SEROQUEL XR®

quetiapine fumarate

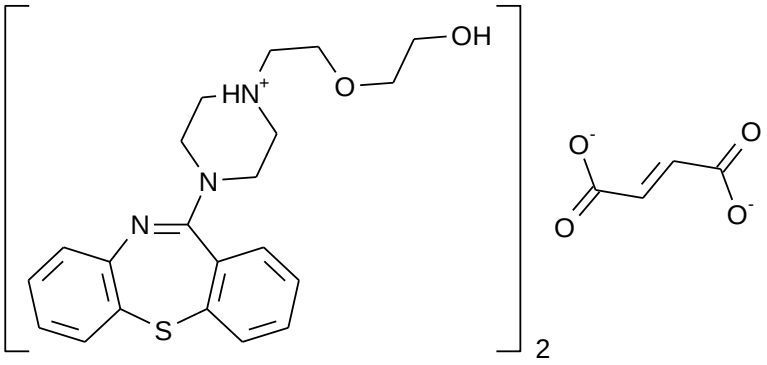
PRODUCT INFORMATION

NAME OF THE MEDICINE

Quetiapine fumarate

Chemical Name: Bis[2-(2-[4-(dibenzo[b,f][1,4]-thiazepin-11-yl)piperazin-1-yl] ethoxy) ethanol] fumarate.

The chemical structure of quetiapine fumarate is:



CAS number: 111974-72-2

DESCRIPTION

Quetiapine fumarate is a weak acid (pKa 3.3, 6.8) which exhibits moderate pH dependent solubility (94.3 mg/mL to 2.37 mg/mL at pH values from 1 to 9) and lypophilicity characteristics (Log P) which vary with pH (0.45 in water, 1.37 at pH 5, 2.65 at pH 7 and 2.59 at pH 9). Quetiapine fumarate has an aqueous solubility of 3.29 mg/mL at 25°C.

SEROQUEL XR 50 mg, 150 mg, 200 mg, 300 mg and 400 mg are capsule shaped modified release tablets which are peach (50 mg), white (150 mg), yellow (200 mg), pale yellow (300 mg) or white (400 mg) in colour. All tablets are embossed with “XR” and the strength on one side, while the other side is plain.

Each tablet contains quetiapine fumarate equivalent to 50 mg, 150 mg, 200 mg, 300 mg or 400 mg of quetiapine free base. The tablets also include the following excipients - microcrystalline cellulose, sodium citrate dihydrate, lactose monohydrate, magnesium stearate, hypromellose, macrogol 400, titanium dioxide, iron oxide red CI77491 (50 mg tablet) and iron oxide yellow CI77492 (50 mg, 200 mg and 300 mg tablets). SEROQUEL XR does not contain gluten.

PHARMACOLOGY

Mechanism of Action

Quetiapine is an atypical antipsychotic agent. Quetiapine and the human plasma metabolite, norquetiapine, interact with a broad range of neurotransmitter receptors. Quetiapine and norquetiapine exhibit affinity for brain serotonin ($5HT_2$) and dopamine D_1 and D_2 receptors; this combination of receptor antagonism with a higher selectivity for $5HT_2$ relative to D_2 receptors is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effects (EPS) liability of quetiapine compared to typical antipsychotics. Quetiapine has no affinity for the norepinephrine transporter (NET) and low affinity for the serotonin $5HT_{1A}$ receptor, whereas norquetiapine has high affinity for both. Inhibition of NET and partial agonist action at $5HT_{1A}$ sites by norquetiapine may contribute to SEROQUEL's therapeutic efficacy as an antidepressant. Quetiapine and norquetiapine have high affinity at histaminergic and adrenergic alpha1 receptors and moderate affinity at adrenergic alpha2 receptors. Quetiapine also has low or no affinity for muscarinic receptors, while norquetiapine has moderate to high affinity for several muscarinic receptor subtypes, which may explain anti-cholinergic (muscarinic) effects. The norquetiapine metabolite 7-hydroxy norquetiapine also has affinity for histaminergic H_1 and $5HT_{2B}$ and $_{2C}$ receptors at clinically relevant concentrations.

Pharmacodynamics

Quetiapine is active in tests for antipsychotic activity, such as conditioned avoidance. It also reverses the action of dopamine agonists, measured either behaviourally or electrophysiologically, and elevates dopamine metabolite concentrations, a neurochemical index of D_2 receptor blockade. The extent to which the metabolites norquetiapine and 7-hydroxy norquetiapine contribute to the pharmacological activity of quetiapine in humans is uncertain.

In pre-clinical tests predictive of EPS, quetiapine is unlike typical antipsychotics and has an atypical profile. Quetiapine does not produce dopamine D_2 receptor supersensitivity after chronic administration. Quetiapine produces only weak catalepsy at effective dopamine D_2 receptor blocking doses. Quetiapine demonstrates selectivity for the limbic system by producing depolarisation blockade of the mesolimbic but not the nigrostriatal dopamine-containing neurones following chronic administration. Quetiapine exhibits minimal dystonic liability in haloperidol-sensitised or drug-naive Cebus monkeys after acute and chronic administration.

Pharmacokinetics

Absorption

Quetiapine is well absorbed and extensively metabolised by the liver following oral administration. Steady state peak molar concentrations of the active metabolite norquetiapine are 35% of that observed for quetiapine.

The pharmacokinetics of quetiapine and norquetiapine are linear across the approved dosage range.

Peak plasma concentrations of quetiapine are achieved approximately 6 hours after administration (T_{max}) of SEROQUEL XR. Dose-proportional pharmacokinetics is

displayed for doses of SEROQUEL XR of up to 800 mg administered once daily. The maximum plasma concentration (C_{max}) and the area under the plasma concentration-time curve (AUC) for SEROQUEL XR administered once daily are comparable to those achieved for the same total daily dose of immediate-release quetiapine fumarate (SEROQUEL immediate release) administered twice daily. When SEROQUEL XR administered once daily is compared to the same total daily dose of SEROQUEL immediate release administered once daily, the AUC is comparable and the C_{max} is 59% lower for SEROQUEL XR. The AUC and C_{max} for the metabolite norquetiapine are 18% and 37% lower than SEROQUEL respectively.

In a study examining the effects of food on the bioavailability of quetiapine, a high-fat meal was found to produce statistically significant increases in the SEROQUEL XR C_{max} (44%-52%) and AUC (20%-22%). In comparison, a light meal had no significant effect on the C_{max} or AUC of quetiapine. It is recommended that SEROQUEL XR is taken once daily without food.

