CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020639Orig1s049

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data
NDA 20-639/SLR-049 and NDA 22-047/SLR-023

Sponsor:	AstraZeneca
NDA/ Drug:	NDA 20-639/Seroquel (quetiapine fumarate) Tabs NDA 22-047/Seroquel XR (quetiapine fumarate) Tabs
Indications:	Schizophrenia, Schizophrenia maintenance, Bipolar depression, Bipolar mania, Bipolar maintenance and Major depressive disorder adjunctive therapy with antidepressants
Materials Submitted:	Annotated and non-annotated versions of revised CBE labeling
Date of Submission:	03/25/2011

The sponsor submitted a set of Changes Being Effected (CBE) labeling supplements regarding QT prolongation for Seroquel (NDA 20-639/SLR-049) and Seroquel XR (NDA 22-047/SLR-023) on 01/15/2010. The Complete Response Letter was sent to the sponsor regarding the above submission on 02/04/2011.

In this submission (dated 03/25/2011), the sponsor has submitted a response to Complete Response Letter, an amendment to above listed labeling supplements, revising the QT-related text has been provided. The proposed revisions include modified text regarding QT prolongation under Highlights, Warnings and Precautions (section 5.21), Drug Interactions (section 7) and Overdosage (section 10).

The sponsor has accepted most of our QT prolongation labeling changes. In addition, the sponsor made some QT prolongation text revisions, as well as editorial changes throughout the label, which were mostly for completeness and accuracy; these changes are acceptable.

This submission also contained some modifications to the label and they are as follows:
1. In the Medication Guide, a new bullet point was added to the list of things to tell your healthcare provider if you take or plan to take medicines for 'abnormal heart beats or rhythm'. This was proposed for consistency with QT labeling text in Section 5.12.
2. In section 8.1 and 8.3, pregnancy labeling is being revised to be consistent with the class labeling text currently approved in the Seroquel XR label.
3. Additional bullet point in the MG about breast feeding that Seroquel can pass into the breast milk to be consistent with labeling language in pregnancy and nursing section.
4. The 500-count bottle for all strengths was removed from Section 16 (How Supplied/Storage and Handling).

I find these above modifications acceptable.

(b) (4)

It should also be noted that the labeling also contains the labeling language for false urine tox screen results which was submitted under NDA 20-639/SLR-51 and NDA 22-047/SLR-24. The reviews of these labeling supplements are being conducted in separate documents.

Recommendations and Conclusions

I recommend this set of labeling supplements be approved. (b) (4)

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Kavneet Kohli-Chhabra, M.D
April 7, 2011
Clinical Reviewer
FDA CDER ODE1 DPP HFD 130

cc: NDA 20639/SLR-049 and 22-047/SLR-023
HFD 130/KUpdegraff
PDavid
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KAVNEET-RIPI KOHLI-CHHABRA
04/07/2011

NI A KHIN
04/12/2011
I agree that this set of labeling supplements be approved.

Review and Evaluation of Clinical Data
NDA 20-639/SLR-049 and NDA 22-047/SLR-023

Sponsor:	AstraZeneca
NDA/ Drug:	NDA 20-639/Seroquel (quetiapine fumarate) Tabs NDA 22-047/Seroquel XR (quetiapine fumarate) Tabs
Indications:	Schizophrenia, Schizophrenia maintenance, Bipolar depression, Bipolar mania, Bipolar maintenance and Major depressive disorder adjunctive therapy with antidepressants
Materials Submitted:	CBE labeling supplement on QT prolongation data with Seroquel overdose
Date of Submission:	01/15/2010

1. Background

The sponsor submitted this set of Changes Being Effected (CBE) labeling supplements regarding QT prolongation data with seroquel overdose under Seroquel NDA (NDA 20-639/SLR-049) and Seroquel XR NDA (NDA 22-047/SLR-023) on 01/15/2010.

The proposed changes to this label include revised text regarding QT prolongation under Highlights, Warnings and Precautions (section 5.21), Drug Interactions (section 7) and Overdosage (section 10).

The sponsor's proposed changes were based on their review of QT prolongation data in AZ's Clinical Trial Safety Database, Global Safety Database, 34 post-marketing cases of QT prolongation and overdose and their finding from medical literature search on this issue.

On 2/12/2010 we requested the sponsor to submit line listing of the post-marketing cases with reported 'verbatim term' and 'coded term' regarding the QT prolongation and Medwatch reports for the 34 post-marketing cases of QT prolongation and overdose. On 2/17/2010 the sponsor submitted the above requested information, a clinical overview on QT Prolongation and a summary of the medical literature findings. On 6/24/2010 we also requested the sponsor to provide QT analysis data from fixed dose placebo controlled study to look for any dose-response relationship. In particular we wanted them to provide us the tables for the following 1) mean QTc change from baseline; 2) shift changes to potentially clinically important QTcF values >500ms; 3) >60 ms increase shift. The sponsor submitted these additional data on 07/14/2010.

2. Review of Clinical Trial Data: AZ Clinical Trial Safety Database

Overview of safety database

A total of 26,454 patients exposed to quetiapine/quetiapine XR are contained in the AstraZeneca integrated clinical trials safety database (Version 17.1). This clinical trial safety database includes patients with diagnoses of schizophrenia, schizoaffective disorder, bipolar disorder (including manic, depressed and mixed) and dementia related psychosis.

The sponsor provided their analyses of data from:
1) Placebo-controlled trials
2) Longer-term relapse prevention studies
3) All controlled and uncontrolled trials combined

This section will primarily focus on sponsor's analysis of placebo-controlled trials and will then briefly describe any relevant sponsor's data from relapse prevention trials and all trials combined (controlled and uncontrolled).

2.1 Adverse Event Data

Search Terms/Methodology

The clinical trial safety database was searched for the following MedDRA terms: "Long QT syndrome" "Electrocardiogram QT prolonged", "Long QT syndrome congenital", "Electrocardiogram QT interval abnormal", "Torsades de pointes", "Ventricular tachycardia", "Ventricular fibrillation" and "Ventricular arrhythmia".

