	0.3273(0.0427)
End of treatment	Mean(SD)	0.3233(0.0438)	0.3277(0.0427)	0.3226(0.0448)	0.3273(0.0427)	0.3239(0.0432)	0.3280(0.0427)
Change	Mean(SD)	-.0071(0.0399)	-.0022(0.0400)	-.0103(0.0405)	-.0064(0.0390)	-.0048(0.0393)	0.0007(0.0405)
	Median	-.006	-.001	-.007	-.002	-.003	.0000
	Min to Max	-0.1477 to 0.1206	-0.1582 to 0.1246	-0.1477 to 0.0912	-0.1582 to 0.0889	-0.1476 to 0.1206	-0.1279 to 0.1246

a Number of patients with assessment at randomization and at least one assessment after randomization.
PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group. HOMA [insulin (uU/ml) x glucose (mmol/l)]/22.5.
QUICKI 1/[log10(insulin n(uU/ml) + log10 (glucose e(mg/dl))]. HbA1c Hemoglobin A1c.
126 D1447C00126. 127 D144700127.

Table A 6 Fasting plasma glucose and two-hour glucose, change from randomization – Trial 125

		Quetiapine	Olanzapine	Risperidone
Fasting plasma glucose (mmol/L)				
n[a]		113	143	132
Randomization	Mean (SD)	5.14 (0.67)	5.199 (0.99)	5.203 (0.66)
Change at Week 24	LS mean (SE)	0.177 (0.08)	0.129 (0.08)	0.244 (0.08)
	95% CI	(0.013, 0.34)	(-0.02, 0.281)	(0.09, 0.399)
Two-hour glucose (mmol/L)				
n[a]		109	145	128
Randomization	Mean (SD)	5.934 (1.86)	6.163 (2.33)	6.266 (2.13)
Change at Week 24	LS mean (SE)	-0.1 (0.23)	0.543 (0.21)	0.587 (0.22)
	95% CI	(-0.56, 0.348)	(0.132, 0.953)	(0.162, 1.013)

a Number of patients with non-missing values at randomization and Week 24.
Note: Analysis using ANCOVA with baseline value, BMI group, age group and treatment as independent variables.
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Table A 7 Overview of post-marketing adverse event reports

	Medically confirmed	Not medically confirmed	Legal[b]	Total
DKA/ketoacidosis	65[a]	1	188	254
Diabetic coma	11	1	4	16
New onset DM or hyperglycemia	464	153	611	1228
Exacerbation of DM	91	46	3	140
Gestational DM	10	0	0	10
Post marketing study reports	31	0	0	31
Total	**672 (40%)**	**201 (12%)**	**806[c] (48%)**	**1679**

[a] Includes three reports of ketoacidosis, which do not describe DKA.
[b] Legal reports are those adverse event reports received by an attorney on behalf of a consumer. These reports are considered not medically confirmed if only a civil complaint and no supporting medical information has been received and are being treated by AstraZeneca as medically confirmed if the patient's medical records or a medical questionnaire filled out by the patient (plaintiff fact sheet) has been received. [c] contains both medically confirmed and non-medically confirmed reports.
DKA=diabetic ketoacidosis, DM=diabetes mellitus. Note: Reports are counted in only one category.

Table A 8 MedDRA preferred terms contained in 1679 reports of glucose dysregulation

Preferred term	Number of cases
Blood glucose	1
Blood glucose abnormal	15
Blood glucose fluctuation	14
Blood glucose increased	246
Diabetes mellitus	935
Diabetes mellitus inadequate control	12
Diabetes mellitus insulin-dependent	47
Diabetes mellitus non-insulin-dependent	194
Diabetic coma	186
Diabetic complication	1
Diabetic hyperglycaemic coma	1
Diabetic hyperosmolar coma	7
Diabetic ketoacidosis	243
Gestational diabetes	10
Glucose tolerance impaired	17
Glucose urine	1
Glucose urine present	3
Glycosylated haemoglobin increased	13
Hyperglycaemia	341
Insulin-requiring type II diabetes mellitus	2
Insulin resistance	5
Ketoacidosis	11
Total events	**2305**

NB: One report may contain multiple preferred terms, therefore the total number of events is larger than the total number of reports.