There are no clinically relevant differences in the observed apparent oral clearance (CL/F) and exposure of quetiapine between subjects with schizophrenia and bipolar disorder.

Distribution

Quetiapine is approximately 83% bound to plasma proteins.

Metabolism

Quetiapine is extensively metabolised by the liver. *In vitro* investigations established that CYP3A4 is likely to be the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. Norquetiapine is primarily formed and eliminated via CYP3A4. CYP2D6 and CYP2C9 are also involved in quetiapine metabolism.

Quetiapine and several of its metabolites (including norquetiapine) were found to be weak to modest inhibitors of human cytochrome P450 3A4, 2C19, 2D6, 1A2 and 2C9 activities *in vitro. In vitro* CYP inhibition is observed only at concentrations approximately 5 to 50-fold higher than those observed at a dose range of 300 to 800 mg/day in humans. Based on these *in vitro* results, it is unlikely that co-administration of quetiapine with other medicines will result in clinically significant drug inhibition of cytochrome P450 mediated metabolism of the other drug. From animal studies it appears that quetiapine can induce cytochrome P450 enzymes. In a specific interaction study in psychotic patients, however, no increase in the cytochrome P450 activity was found after administration of quetiapine.

Elimination

The elimination half-lives of quetiapine and norquetiapine are approximately 7 and 12 hours respectively.

Following administration of radiolabelled quetiapine, less than 5% of unchanged drug related material is accounted for in the urine or faeces. Approximately 73% of the radioactivity is excreted in the urine and 21% in the faeces. The average molar dose fraction of free quetiapine and the active human plasma metabolite norquetiapine is <5% excreted in the urine.

Special populations

Gender

The kinetics of quetiapine do not differ between men and women.

Use in renal impairment

The mean plasma clearance of quetiapine was reduced by approximately 25% in subjects with severe renal impairment (creatinine clearance less than 30mL/min/ 1.73m^2), but the individual clearance values are within the range for normal subjects.

Use in hepatic impairment

The mean plasma clearance of quetiapine was reduced by approximately 25% in subjects with hepatic impairment (stable alcoholic cirrhosis), but the individual clearance values are within the range for normal subjects. Since quetiapine is extensively metabolised by the liver, higher plasma levels are expected in the hepatically impaired population, and dosage adjustment may be needed in these patients (see **DOSAGE AND ADMINSTRATION**).

Use in elderly

The mean clearance of quetiapine in the elderly is approximately 30 to 50% lower than that seen in adults aged 18 to 65 years (see **DOSAGE AND ADMINISTRATION**).

CLINICAL TRIALS

Clinical pharmacology studies in patients with schizophrenia, schizo-affective disorder and bipolar disorder were conducted to assess the tolerability of a 300 mg starting dose. Key safety assessments included vital sign measurements, adverse events, ECG, clinical laboratory tests and physical examinations. A starting dose of 300 mg/day of SEROQUEL XR was well tolerated in terms of the key assessments and the safety profile was similar to that seen with the recommended starting dose for SEROQUEL immediate release tablets. The recommended SEROQUEL XR starting dose was further supported by the SEROQUEL XR clinical efficacy studies in schizophrenia.

Bipolar disorder (adults)

Efficacy of SEROQUEL XR in the treatment of bipolar disorder indications was established in part, on the basis of extrapolation from the established effectiveness of SEROQUEL.

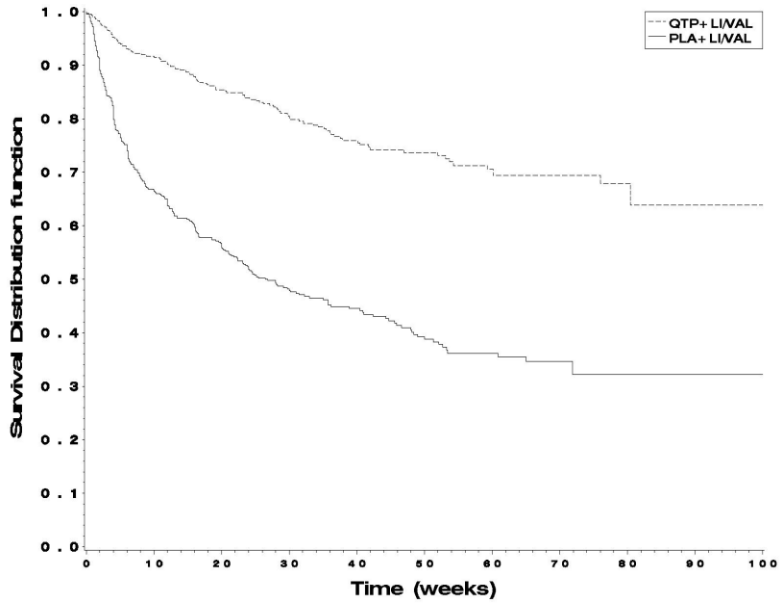
Maintenance treatment in combination with lithium or sodium valproate

The efficacy of SEROQUEL in the maintenance treatment of bipolar disorder was established in two similarly designed placebo-controlled trials in patients who met DSM-IV criteria for bipolar I disorder. These trials included patients whose most recent mood episode was mania (approximately 36%), depression (approximately 30%) or mixed state (approximately 34%); and patients with or without psychotic features. Patients with rapid cycling (approximately 37%) were also included.

Both trials consisted of an open label phase followed by a randomised treatment phase. In the open label phase (n=3414), patients were required to be stabilised on SEROQUEL (400-800 mg/day) in combination with a mood stabiliser (lithium or valproate) for at least 12 weeks prior to randomisation. In the randomisation phase, patients who were symptomatically stable for at least 12 weeks (n=1326) either continued treatment with SEROQUEL (at the same dose, then adjusted as clinically indicated) in combination with a mood stabiliser or received placebo in combination with a mood stabiliser for up to 104 weeks. Approximately 40% of patients received lithium and 60% received valproate.

The primary endpoint was time to recurrence of any mood event (mania, depression or mixed state). A mood event was defined as medication initiation, hospitalisation, Young Mania Rating Scale (YMRS) score ≥20 or Montgomery-Asberg Depression Rating Scale (MADRS) score ≥20 on two consecutive assessments or study discontinuation due to a mood event. SEROQUEL was superior to placebo in increasing the time to recurrence of a mood event in both studies. Patients on SEROQUEL had a 70% less risk of experiencing a recurrence of a mood event (refer Figure 1 and Table 1) compared to patients on placebo. Patients on SEROQUEL had a lower risk of experiencing a mood event prior to week 28 and week 52 compared to patients on placebo (refer Table 2).