Placebo-Controlled and All Trial (controlled and uncontrolled) Data

QT interval prolongation

Out of 8,853 patients exposed to quetiapine in placebo-controlled clinical trials, there were 5 patients who experienced an AE of QT interval prolongation with an incidence rate of 0.06% as compared to 3 patients out of 4,359 patients exposed to placebo with an incidence rate of 0.07%. Out of 26, 454 patients exposed to quetiapine in all clinical (controlled and uncontrolled) trials there were 24 patients who experienced adverse events (23 AEs, 1 SAE) of QT interval prolongation with a 0.3% incidence rate.
See Table 1.

Table 1: Patients in placebo-controlled and all trials that experienced an AE of electrocardiogram QT prolonged

MedDRA term	Tx	Patients with event	Total patients[a]	Exposure[b]	Incidence rate[c]
Electrocardiogram QT Prolonged in placebo-controlled trials	QTP	5 (5 AEs)	8,853	981.7	0.06
	Pla	3 (3 AEs)	4,359	492.6	0.07
Electrocardiogram QT Prolonged in all trials	QTP	24 (23 AEs, 1 SAE)	26,454	7889.5	0.3

[a]The number of patients with any of the adverse events. Since a patient can have more than one adverse event, the number does not necessarily equal the sum of the numbers below.
[b]Patients must have received at least one dose of trial medication.
[c]Per 100 patient-years

Only one patient in the quetiapine group was reported as an SAE of electrocardiogram QT prolonged. Patient (5077IL/0048/0013/1305) was a 69 year old female on 25 mg of quetiapine. She was also taking paroxetine, risperidone, lorazepam, valproate and other non-psychiatric drugs. On day 85, patient experienced prolonged QT 0.520 sec from her baseline QT interval of 0.384 sec (QTcF values not provided) and patient was hospitalized for observation. The patient recovered from the event, quetiapine was discontinued and patient was withdrawn from the study.

Arrhythmia

Out of 8,853 patients exposed to quetiapine in placebo-controlled clinical trials there was 1 patient who experienced an SAE of ventricular arrhythmia with an incidence rate of 0.01 % as compared to none in the placebo group. Out of 26, 454 patients exposed to quetiapine in all clinical (controlled and uncontrolled) trials there were 2 patients who experienced AEs (1 AE, 1 SAE). See Table 2.

Table 2: Patients in placebo-controlled and all trials that experienced an AE related to Arrhythmia

MedDRA term	Tx	Patients with event	Total patients[a]	Exposure[b]	Incidence rate[c]
Any (Ventricular arrhythmia/ Ventricular tachycardia) in placebo-controlled trials	QTP	1 (1 SAE)	8,853	981.7	0.01
	Pla	0	4,359	492.6	0
Any (Ventricular arrhythmia/ Ventricular tachycardia) in all trials	QTP	2 (1 AE, 1 SAE)	26,454	7889.5	0.00

See Table 1 footnotes

The patient (5077IL/0056/0028/0007) with an SAE of ventricular arrhythmia was a 53 y/o male with cardiac history of coronary artery stent s/p silent MI and controlled hypertension who was on a long list of concomitant cardiac medications. He experienced ventricular arrhythmia on day 206 of taking Seroquel 250 mg/day. No ECG or other lab data available. Patient recovered after 8 days and study treatment was not completed as per the investigators decision to withdraw patient from the trial. The other patient with an AE of ventricular tachycardia had it one-day post treatment. Medical history was not provided for this patient. However, it was noted the patient recovered from the event.

2.2 ECG Data

Methodology

As of 2001, all multicenter studies included in the quetiapine XR development used a central ECG laboratory as their vendor for the central reading and reporting of ECG tracings by a cardiologist. In these studies ECG were obtained at baseline, at end of treatment and at intervals during study. It should be noted that on-treatment ECGs were not timed with respect to timing of dose but rather represent steady state exposure to drug. As quetiapine is known to increase heart rate, corrected QTc Fridericia (QTcF) data used.

At our request, the sponsor has submitted additional tables of:
1. Mean QTcF change from baseline by fixed dose
2. Shift changes to potentially clinically important QTcF values >500ms by fixed dose
3. Shift changes to >60 ms increase shift by fixed dose

Mean QTc changes in all short term placebo controlled trials (pooled analysis)

Mean changes in QTcF for quetiapine (IR and XR pooled) compared to placebo in short term placebo controlled studies from baseline to end of treatment was 0.46 msec. The change from baseline to maximum value was 0.37 msec. The mean change in QTcF values for quetiapine and placebo are provided in Table 3.

Table 3: Least Square adjusted mean change (ms) in QTcF in short-term placebo controlled studies (<13 weeks)

Change from baseline	Quetiapine LS mean	Placebo LS mean	Difference LS mean
N	7,111	3,544	
To final	-0.44	-0.90	0.46
To maximum	0.58	0.21	0.37

Mean QTc changes in short term fixed-dose placebo controlled trials (by dose analysis)

The mean changes in QTcF (ms) from baseline to end-of-treatment did not follow a linear dose-related signal. See Table 4.

Table 4: Mean Change in QTcF (ms) from baseline to end-of-treatment by dose (All fixed dose, placebo-controlled trials)

	QTP 50mg N=548	QTP 150mg N=1078	QTP 300mg N=1648	QTP 400mg N=471	QTP 600mg N=1141	QTP 800mg N=548	QTP - ALL N=5333	Placebo N=2171
Baseline	403 5(20.8)	405.8 (20.3)	399 9 (22.1)	394 1 (19.8)	396 5 (21.8)	392.7 (21.8)	399.6 (21.7)	401.4 (21.4)
End of Treatment	401.6 (20.4)	404.7 (20.2)	398.8 (21.8)	392.4 (19.7)	395 3 (20.7)	393 5 (20.5)	398 5 (21.2)	399.6 (21.1)
Mean (SD) Change	**-1.9 (17.3)**	**-1.0 (16.8)**	**-1.1 (18.7)**	**-1.8 (17.8)**	**-1.2 (18.4)**	**-1.9 (17.3)**	**-1.1 (18.1)**	**-1.8 (17.7)**
p-value (vs. placebo)	-0.7	1 1	0.1	0.5	0.2	-0.7	0.5	N/A

Shift changes in all short term placebo controlled trials (pooled analysis)

There were 3 patients in the quetiapine group who had a shift to potentially clinically important QTcF value ≥500 ms at any time representing an incidence rate of 0.04% compared to 2 patients in the placebo group who had a shift to ≥500 ms value with an incidence rate of 0.06%. None of which were SAEs. See Table 5.