Figure 1 Time to recurrence of a mood event for the combined maintenance treatment studies, Kaplan Meier curves (ITT population)



ITT Intent-to-treat. PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate.

Table 1 Summary of efficacy results (ITT population) for maintenance treatment

	Study 1	Study 2	Combined studies
	QTP + LI/VAL vs PLA + LI/VAL QTP N=336 / PLA N=367	QTP + LI/VAL vs PLA + LI/VAL QTP N=310 / PLA N=313	QTP + LI/VAL vs PLA + LI/VAL QTP N=646 / PLA N=680
Analysis of time to recurrence of a mood event			
Hazard ratio [95% CI]	0.28 [0.21, 0.37]	0.32 [0.24, 0.42]	0.30 [0.24, 0.37]
p-value	<0.0001	<0.0001	<0.0001
Analysis of time to recurrence of a manic event			
Hazard ratio [95% CI]	0.30 [0.20, 0.44]	0.30 [0.18, 0.49]	0.30 [0.22, 0.41]
p-value	<0.0001	<0.0001	<0.0001
Analysis of time to recurrence of a depressive event			
Hazard ratio [95% CI]	0.26 [0.17, 0.41]	0.33 [0.23, 0.48]	0.30 [0.23, 0.40]
p-value	<0.0001	<0.0001	<0.0001

ITT Intent-to-treat. PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group.

Table 2 Kaplan Meier estimates of mood, manic and depressive event rates at weeks 28 and 52 (ITT population) – combined studies

Time to event	Kaplan Meier survival estimate of event rates (%)		p value
	QTP + LI/VAL (N=646)	PLA + LI/VAL (N=680)	
Mood event rates			
Week 28	82.5%	49.7%	<0.0001
Week 52	73.7%	38.8%	<0.0001
Manic event rates			
Week 28	91.9%	73.6%	<0.0001
Week 52	86.0%	63.8%	<0.0001
Depressive event rates			
Week 28	89.9%	68.4%	<0.0001
Week 52	85.8%	61.8%	<0.0001

ITT Intent-to-treat. PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group.

Maintenance treatment with SEROQUEL was superior to placebo in increasing the time to recurrence of a depressive or a manic event (refer Table 1). Patients on SEROQUEL also had a lower risk of experiencing a depressive or a manic event prior to week 28 and week 52 compared to patients on placebo (refer Table 2).

Efficacy was demonstrated to be independent of the nature of the most recent episode (manic, mixed or depressive), the mood stabiliser (lithium or valproate), rapid cycling course, gender, age or ethnicity.

Maintenance treatment as monotherapy

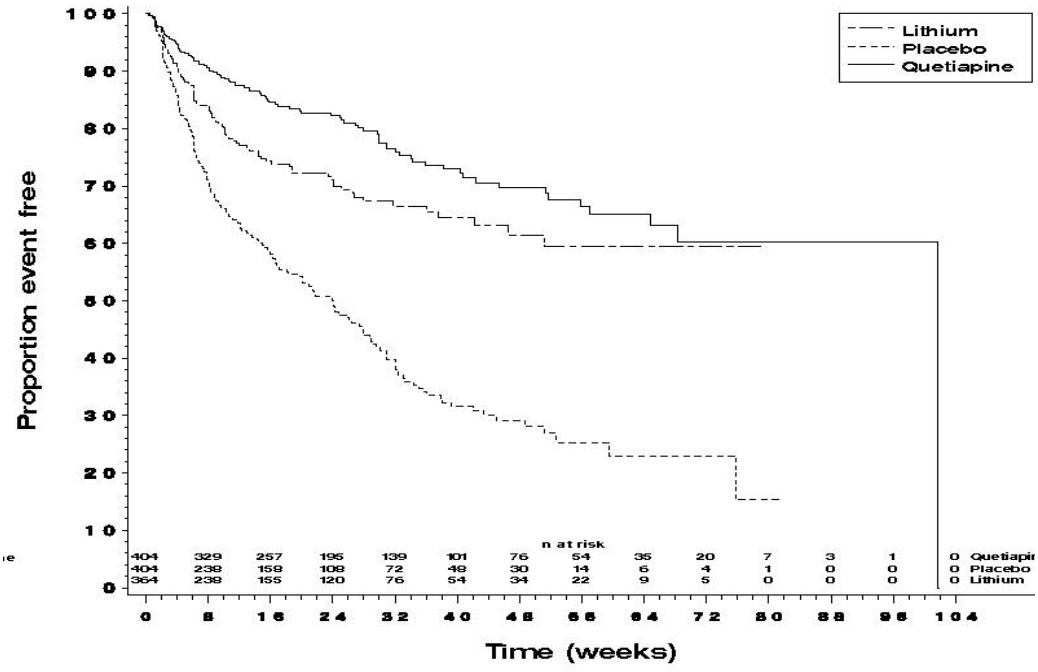
The efficacy of SEROQUEL in the maintenance treatment of bipolar disorder as monotherapy was established in a placebo-controlled trial in 1172 patients who met

DSM-IV criteria for bipolar I disorder. Approximately 50% of the 2438 patients initially treated with quetiapine for their index episode achieved stabilisation and were eligible for enrolment in the placebo-controlled randomised phase. The most recent mood episode of patients included was mania (approximately 54%), depression (approximately 28%) or mixed state (approximately 18%). Patients with rapid cycling were also included.

The trial consisted of an open label phase followed by a randomised treatment phase. In the open label phase, patients were required to be stabilised on SEROQUEL (300-800 mg/day) for at least 4 weeks prior to randomisation to SEROQUEL, placebo or lithium. In the randomisation phase, the dose of SEROQUEL and lithium could be adjusted as clinically indicated. Randomised treatment was intended for up to 104 weeks however the study was stopped early following a positive interim analysis.

The primary endpoint was time to relapse/recurrence of any mood event (mania, depression or mixed state). A mood event was defined as medication initiation, hospitalisation, YMRS score ≥20 or MADRS score ≥20 on two consecutive assessments or study discontinuation due to a mood event. SEROQUEL was superior to placebo in increasing the time to relapse/recurrence of a mood event. Patients on SEROQUEL had a 71% less risk of experiencing a relapse/recurrence of a mood event (refer Figure 2 and Table 3) compared to patients on placebo. SEROQUEL was also superior to placebo in increasing time to relapse/recurrence of manic events and depressive events (refer Table 3). Efficacy was demonstrated to be independent of the nature of the most recent episode (manic, mixed or depressive), rapid cycling course, gender, age or ethnicity.

Figure 2 Time to relapse/recurrence of a mood event, manic event and depressive event, Kaplan Meier curves (ITT population)



ITT Intent-to-treat. The numbers above the x-axis indicate the number of patients at risk of having an event at given time-points

Table 3 Summary of efficacy results (ITT population) for maintenance treatment

	Quetiapine vs Placebo N_{QTP} =404/ N_{PLA} =404	Lithium vs Placebo N_{LI}=364/ N_{PLA}=404	Quetiapine vs Lithium N_{QTP}=404/ N_{LI}=364
Analysis of time to relapse/recurrence of a mood event			
Hazard ratio [95% CI]	0.29 [0.23, 0.38]	0.46 [0.36, 0.59]	0.66 [0.49, 0.88]
p-value	<0.0001	<0.0001	0.005
Analysis of time to relapse/recurrence of a manic event			
Hazard ratio [95% CI]	0.29 [0.21, 0.40]	0.37 [0.27, 0.53]	0.78 [0.53, 1.16]
p-value	<0.0001	<0.0001	0.226
Analysis of time to relapse/recurrence of a depressive event			
Hazard ratio [95% CI]	0.30 [0.20, 0.44]	0.59 [0.42, 0.84]	0.54 [0.35, 0.84]
p-value	<0.0001	0.004	0.006

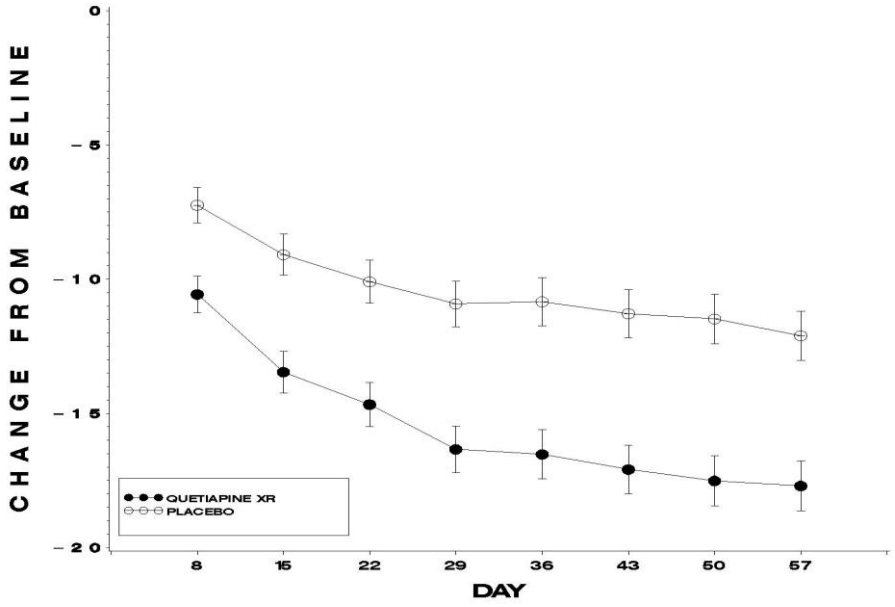
ITT Intent-to-treat. PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group.

Bipolar depression

The safety and efficacy of SEROQUEL XR for treatment of bipolar depression was demonstrated in an 8 week placebo controlled study (n=270) at a dose of 300 mg/day. Patients met the DSM-IV criteria for bipolar I or II disorder, with or without rapid cycling courses.

Anti-depressant activity was assessed by the change from baseline for MADRS total score (primary endpoint), at 8 weeks (day 57). The anti-depressant effect of SEROQUEL XR was superior compared to placebo as early as day 8 (week 1) and was maintained through to week 8 (refer Figure 3). The proportion of patients showing ≥50% reduction in MADRS total score (responders) was higher for SEROQUEL XR compared to placebo by week 2 and continued to end-of-treatment ($p<0.001$). The proportion of patients showing a MADRS total score ≤12 (remission) was higher for SEROQUEL XR compared to placebo group by Week 1 and continued to end-of-treatment ($p<0.05$). The Clinical Global Impression – Bipolar – Severity of Illness (CGI-BP-S) and CGI-BP – Improvement (CGI-BP-I), measures of the clinicians impression of the severity of the patients overall illness and improvement from baseline, were also assessed with SEROQUEL XR superior to placebo at week 8. Efficacy was demonstrated to be independent of bipolar I or II diagnosis, rapid cycling course, gender, age or ethnicity.

Figure 3 MADRS total score change from baseline – LS mean (95% CI) (LOCF, MITT population)

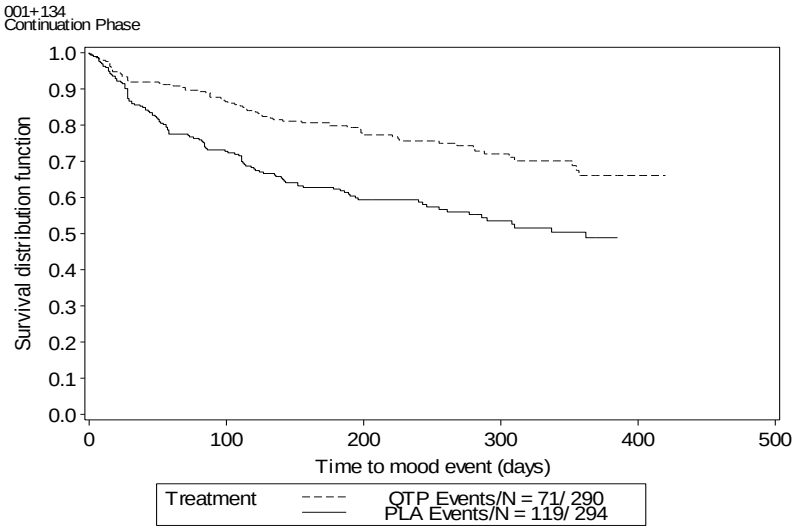


CI Confidence interval; LOCF Last observation carried forward; LS Least square; MITT Modified Intention to Treat; XR Extended-release; MADRS Montgomery-Asberg Depression Rating Scale.