Table 5: Incidence of shift to ≥500 ms QTc prolongation values at any time in placebo-controlled trials

MedDRA term	Tx	Patients with event	Total patients[a]	Exposure[b]	Incidence rate[c]
QTc (Fridericia corrected) interval ms	QTP	3 (all female)	7,111	847.2	0.04
	Pla	2 (all female)	3,543	422.4	0.06

See Table 1 footnotes

There was 1 patient in the quetiapine group who had a shift to ≥500 msec QTcF value at any time combined with an increase in QTcF from baseline of ≥ 60 msec compared to none in the placebo group. This patient had a QTcF value of ≥500 ms and increase from baseline of 80 msec on day 1 post treatment. This patient had an AE described as "dizziness upon arising from sleep" and they completed the study without sequelae. See Table 6.

Table 6: Incidence of ≥60 ms increase shift and ≥500 ms QTc prolongation values at any time in placebo-controlled trials

MedDRA term	Tx	Patients with event	Total patients[a]	Exposure[b]	Incidence rate[c]
QTc (Fridericia corrected) interval ms	QTP	1	7,111	847.2	0.01
	Pla	0	3,543	422.4	0.00

See Table 1 footnotes

There were 20 patients in the quetiapine group with ≥60 ms increase in QTc representing an incidence rate of 0.28% compared to 6 patients in the placebo group with an incidence rate of 0.17%. No SAEs were reported for all 26 patients. See Table 7.

Table 7: Incidence of ≥60 ms increase shift QTc prolongation values at any time in placebo-controlled trials

MedDRA term	Tx	Patients with event	Total patients[a]	Exposure[b]	Incidence rate[c]
QTc (Fridericia corrected) interval ms	QTP	20(16 female/4 male)	7,111	847 2	0.28
	Pla	6 (4 males/female)	3,543	422.4	0.17

See Table 1 footnotes

Shift changes in short term placebo controlled fixed dose trials (by dose analysis)

The sponsor has submitted incidence of shift to a clinically important (>500) QTcF prolongation value at 'any time during treatment' and 'end of treatment' for all indications and for all placebo controlled fixed dose trials that have had a central ECG evaluation. There was one subject (0.06 %) with a shift increase (>500) QTcF prolongation in the quetiapine 300 mg (n =1648) fixed dose group compared to no subjects with shift changes in the placebo group. No dose-related signal emerged as there were no other shift changes seen in the 50mg, 150mg, 400mg, 600mg and 800mg quetiapine treatment groups. The shift change percentage was similar (0.02%) in the quetiapine all dose (n=5333) group weather it was at any time during treatment or at end of treatment timeframe, compared to no subjects with shift changes in the placebo group.

The sponsor has also submitted incidence of shift to a clinically important (≥60 ms increase) QTcF prolongation value at 'any time during treatment' and 'end of treatment' for all indications and for all placebo controlled fixed dose trials that have had a central ECG evaluation. The highest incidence rate of shift (0.30 %) to a clinically important (≥60 ms increase) QTcF prolongation value at 'any time during treatment' was in the QTP 300 mg dose (n=1648) compared to shift change of 0.05 % in placebo (n=2171). The highest incidence rate of shift (0.24 %) to a clinically important (≥60 ms increase) QTcF prolongation value at 'end of treatment' was in the QTP 300 mg dose (n=1648) compared to shift change of 0.05 % in placebo (n=2171). Other small shift change signal was also seen at the QTP 600mg and QTP 800 mg dose groups but none of them were significant enough to produce a dose-related shift change signal. See table 8.

Table 8: Incidence of shift to clinically important (≥60 ms increase) QTcF prolongation values at any time during treatment and at end of treatment for all indications (all placebo-controlled fixed dose trials)

Treatment group and Patients with shift n (%)a	QTP At any time during treatment	Placebo n =2171 At any time during treatment	QTP At end of treatment	Placebo n =2171 At end of treatment
QTP 50 mg /n =548	0 %	1 (0.05) %	-	-
QTP 150 mg /n =1078	0 %	1 (0.05) %	-	-
QTP 300 mg /n =1648	5 (0.30) %	1 (0.05) %	-	-
QTP 400 mg /n =471	0 %	1 (0.05) %	-	-
QTP 600mg /n =1141	3 (0.26) %	1 (0.05) %	-	-
QTP 800mg /n =447	1 (0.22)	1 (0.05) %	-	-
QTP 50 mg /n =548	-	-	0 %	1 (0.05) %
QTP 150 mg /n =1078	-	-	0 %	1 (0.05) %
QTP 300 mg /n =1648	-	-	4 (0.24) %	1 (0.05) %
QTP 400 mg /n =471	-	-	0 %	1 (0.05) %
QTP 600mg /n =1141	-	-	2 (0.18) %	1 (0.05) %
QTP 800mg /n =447	-	-	1 (0.22) %	1 (0.05) %

a - Number of patients with shift. Event defined as first shift from baseline.

Additional study: Study 5077IL/0093

Study 5077IL/0093 was designed by the sponsor to prospectively evaluate the association between quetiapine and the QT interval. This study was previously reviewed by Dr. Andrew Mosholder (Review dated 2/26/2001). This was an inpatient, open label, multiple dose pharmacokinetic-pharmacodynamic study, involving 12 patients with psychiatric disorders. After 3 days of placebo as a "washout" from their prior medication, all subjects received quetiapine at a dose of 25 mg BID, titrated up to 400 mg BID by the 7th day. Multiple ECGs were obtained prior to quetiapine treatment and on the 10th (final) day of quetiapine administration, by which time it was expected that subjects were at steady state.