The safety and efficacy of quetiapine 300 mg and 600 mg once daily for the treatment of bipolar depression was established in 4 similarly designed placebo controlled clinical trials (n=2461) over 8 weeks with 2 of these studies assessing maintenance of effect for up to 52 weeks. In all 4 studies quetiapine doses of 300 mg/day and 600 mg/day demonstrated clinical and statistical superiority to placebo in the treatment of depression at 8 weeks. The magnitude of the anti-depressant effect was also supported by the secondary outcome variables. Alleviation of anxiety symptoms by quetiapine in all 4 studies was confirmed by a statistically superior Hamilton Rating Scale for Anxiety (HAM-A) total score change from baseline compared to placebo. Efficacy was demonstrated to be independent of bipolar I or II diagnosis, rapid cycling course, gender, age or ethnicity.

Maintenance of the quetiapine effect in bipolar depression was demonstrated during the continuation phase with patients treated with quetiapine experiencing a significantly longer time to recurrence of any mood event (depression, mixed state or mania; defined as a MADRS score ≥20 or a YMRS score ≥16; initiation of an antipsychotic, anti-depressant, mood stabilizer etc; hospitalization for symptoms of depression and/or mania/hypomania; discontinuation due to symptoms of depression and/or mania/hypomania), compared to placebo as shown in Figure 4. Quetiapine patients had a lower risk of experiencing a mood event at weeks 26 and 52 compared to patients on placebo. Patients on quetiapine had a 49% less risk of experiencing a mood event compared with patients treated with placebo [HR 0.51 (95% CI 0.38, 0.69; p <0.001)]. The risk of a mood event for quetiapine versus placebo was reduced by 41% for the 300 mg dose and by 55% for the 600 mg dose.

Figure 4 Time to recurrence of a mood event, Kaplan Meier curves (combined ITT population)



ITT Intention-to-treat. N Number of patients in treatment group. PLA Placebo. QTP Quetiapine.

Quetiapine patients also had a lower risk of experiencing a depressive event at weeks 26 and 52 compared to patients on placebo. The analysis of time to a depressive event mirrored the overall mood event results with patients on quetiapine having a 57% less risk of experiencing a depressive event compared with patients treated with placebo (HR 0.43, 95% CI 0.30, 0.62, p<0.001). The risk of a depressive event for quetiapine versus placebo was reduced by 52% for the 300 mg dose and by 61% for the 600 mg dose.

No increased risk for a manic or hypomanic event was observed. Quetiapine treatment of a depressive episode was also not associated with a switch to mania or hypomania.

Time to all cause discontinuation, including the composite mood event, was also examined with the Kaplan-Meier estimate of time to 50% all cause discontinuation being 311 days for quetiapine treatment, compared to 156 days for placebo treatment.

The maintenance of effect observed in patients treated with quetiapine was demonstrated to be independent of bipolar diagnosis (i.e. I or II), gender or age.

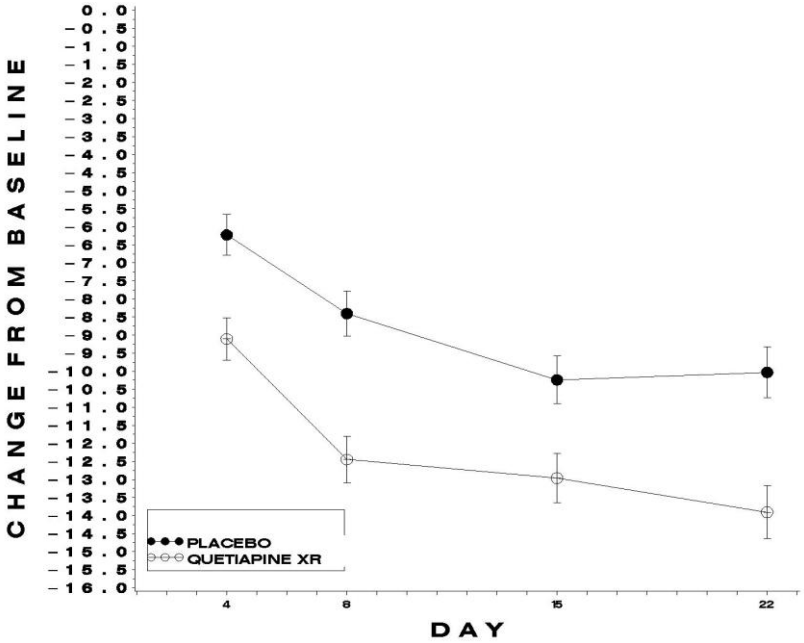
There was no increased risk of suicidal behaviour or ideation associated with quetiapine treatment for bipolar depression in either the acute or continuation phase.

Acute mania

The safety and efficacy of SEROQUEL XR for treatment of bipolar mania was demonstrated in a 3 week placebo controlled study (n=308) at doses of 400-800 mg/day. Patients met the DSM-IV criteria for bipolar I disorder, with the most recent episode being either manic or mixed. Patients with or without rapid cycling courses were also included.

The primary outcome variable for this trial was change from baseline to day 22 in the YMRS total score. SEROQUEL XR was demonstrated to be superior to placebo in reducing the level of manic symptoms as early as day 4 and for up to 3 weeks (day 22) of treatment (refer Figure 5).

Figure 5 YMRS total score change from baseline – LS mean (95% CI) (LOCF, MITT population)



CI Confidence interval. LS Least square. LOCF Last Observation-Carried forward. MITT Modified-Intent-to-Treat. YMRS Young Mania Rating Scale.

The proportion of patients showing ≥50% reduction in YMRS total score (responders) was statistically significantly higher for the SEROQUEL XR group compared to the placebo group at day 8 (week 1) and at the end of treatment. The proportion of patients showing a YMRS total score ≤12 (remission) was statistically significantly higher for the SEROQUEL XR group compared to the placebo group by day 8 (week 1) and at the end of treatment. The changes in CGI-BP-S and CGI-BP-I overall illness scores were statistically significant in favour of SEROQUEL XR at day 4 and at end of treatment.

The efficacy of quetiapine in the treatment of manic episodes was further established in three short-term placebo-controlled trials in patients who met DSM-IV criteria for bipolar I disorder. The primary outcome variable for these trials was change from baseline to day 21 in the YMRS total score. In two 12-week trials (n=300, n=299) comparing quetiapine to placebo, quetiapine was superior to placebo in reducing manic symptoms. The majority of patients who responded at day 21 maintained responses to day 84. In a 3-week placebo controlled trial (n=170) comparing quetiapine to placebo in patients on a mood stabiliser (lithium or valproate), quetiapine was superior to placebo in reducing manic symptoms.