According to Dr. Mosholder's review, a total of 13 subjects participated in this study; one was discontinued for noncompliance. Mean heart rate increased after quetiapine treatment, with the mean increase from baseline ranging from 7-15 bpm during the day (day 10 versus baseline). In view of this, the Fridericia QT correction was employed. The mean QTc (Fridericia) was consistently higher at all timepoints throughout day 10 in comparison to baseline, with a mean change from baseline at tmax (1 hr) of +22 msec (95% CI +14 to +30 msec).

Dr. Mosholder thought the study design and the interpretation of its results were hampered by the lack of a control group in this study. I agree with him.

3. Post-Marketing Data

As per the sponsor, it is estimated that ~ 22.8 million patients have been exposed to quetiapine/ quetiapine XR since launch through end of February 2008. 'Sapphire' is the sponsor's global clinical drug safety database that contains all SAE reports from spontaneous sources. Non-serious reports from clinical studies are usually entered onto the clinical study database.

A search was performed of the global safety database by the sponsor through 11/11/2008 for quetiapine/quetiapine XR reports containing MedDRA (version 11.0) preferred terms (PTs) associated with QT prolongation, Torsade de Pointes and other arrhythmias of interest, resulting in a total of 276 events in 252 unique patients. An overview of the search terms and the events identified for these are summarized in Table 9.

Table 9: Search terms for post marketing reports of QT prolongation, Torsades de Pointes, arrhythmias of interest

Search grouping	Preferred terms
QT prolongation grouping (221 events/221 unique reports)	Long QT syndrome (3 reports), Electrocardiogram QT prolonged (214 reports), Long QT syndrome congenital (0 reports), Electrocardiogram QT interval abnormal (4 reports)
Arrhythmia grouping (55 events/48 unique reports)	Torsades de pointes (14 reports), ventricular tachycardia (29 reports), ventricular fibrillation (10 reports), ventricular arrhythmia (2 reports)

Additionally, a search was conducted for reports of "Sudden cardiac death", "Cardiac arrest", "Sudden death" and "Death unexplained" to identify those reports in which QT prolongation was mentioned or discussed but not reported as an event term. A total 163 reports were identified with these search terms but only 2 reports regarding discussion of QT prolongation were identified. However, there was no QT interval data accompanied with these 2 reports.

3.1 Post-marketing reports of QT prolongation with quetiapine overdose

The post-marketing case reports of QT prolongation are divided into reports of 'QT prolongation with overdose' and 'QT prolongation without overdose'. There were total 220 post-marketing reports on QT prolongation, of which 34 described abnormal QT prolongation associated with quetiapine overdose. Among the 34 overdose reports, 17 reports were confounded secondary to multi-drug overdose and in the other 17 reports (13 SAEs and 4 AEs) quetiapine was the only known drug taken.

Most of the overdose case reports lacked medical history, baseline QT interval data, laboratory investigations and/or specified QT correction methods. Table 10 below provides a brief summary of case reports observing QT prolongation following a quetiapine overdose.

Table 10: Brief summary of post-marketing cases with QT prolongation following quetiapine overdose

#	Case ID PT	AGE/SEX	QTP DOSE	CASE DESCRIPTION/AZ COMMENT
1	2005AC00094	14/M	1900 mg	Source is a literature report. Patient was inpatient and on day 14 of admission, the pt. attempted suicide. ~3 mths prior to the event, an EKG = NSR & QTc = 411 msec. An hour after OD, an EKG Showed QTc= 453 msec on the EKG printout. Pt. was responsive & conscious. A second EKG approx. 40 minutes later showed a QTc interval of 618 msec on printout, and 500 msec when calculated manually with u-waves noted in leads V2-V3. Pt. transferred to ICU for monitoring & 60gms of charcoal was administered. 6 hrs later QTc was 436 msec on printout, and was calculated the same manually with no further elevations. Labs, including metabolic + LFTs were WNL, however the pt was reported as neutropenic (WBC=3.8, neutrophils=43%). Pt monitored in the ICU for 24 hours, and then readmitted to

13	2007UW12036 (NS)	Unk/F	17 tab	Patient took 17 Seroquel tab (dose unknown) in ER as intentional OD and 'elevated QTC' reported. No further info was available.
14	2007UW07880 (S)	Unk/Unk	Unk	Patient presented to ER after OD of handful of quetiapine with slight QT prolongation. No further info was available.
2	2005AP05325 (NS)	42/F	800-2000 mg/day x approx 2 mths	Patient had a past medical h/o of irregular heartbeats and did an accidental OD, they were hospitalized with ECG ='QT changes', Seroquel was discontinued and the event resolved.
3	2008AC02072 (S)	34/F	30,000 mg (100 x 300 mg tablets)	Source is a literature report. By the time of hosp admission, Pt was found unconscious; comatose with GCS 7 rapidly ↓ to 5, the BP was 110/58, RR 15, HR 159 bpm. Urine drug screen was + for cannabis. CBC= 22,300/mL. Electrolytes and LFTs were all WNL. ECG = PQ and QRS intervals normal, the QT= interval = 400 ms, and the QTc =620 ms (Bazett's correction), HR=143 bpm. Pt was intubated and tx with 50 gms of activated charcoal and a bolus of 1500 mL of LR was given over 2 hours to treat mild hypotension. Pt was transferred to ICU. Outcome unknown
4	2008AP02010 (S)	39/F	3000mg	Patient experienced QTc prolongation, palpitation and dizziness after OD. Pt had been taking quetiapine for 15 months prior to incident. Pt did not experience cardiac arrest or syncope. There was no prior med hx of arrhythmia, CAD, or relevant family hx. ECG value not provided. Unknown if patient continued therapy with quetiapine but they recovered without any sequelae.
5	2008PK00864 (S)	19/F	4000mg	Patient was being treated with quetiapine, the concomitant meds and med hx not reported, after OD pt experienced somnolence and QT prolongation. No other details were reported. Pt's outcome is unknown.
6	2003AP04306 (S)	19/F	24 grams	Source is a literature report. After patient OD'ed pulse was117 bpm, systolic BP = 100 mmHg, they were intubated and gastric lavage done, 4 hr after ingestion pt had general tonic clonic seizure (15-20 sec) that resolved without tx followed by hypotension occurred (78/42). ECG = QT/QTc = 390/535 msec. 25 hrs after OD patient was extubated and they recovered. No baseline QTc interval was known. No other info was provided.
7	1998UW49037 (S)	19/M	9.6 grams	Within 1 hr of OD Pt was unresponsive, hypotensive, tachycardia, GCS = 6. 3 hrs post-overdose QTc=581 ms and 710 ms HR= 96 bpm. 22 hrs post-overdose, BP = 180/83, pulse = 138 bpm, temp = 36.3 C, QT = 400 msec (QTcB = 0.56 sec, QTcF = 0.486sec), Blood screen = neg, Mild hypokalemia (K = 3.3 mEq/L), ↑ glucose (137 mg/dL). Treatment included intubation, IV saline, gastric lavage done and 60 gms of activated charcoal, given. Within 3 hr of treatment, Pt was localizing pain, GCS = 7, and 19 hr post treatment Pt awake and following commands, GCS = 11. patient was extubated and BP was stable. Next day QTc=417 ms, seven days post-overdose QTc=374 ms (correction unknown). Mild sinus tachycardia persisted for 48 hr. Pt recovered from prolonged QT. Pt also had atypical chest pain—MI ruled out. No baseline QTc interval was provided. No other info was provided.
8	2003UW06219 (S)	35/F	Unk	Patient taking 300 mg/day quetiapine for unknown amount of time. Pt OD'ed on quetiapine and had altered mental status, seizure, hypotension, cardiac arrhythmia, prolonged QT (no values provided), heart block. Patient was tx with dopamine, charcoal, norepinephrine, lorazepam, bicarbonate, glucagon, blood transfusion. No baseline QTc interval or other info was provided and Pt outcome was unknown.
9	2002AP01226 (S)	36/F	15 grams	Source is a literature report. Pt OD'ed on quetiapine and developed obtundation, hypotension, tachycardia, prolonged QT (no values provided). Urine enzyme immunoassay was positive for TCA (Pt reported not to be taking anti-depressants or cyclobenzaprine). Search of Pts home revealed only quetiapine present. It was determined to be false positive immunoassay for TCA. Pts outcome was unknown. No other info was provided.
10	2007UW09396 (S)	Unk/Unk	5600mg	Patient OD'ed and experienced hypokalemia and QT wave changes. No further info. One hour after admission, the repetitive myclonic jerks resolved after IV administration of lorazepam 4 mg in 2 divided doses. Four hours after admission, 2 generalized tonic clonic seizures were successfully treated with IV lorazepam 2 mg. The GCS ↓to 3 six hours after initial presentation and remained for the next 3 hrs. 17 hours after admission, GCS ↑ to 8 and pt was extubated. Pt remained hemodynamically stable but tachycardic up to 40 hours after admission. Blood glucose, lactate, and leukocyte returned to normal with no intervention. 11 hours after presentation, QT 360 ms and QT 320 ms. The QTcB interval returned to normal (430 ms). Pt transferred to a psychiatric clinic for further observation.
11	2008UW01809 (S)	Unk/F	30 x 300 mg or 20 x 200 mg	After starting tx (300 mg, duration unknown), patient w/ borderline personality disorder experienced OD (dose reported from 4 g to 9 g) and was admitted, ECG revealed QTc prolongation ≥550 ms. Follow-up reports showed ECG normalized and quetiapine was continued.
12	2007UW26517 (NS)	Unk/Unk	>5 g	Physician reported several quetiapine ODs with 'doses in excess of 5000 mg' and pt 'often had significant QTc prolongation' (values and correction method not provided). Very limited info or follow-up info available.

Approx approximately. BP blood pressure. BPM beats per minute. CBC complete blood count. Cont'd continued. D/t due to. ECG electrocardiogram. ER emergency room. F female. F/u follow up. g grams GCS Glasgow coma scale. Hosp hospital, hospitalized, hospitalization. HR heart rate. Hx history. ICU intensive care unit. Info information. IV intravenous. kg kilograms. LR lactated ringer's. Med hx medical history. mg milligrams. Mo(s) month (s). NS not serious. NSAIDS nonsteroidal antiinflammatory drug. OD overdose. Pt patient. PT preferred term. RR respiratory rate. S serious. Tabs tablets Tx treatment. unk unknown. WBC white blood cell. W/ with. w/ drawn withdrawn. Y year(s). + and. ↑ increased, elevated, or high. ↓ decrease/low

3.2 Post-marketing reports of QT prolongation without quetiapine overdose

Of the 220 post-marketing reports of QT prolongation, 186 reports did not include an event of overdose. These reports are discussed in three groupings:

- Reports with QT interval data at baseline and at time of event
- Reports with QT interval data at the time of event and no baseline values
- Reports with no QT interval data provided

Reports of QT prolongation with QT interval data at baseline and at time of event

Of the 220 post-marketing reports of QT prolongation, 73 reports (48 SAEs and 25 AEs) described events of prolonged QT interval. Of these, 12 reports (8 SAEs and 4 AEs) included QT interval data at baseline and at the time of the event. The baseline QT interval data described cardiac risk factors or comorbidity and/or confounding concomitant medications for which QT prolongation or cardiac dysrhythmias (Torsades de Pointes, ventricular tachycardia, ventricular fibrillation) were reported in 10 out of 12 reports. For one report no medical history or concomitant medication information was provided. In the remaining reports that did not describe any obvious confounding factors, QTc values did not exceed 500 msec and the method of correction was not specified. Sponsor stated that for all 12 cases the QTc correction method was not known at the time of the event, thus limiting assessment as Bazett's correction might result in an overcorrection for drugs that increase heart rate, such as quetiapine.

Reports of QT prolongation with QT interval data at time of event (no baseline provided)

Of the 220 post-marketing reports of QT prolongation, 61 reports (40 SAEs and 21 AEs) described events of prolonged QT interval. Of these 36 described cardiovascular risk factors, relevant comorbidity, cardiovascular medical history, electrolyte abnormality, confounded by concomitant medication for which QT prolongation, Q and T wave distortions, or cardiac arrhythmias (Torsades de Pointes, ventricular tachycardia, ventricular fibrillation) have been reported. One report was determined to be a miscalculation of QT interval. Another report described an unlikely temporal relationship. The remaining 10 reports that provided QT interval data were lacking critical medical information for assessment. In 15 reports the event of QT prolongation resolved after quetiapine alone was discontinued; 11 of these reports were confounded by concomitant medication and cardiac risk factors. There were no reports of positive rechallenge.