Schizophrenia (adults)

The efficacy of SEROQUEL XR in the treatment of schizophrenia was demonstrated in the following clinical studies:

- a 6-week placebo-controlled trial in patients who met DSM-IV criteria for schizophrenia,
- an active-controlled SEROQUEL immediate release-to-SEROQUEL XR switching study in clinically stable outpatients with schizophrenia
- a placebo-controlled relapse prevention study conducted in patients with stabilised schizophrenia

Placebo-controlled efficacy and safety data

The primary outcome variable in the placebo-controlled trial was change from baseline to final assessment in the Positive and Negative Symptom Scale (PANSS) total score. SEROQUEL XR (once daily) was administered as 300 mg on (Day 1), and increased up to the required dose by Day 2 or 3. SEROQUEL XR 400 mg/day, 600 mg/day and 800 mg/day were associated with statistically significant improvements in psychotic symptoms compared to placebo. The effect size of the 600 mg and 800 mg doses was greater than that of the 400 mg dose.

In three, 6-week clinical studies in patients with schizophrenia (N=951) the incidence of treatment emergent suicidal ideation or suicide attempt, as measured by the Columbia Analysis of Suicidal Behaviour, was low in SEROQUEL XR treated patients (0.6%) and similar to placebo (0.9%).

Switching from SEROQUEL immediate release to SEROQUEL XR

In the 6-week active-controlled switching study the primary outcome variable was the proportion of patients who showed lack of efficacy, i.e. who discontinued study treatment due to lack of efficacy or whose PANSS total score increased 20% or more from randomization to any visit. In patients stabilised on SEROQUEL immediate release 400 mg to 800 mg, efficacy was maintained when patients were switched to an equivalent daily dose of SEROQUEL XR given once daily. Switching patients from SEROQUEL immediate release to SEROQUEL XR at equivalent total doses was safe and well tolerated in terms of adverse events, vital signs, ECG and laboratory parameters. The safety profile of SEROQUEL XR was comparable to SEROQUEL immediate release.

Relapse prevention

A long-term placebo-controlled relapse prevention study was conducted in patients with stabilised schizophrenia who had been maintained on SEROQUEL XR for 16 weeks. Randomised treatment was planned for 12 months (or until relapse), however the maximum duration was approximately 9 months due to early termination as a result of a positive interim analysis. This study concluded that SEROQUEL XR was significantly more effective than placebo in preventing relapse (hospitalisation due to worsening of schizophrenia, and increase in PANSS total score of 30% from baseline, score 6 or 7 on CGI-I scale or need for other antipsychotic medication to treat psychosis) with 11 (11.7%) with relapse in the SEROQUEL XR group and 50 (48.5%) in the placebo group ($p<0.0001$). The estimated risks of relapse after 6 months treatments was 14.3% for the SEROQUEL XR treatment group compared to 68.2% for placebo ($p<0.0001$). The mean dose of SEROQUEL XR was 669 mg. There were no additional safety findings associated

with treatment with SEROQUEL XR for up to 12 months. In particular, reports of adverse events related to EPS and weight gain did not increase with longer-term treatment with SEROQUEL XR.

Major depressive disorder (adults)

The efficacy of SEROQUEL XR in the treatment of major depressive disorder (MDD) was established in 4 placebo-controlled monotherapy clinical trials (including 1 study in elderly patients), 2 clinical trials as combination therapy with an antidepressant, and 1 monotherapy, placebo-controlled maintenance trial. All trials included patients who met DSM-IV criteria for MDD, single or recurrent episodes, with and without psychotic features. The majority of patients in all studies were diagnosed as having recurrent MDD.

Acute treatment of major depressive disorder

The efficacy of SEROQUEL XR as monotherapy in the treatment of MDD was demonstrated in two 6-week placebo-controlled, fixed dose trials, and one 8 week placebo-controlled, modified fixed dose trial [n=1445]. The majority of patients were dosed once daily with either 150 mg or 300 mg with one trial (Study 1) assessing a 50 mg dose. The primary endpoint in these trials was the change from baseline to week 6 or 8 in the MADRS total score.

SEROQUEL XR at a dose of 50 mg, 150 mg, and 300 mg once daily was superior to placebo in reduction of depressive symptoms as measured by change in MADRS total score, with significant improvement observed within the first week and continuing throughout the study. Duloxetine included as an active comparator in one study (Study 2) did not demonstrate statistically significant superiority compared to placebo until day 15.

Table 4 Efficacy results for short-term studies in MDD (LOCF) (MITT population)

		MADRS total score change from baseline		
		LS Mean	**95% CI**	**Adjusted p-value**
Acute treatment of MDD - monotherapy				
Study 1	Placebo	-11.1	[-12.8; -9.3]	
	Quetiapine XR 50 mg	-13.6	[-15.3; -11.8]	0.042
	Quetiapine XR 150 mg	-14.5	[-16.3; -12.7]	0.002
	Quetiapine XR 300 mg	-14.2	[-15.9; -12.5]	0.004
Study 2	Placebo	-11.2	[-12.9; -9.4]	
	Quetiapine XR 150 mg	-14.8	[-16.6; -13.0]	<0.001
	Quetiapine XR 300 mg	-15.3	[-17.1; -13.5]	<0.001
	Duloxetine 60 mg	-14.6	[-16.5; -12.8]	0.001 [a]
Study 3	Placebo	-13.1	[-14.6; -11.6]	
	Quetiapine XR 150/300 mg	-16.5	[-18.0; -15.0]	0.002
Acute treatment of MDD – combination therapy				
Study 6	Placebo	-11.7	[-13.3; -10.1]	
	Quetiapine XR 150 mg	-13.6	[-15.2; -12.0]	0.067
	Quetiapine XR 300 mg	-14.7	[-16.3; -13.1]	0.008

		MADRS total score change from baseline		
		LS Mean	**95% CI**	**Adjusted p-value**
Study 7	Placebo	-12.2	[-13.7; -10.8]	
	Quetiapine XR 150 mg	-15.3	[-16.7; -13.9]	0.003
	Quetiapine XR 300 mg	-14.9	[-16.4; -13.5]	0.005
Acute treatment of MDD in elderly patients - monotherapy				
Study 14	Placebo	-8.8	[-10.6; -7.0]	
	Quetiapine XR 150/300 mg	-16.3	[-18.2; -14.5]	<0.001

[a] Unadjusted p-value; LOCF last observation carried forward: MITT Modified intent to treat: LS Least square; MADRS Montgomery-Asberg Depression Rating Scale; CI Confidence interval

The efficacy of SEROQUEL XR in the treatment of MDD was further demonstrated in two 6-week placebo-controlled, fixed dose trials (n=936) as combination therapy with an antidepressant in patients who had previously shown an inadequate response to at least one antidepressant. SEROQUEL XR 300 mg once daily in combination with ongoing antidepressant therapy was superior to antidepressant therapy alone in reduction of MADRS total score in both trials while SEROQUEL XR 150 mg was superior to antidepressant therapy alone in one study only. Improvement in depressive symptoms was seen at week 1 through end of study (week 6).

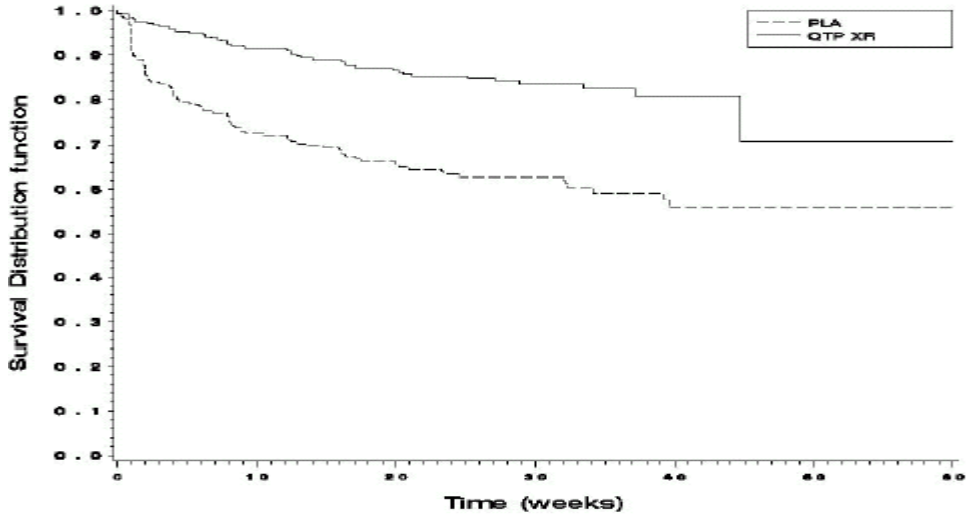
Use in elderly patients

The safety and efficacy of SEROQUEL XR was evaluated in an 11-week, double-blind, randomised, placebo-controlled study in non-demented elderly patients (aged 66-89 years) with MDD. The mean dose of SEROQUEL XR was 160 mg/day. SEROQUEL XR flexibly dosed in the range of 50 to 300 mg per day demonstrated superiority over placebo in reducing depressive symptoms as measured by improvement in MADRS total score, with significant improvement observed within the first week and continuing throughout the study (week 9).

Maintenance treatment in major depressive disorder

The efficacy of SEROQUEL XR in the prevention of relapse in MDD was established in a long-term clinical trial consisting of an open label phase followed by a double-blind randomised treatment phase. Patients stabilised in the open label phase (n=771) were randomised to placebo or to continue on SEROQUEL XR for up to 52 weeks. At the end of the open-label phase 21%, 46% and 32% of patients were prescribed SEROQUEL XR 50 mg, 150 mg and 300 mg respectively. The dose of SEROQUEL XR could be adjusted during the randomisation period based on clinical need with 91.7% of patients remaining on the same dose throughout the randomisation period. The primary endpoint was time to occurrence of a depressive event. Patients on SEROQUEL XR (mean dose 177 mg/day) experienced a statistically significant longer time to relapse than did patients on placebo with patients on SEROQUEL XR having a 66% less risk of experiencing a depressive event compared to patients on placebo (HR [95% CI]=0.34[0.25,0.47], p<0.0001) (see Figure 6). Based on analysis of the dose at randomisation, the risk of experiencing a depressive event decreased with increasing dose (hazard ratios: 50 mg, 0.46 [95% CI 0.23, 0.91], p=0.025; 150 mg, 0.36 [95% CI 0.22, 0.57], p<0.001; 300 mg, 0.26 [CI 0.15, 0.45], p<0.001).

Figure 6 Time to recurrence of a depressive event, Kaplan-Meier curves (ITT population)



PLA Placebo: QTP XR Quetiapine XR

Generalised anxiety disorder (adults)

The efficacy of SEROQUEL XR in the monotherapy treatment of generalised anxiety disorder (GAD) was established in 4 placebo-controlled clinical trials (including 1 study in elderly patients) and 1 placebo-controlled maintenance trial. All trials included patients who met DSM-IV criteria for GAD.

Acute treatment of generalised anxiety disorder

The efficacy of once daily SEROQUEL XR monotherapy in the treatment of GAD was demonstrated in three 10-week placebo-controlled, fixed dose trials (n=2588 MITT population). Three SEROQUEL XR doses were assessed – 50, 150 and 300 mg/day. Two trials also included an active comparator (escitalopram 10mg/day in one, and paroxetine 20mg/day in another). Patients had a mean HAM-A total score of 26 at enrolment.

SEROQUEL XR at a dose of 50, 150 and 300 mg once daily was superior to placebo in reduction of anxiety symptoms as measured by HAM-A total score. Efficacy was demonstrated as early as day 4 and the treatment effect continued throughout the trial (8 weeks – primary endpoint; see Table 5). No additional benefit was provided by the 300 mg/day dose compared with the 150 mg/day dose. Both active comparators (escitalopram and paroxetine) were statistically superior to placebo at week 8, however neither demonstrated superiority to placebo at day 4. The magnitude of the anti-anxiety effect of SEROQUEL XR was supported by various secondary outcome variables. Statistically significant improvements were also seen with SEROQUEL XR in depressive symptoms (as measured by MADRS total score; mean total score at enrolment was ≤16) and sleep symptoms (as measured with the Pittsburgh Sleep Quality Index [PSQI] global score).