Reports of QT prolongation without QT interval data at anytime

Of the 220 post-marketing reports of QT prolongation, 113 reports (61 SAEs and 52 AEs) described events of prolonged QT interval. Since no QT values, baseline or otherwise, were provided for this grouping of reports, there is no documentation that the QT interval was prolonged while the patient was taking quetiapine. Most of the reports were confounded by concomitant medications or were complicated by medical conditions, or had limited clinical information.

3.3 Post-marketing reports of ventricular arrhythmias

A total of 41 events of the following MedDRA preferred terms "Ventricular tachycardia" (29 reports), "Ventricular arrhythmia" (2 reports) and "Ventricular fibrillation" (10 reports) were reported. Of these, 38 reports of arrhythmias were medically confirmed and one report was a consumer report that was not medically confirmed.

3.4 Post-marketing reports of *Torsades de Pointes*

There were a total of 14 post-marketing reports with the term "*Torsade de Pointes*". There were no fatal reports of *Torsade de Pointes*. Of the 14 Torsades de Pointes reports, 11 contained additional terms "Electrocardiogram QT prolonged" (8 reports) and "Long QT syndrome" (3 reports). In addition, 7 reports of Torsade de Pointe contained additional arrhythmia terms, "Ventricular tachycardia" (2 reports) and "Ventricular fibrillation" (5 reports). All 14 patients with events of Torsade de Pointes were female with age range from 26 to 80 years (mean 58 y/o). Of the 14 total reports, 13 were medically confirmed and one was a consumer report that was not medically confirmed. One report described a multidrug overdose, in two reports minimal medical information were known and 11 reports were confounded by concomitant medication, concurrent illness and/or relevant medical history. None of the 14 reports included ECG rhythm strips.

3.5 Post-marketing reports of Cardiac arrest/Sudden death containing information on QT prolongation

A total of 163 reports were identified that contained the following MedDRA preferred terms, "Sudden cardiac death", "Cardiac arrest", "Sudden death" and "Death unexplained". Of the 163 reports, two reports of sudden death included discussion of QT prolongation in the narratives where the investigator suspected the possibility of QT prolongation. No ECG rhythm strips available. No other confirmation of QT prolongation events (neither baseline data and nor data around the time of the event) was provided for both reports.

4. Literature Search

Methodology

The sponsor conducted an in-house database (the database indexes biomedical literature and searches 8,000 journals daily) search for medical/scientific literature to identify all reported cases of QT prolongation, Torsade de Pointes and arrhythmias attributed to quetiapine/quetiapine XR. The database was searched through November 6, 2008 however the sponsor failed to identify the start date for the search.

In addition, I conducted a PubMed search, looking for any articles on quetiapine/quetiapine XR related to the search terms QT prolongation, Torsade de Pointes, arrhythmias and sudden cardiac death from September 1997 to June 2010. 6 articles were identified. I reviewed those articles and the ones the sponsor has sent. The summary of those individual studies are as follows (section 4.1).

4.1 Clinical Studies

Pfizer Study 54 (Harrigan et al 2004) [1]

[1] Harrigan E, Miceli J, Anziano R, Watsky E, Reeves K, Cutler N, et al. A Randomized Evaluation of the Effects of Six Antipsychotic Agents on QTc,In the Absence and Presence of Metabolic Inhibition. Journal of Clinical Psychopharmacology 2004;24:62-69.

This was the prospective randomized, open label, parallel-group, fixed-sequence, inpatient study to look at the effects of 6 antipsychotics (haloperidol, thioridazine, ziprasidone, quetiapine, olanzapine and risperidone) on the QTc interval in and around the time of estimated peak plasma/serum concentrations in the absence and presence of metabolic inhibition (co-administration of agents that block CYP450). This study used 'baseline-corrected' QTc interval as the primary analysis in assessing QTc changes from baseline, instead of the Bazett calculated QTc changes. The results showed the mean heart rate for the quetiapine group was 73 beats per minutes (bpm) (range was 58 - 96 bpm), the mean QT interval was 362 msec (range was 314 - 402 msec), the mean QTc interval was 387 msec (range was 380 - 394 msec). The mean baseline-corrected QTc change was greatest with thioridazine (30 msec) followed by ziprasidone (16 msec), haloperidol (7 msec), quetiapine (6 msec; n=27; 750 mg/day) and olanzapine (2 msec). No patients had a QTc interval of 500 msec at anytime with or without metabolic inhibition.

McManus et al 1999[2]

An uncontrolled, multicenter, open label, 52-week study designed to evaluate the safety of quetiapine in elderly patients (≥65 y/o; n= 151; 25 to 800 mg/day) with psychotic disorders. Results showed no clinically significant changes from baseline on ECG in heart rate or QT intervals. However, one patient withdrew from the study because of prolonged QT and the journal and the sponsor stated that no further information about this patient was available.

Kuehnl et al 2002 [3]

A poster presentation at the 7th International Congress of Parkinson's disease and Movement Disorders described a study in which 19 Parkinson patients with drug-induced psychosis were administered quetiapine (50 to 225 mg/day). The QTc interval was assessed at baseline and at discharge 21 days later, method of QT correction was not provided. The average QTc time was 451 msec at baseline and 458 msec at discharge. In 14 patients the average QTc interval was prolonged by 20 msec, one patient reached 80 msec and five patients kept a constant QTc interval. In summary, these authors concluded that quetiapine did not cause pathological QTc prolongation in this patient group.

McConville et al 2003[4]

This was an 88-week open label trial that provided the long-term efficacy, tolerability and safety of quetiapine in the adolescents (12 to 16 y/o; 25 to 800 mg/day) with diagnoses of schizoaffective disorder (n=7) or bipolar disorder (n=3). ECGs were done routinely and 3 patients were identified with abnormal ECGs. Two had intermittent, asymptomatic, prolonged QTc intervals (maximum 0.470 msec), for which no further information (including the correction method) was provided. Another patient had first-degree AV block, with possible ventricular hypertrophy, which improved during the course of the trial. The AV block was present at the beginning of the trial and the pediatric cardiologist's opinion was that it did not require medication. The sponsor states limited clinical information was available on these three patients thus causality is hard to assess.

Preskorn and Panagides 2008[5]

A16-day multicenter double-blind study in which the effects on QTcF for asenapine versus quetiapine and placebo were assessed. A total of 148 patients with schizophrenia or schizoaffective disorder were randomized to 1 of 4 treatment groups for 16 days (asenapine 10 mg/day for 10 days followed by asenapine 20 mg/day for 6 days; asenapine 30 mg/day for 10 days followed by asenapine 40 mg/day for 6

[2] McManus DQ, Arvanitis LA, Kowalcyk BB. Quetiapine, a novel antipsychotic: experience in elderly patients with psychotic disorders. J Clin Psychiatry 1999;60(5):292-8.
[3] Kuehnl N, Strothjohann M.H., Emmans D, Quetiapine: No QTc interval prolongation in psychotic Parkinson patients. Movement Disorders 2002; 17 (5) S68-S69.
[4] McConville B, Carrero L, Sweitzer D, Potter L, Chaney R, Foster K, Sorter M, et al. Long-Term Safety, Tolerability, and Clinical Efficacy of Quetiapine in Adolescents: An Open-Label Extension Trial. Journal of Child and Adolescent Psychopharmacology 2003;13(1):75-82.
[5]Preskorn S, Panagides J. Effect of asenapine on QTc interval in patients with schizophrenia. J
Am Pharm Assoc 2008;48:2:269.

days; quetiapine 750 mg/day for 16 days; or placebo for 16 days). On Day 16, the QTc LS mean difference from placebo for asenapine 20 mg/day was 10.5 msec; for asenapine 40 mg/day was 5.2 msec and for quetiapine 750 mg/day it was 9.9 msec. There were no statistical differences observed between asenapine and quetiapine. There were no instances of QTc interval ≥500 msec in any treatment group. Increases ≥60 msec from baseline for QTc was reported for 1 quetiapine patient and for 2 placebo patients. In summary, results for quetiapine treated patients in this study showed minor QTc prolongation.

De Castro et al 2008[6]

This was a recent study in a small group of children and adolescents (mean age 15 years, 26 male, 12 female) where subjects were treated with olanzapine (21%), quetiapine (47%) and risperidone (32%). In addition, 14 healthy children were used as control subjects. Patients had an ECG performed at baseline and after 6 months of therapy. Abnormal prolongation of the QTc interval for males was defined as 450 msec and 470 msec for females. Mean QTc duration (for all three antipsychotics) at baseline was 387 msec (corrected using the Bazett's formula) and mean QTc duration after 6 months was 394 msec. The change in these values was not considered statistically significant (P=0.134) by the sponsor. No patients in any of the three antipsychotic treatment groups exceeded a QTc value greater then 450 msec.

Kramer et al 2008[7]

This was a cohort study conducted to evaluate the minimal dose that can cause severe symptoms in quetiapine overdose. The analysis included all reports of mono intoxications of quetiapine reported to the Swiss Toxicological Information Center from 2000-2007. In the 83 cases evaluated (mean age 31 y/o, 22 male, 61 female, median dose ingested 2grams) the most common symptoms included CNS depression (83%), tachycardia (46%), hypotension (20%) and prolonged QTc interval (15%). The median dose consumed of quetiapine was 0.88grams for asymptomatic patients, 1.5grams (range was 0.05g-11g; n=53) for mild symptoms, 4grams (range was 0.2-20g; n=13) for moderate symptoms and 6grams (range was 2.5-22g n=11) for severe symptoms. The authors concluded that severe symptoms which include respiratory depression, coma and seizures can be expected when 2.5grams or more of quetiapine is ingested.

Ray et al 2009[8]

In the Wayne A. Ray study, they analyzed Tennessee Medicaid records for 44,218 patients (users of typical antipsychotics), 46,089 patients (users of atypical antipsychotics) and 186,600 patients (nonusers of antipsychotic drugs). The age range varied from 30 to 74 years of age and the time period measured of drug intake was from 1990 to 2005. The method consisted of adjusting the incidence of sudden cardiac death (SCD) among users of antipsychotic drugs in a retrospective cohort study. Results showed there were 478 sudden cardiac deaths among those taking the typical and atypical antipsychotic drugs, about twice the rate of the control group. The authors claim the risk of SCD to 3 deaths for every 1,000 patients taking the drugs for a year. The risk of SCD was noted to be similar among typical and atypical antipsychotic users. The study also noted the dose-relatedness of the SCD risk. .

Reviewer's comment: QTP was one of the atypical antipsychotics included in the Ray study. The finding from this study was part of discussion at the Psychopharmacologic Drug Advisory Committee (PDAC) meeting including members with cardiology expertise on April 8, 2009 regarding prior QTP XR efficacy supplements for MDD and GAD in adults. Following the PDAC discussion, the Division of Psychiatry Products has requested that the sponsors of atypicals provide all clinical trial data to conduct a meta-analysis study the effects on sudden cardiac deaths. The sponsors have been submitting these

[6] de Castro MJ, Fraguas D, Laita P, Moreno d, Parellada M, Pascual D, et al. QTc changes after 6 months of second-generation antipsychotic treatment in children and adolescents. Journal of Child and Adolescent Psychopharmacology. 2008;18(4): 381-383.

[7] Kramer I, Rauber-Luthy C, Kupferschmidt H. Acute intoxication with quetiapine: a cohort study. Clinical Toxicology. 2008;46(7):643 (NACCT Abstracts).

[8] Ray, WA et.al., Atypical Antipsychotic Drugs and the Risk of Sudden Cardiac Death, N Engl J Med (2009) vol. 360:3, pp. 226-235.

requested data and the submitted data are currently under review by the Division's safety team. Further modifications to product labeling may be made upon completion of our review of these submitted data.

4.2 Epidemiology Study

An epidemiologic study (Balit C.R et al 2003)[9] utilizing a prospective database of poisoning admissions to a regional toxicology center to identify quetiapine overdoses for evaluation of QT prolongation associated with quetiapine overdoses. There were total 45 confirmed cases of quetiapine overdoses through 02/01/2001 to 02/01/2002, of which 18 were included in the study. No arrhythmias or deaths occurred. Of the 10 patients for whom ECGs were available, 8 experienced tachycardia. The corrected (Bazett's formula) QTc interval was considered abnormal if longer than 440 msec. The author states the mean corrected QTc interval in the study was 487 msec and the mean uncorrected QTc interval was 349 msec. Although a prolonged QTc occurred, the authors concluded that its clinical significance was unclear because it was most likely caused by an overcorrection caused by the tachycardia. They further suggested that the use of QTc interval with rapid pulse rates is erroneous as it has little predictive value for malignant arrhythmias.

4.3 Case Reports

There was 1 case report (Gupta et al 2003)[10] of prolonged QT interval not indexed in AstraZeneca's safety database (Sapphire). This was a 50 y/o woman hospitalized with schizoaffective disorder whose concomitant medications included citalopram, fluticasone inhaler, theophylline, ipratropium multidose inhaler, furosemide, amlodipine, and perindopril. There was no baseline ECG. When quetiapine was increased to 100 mg AM and 300 mg PM, the patient experienced chest pain combined with a prolonged QT interval of 612 msec as seen on ECG printout. The manual check of ECG read QTc interval of 480 msec. Cardiology consult was sought and she was monitored over 5 days with repeat ECGs. The cardiologist diagnosed a systolic ejection murmur over the aortic area and a presence of a 'U' wave. The investigator felt that above findings most likely led to an abnormal prolonged QTc interval reading. She remained asymptomatic, thus quetiapine dose was increased to 800 mg/day and at time of discharge her QTc interval was 411 msec.

5. Reviewer's Labeling Comments

The proposed changes to this label include revised text regarding QT prolongation under Highlights, Warnings and Precautions (section 5.21), Drug Interactions (section 7) and Overdosage (section 10). The following is the sponsor's proposed text.

Highlights/Recent Major Changes

(b) (4)

Reviewer's Comment:
This statement should be deleted from highlights as part of recent major changes. See other labeling comments below.

Section 5.21 Use in Concomitant Illness

In clinical trials quetiapine was not associated with a persistent increase in absolute QT intervals. However, in post marketing experience there were cases reported of QT prolongation in patients who overdosed on quetiapine [see Overdosage (10.1)], in patients with concomitant illness, and in patients

[9] Balit C.R., Isbister G.K., Hackett P, Whyte, I.M. Quetiapine Poisoning: A Case Series. Annals Emergency Med 2003; 42 (6), 751-758.
[10] Gupta S, Nienhaus K, Shah S.A. Quetiapine and QTc Issues: A Case Report. Letter to the Editor. Jr Clin Psychiatry 2003; 64 (5) 612-613.

taking medicines known to cause electrolyte imbalance or increase QT interval [see Drug Interactions (7)]. Caution should be exercised when quetiapine is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also caution should be exercised when quetiapine is prescribed with medicines known to cause electrolyte imbalance or increase QT interval or with concomitant neuroleptics, especially for patients with increased risk of QT prolongation, i.e., the elderly, patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalemia, or hypomagnesemia.

Reviewer's Comment:
The first sentence should be deleted. The cases of QT prolongation in patients who overdosed on quetiapine should be described in the overdose section (Section 10) of the labeling. The standard cautionary statements regarding use of quetiapine concomitantly with drugs known to cause QT interval or electrolyte imbalance, history of congenital long QT syndrome, CHF, hypokalemia or hypomagnesemia should also be moved to describe in the overdose section (section 10).

Section 7 Drug Interactions
Caution should be exercised when quetiapine is used concomitantly with drugs known to cause electrolyte imbalance or to increase QT interval [see Warnings and Precautions (5.21)].

Reviewer's Comment:
There is no objection of adding this sentence in the drug interaction but it should be cross-referenced to section 10, not to the warnings/precautions, 5.21 as proposed.

Section 10 Overdose
In post-marketing experience, there were cases reported of QT prolongation with overdose.

Reviewer's Comment:
I have no objection to the sponsor's proposal in this section. The 2nd and 3rd sentence from the sponsor's proposed labeling changes under Section 5.21 Use in Concomitant Illness should be moved to this Overdose section.

In addition, the sponsor also made some editorial revisions in the highlights and throughout the labeling. These editorial changes are acceptable.

6. Conclusions and Recommendations

After reviewing the sponsor's reports of clinical and post-marketing safety data as well as the review of medical/scientific literature, I did not observe any strong evidence of direct correlation between the use of quetiapine/quetiapine XR and the adverse event reports of QT prolongation, Torsade de Pointe and/or ventricular arrhythmia. Most of the AEs and SAEs occurred in the setting of co-morbid risk factors and/or concomitant confounding medications. The QT prolongation cases observed were with quetiapine overdose.

There are no major objections to labeling changes proposed in this set of labeling supplements adding the statement of QT prolongation with QTP overdose has been observed as post-marketing event and adequately supported by the submitted data.

7. Comments to the Sponsor

Please refer to section 5 for reviewer's comments to be made to the sponsor. We should negotiate the placement of labeling language with the sponsor prior to approval of this set of labeling supplements.

_____
Kavneet Kohli-Chhabra, M.D
August 3, 2010
Clinical Reviewer
FDA CDER ODE1 DPP HFD 130

cc: NDA 20639/SLR-049 and 22-047/SLR-023
HFD 130/KUpdegraff
KKohli-Chhabra
NKhin
TLaughren
MMathis

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20639	SUPPL-49	ASTRAZENECA LP	SEROQUEL(QUETIAPINE FUMARATE)25/100/200M
NDA-22047	SUPPL-23	ASTRAZENECA PHARMACEUTICALS LP	SEROQUEL XR

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/s/

KAVNEET-RIPI KOHLI-CHHABRA
08/04/2010

NI A KHIN
08/10/2010

I agree with Dr. Kohli-Chhabra's recommendation that this set of labeling supplements be approved. However, it will be contingent on the conclusion of labeling negotiation with the sponsor.