Table 5 Summary of HAM-A efficacy results (LOCF, MITT population) for short-term GAD trials [pooled analysis non-elderly trials and elderly trial]

		HAM-A endpoint (Week 8 Non-elderly; Week 9 elderly trial)		
	N (QTP/PLA)	**Total score, LS mean change from randomisation [95% CI]***	**Response[a] rate (% patients)**	**Remission[b] rate (% patients)**
Pooled analysis – three short-term non-elderly trials				
QTP 50 mg vs PLA	438/654	-13.31 vs -11.30 p<0.001	61.4 vs 49.7 p=0.001	34.2 vs 27.4 p=0.036
QTP 150 mg vs PLA	654/654	-14.39 vs -11.30 p<0.001	65.0 vs 49.7 p<0.001	39.0 vs 27.4 p<0.001
QTP 300 mg vs PLA	425/654	-12.50 vs -11.30 p=0.010	53.9 vs 49.7 NS	28.5 vs 27.4 NS
Elderly trial				
QTP [c] vs PLA	222/226	-14.97 vs -7.21 p<0.001	68.5 vs 23.9 p<0.001	40.1 vs 12.8 p<0.001

HAM-A Hamilton Rating Scale for Anxiety, LOCF – last observation carried forward, MITT – modified intent-to-treat, PLA Placebo, QTP Quetiapine, N Number of patients in treatment group, LS – least squares, *primary endpoint, CI – confidence interval; [a] ≥50% improvement in HAM-A total score, [b] ≤7 HAM-A total score, [c] flexible dose (50-300 mg/day; mean dose 168 mg/day) NS – not significant

Use in elderly patients

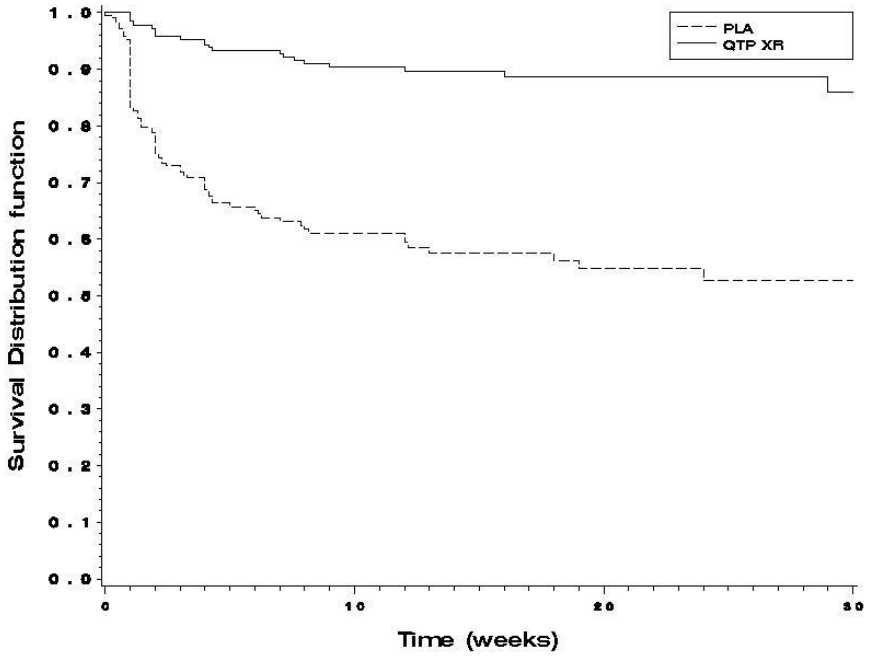
The safety and efficacy of SEROQUEL XR was evaluated in an 11-week, double blind, randomised, placebo-controlled study in non-demented elderly patients (aged 66-86 years) with GAD. The proportion of randomised patients over 75 years of age was 13%. SEROQUEL XR demonstrated superiority over placebo in reducing anxiety symptoms as measured by improvement in HAM-A total score, with significant improvement observed within the first week and continuing throughout the study (week 9 – primary endpoint; see Table 5). All assessed secondary variables (including health-related quality of life and sleep quality) also demonstrated superiority of SEROQUEL XR to placebo in elderly patients.

Maintenance treatment of anti-anxiety effects

The efficacy of SEROQUEL XR 50 mg, 150 mg, or 300 mg once daily in the maintenance treatment of the anti-anxiety effect was established in a long-term clinical trial consisting of an open label phase (4 to 8 week run-in phase and 12 to 18 week stabilisation phase) followed by a double-blind randomised treatment phase. Patients meeting randomisation criteria (i.e. patients who remained stable for at least 12 weeks; n=433) were randomised to placebo or to continue on SEROQUEL XR (at the same dose as the open label phase) for up to 52 weeks. Due to the efficacy of SEROQUEL XR, the mean randomised time of exposure was 56% greater in the SEROQUEL XR arm compared to placebo (106.9 vs 68.6 days), with 64 SEROQUEL XR patients on treatment for more than 28 weeks. The dose of SEROQUEL XR could be adjusted based on clinical need during both the open label and the randomisation phases. At the end of the open-label period 49% of patients received 150 mg/day, with 26% and 25% receiving 50 mg/day and 300 mg/day, respectively. 93% of patients remained on the same dose throughout the randomisation period.

Patients on SEROQUEL XR (mean dose 163 mg/day) experienced a statistically significant longer time to occurrence of an anxiety event (primary endpoint) than did patients on placebo, with patients on SEROQUEL XR having an 81% less risk of experiencing an anxiety event compared to patients on placebo (Hazard ratio [HR] 0.19; 95% CI 0.12, 0.31; p<0.0001) (see Figure 7). The efficacy of SEROQUEL XR in the maintenance treatment of patients with GAD was further supported by the secondary variables, including maintaining reduction of anxiety and depressive symptoms, and improved level of functioning, health related quality of life and sleep quality.

Figure 7 **Time to occurrence of an anxiety relapse, Kaplan-Meier curves (ITT analysis set, randomised period)**



ITT Intention-to-treat; PLA – placebo; QTP XR – quetiapine XR

Children and adolescents (<18 years of age)

The safety and efficacy of SEROQUEL XR have not been evaluated in patients under 18 years of age, however three clinical trials have been conducted with SEROQUEL in children and adolescents; two short-term randomised placebo-controlled trials – a 6 week trial in schizophrenia (patients aged 13-17 years) and a 3 week trial in bipolar mania (patients aged 10 to 17 years) – and an open-label 26 week safety and tolerability trial (see **ADVERSE EFFECTS – Clinical study experience**) which also assessed efficacy measures. The safety and efficacy of SEROQUEL in children and adolescents have not been assessed beyond these time periods.

INDICATIONS

SEROQUEL XR is indicated for:

Bipolar disorder

- Maintenance treatment of bipolar I disorder, as monotherapy or in combination with lithium or sodium valproate, for the prevention of relapse/recurrence of manic, depressive or mixed episodes
- Treatment of depressive episodes associated with bipolar disorder (see **DOSAGE AND ADMINISTRATION**)
- Treatment of acute mania associated with bipolar I disorder as monotherapy or in combination with lithium or sodium valproate

Efficacy of SEROQUEL XR in the treatment of bipolar disorder indications was established in part, on the basis of extrapolation from the established effectiveness of SEROQUEL.

Schizophrenia

Treatment of schizophrenia, prevention of relapse and maintenance of clinical improvement during continuation therapy.

Major depressive disorder

Treatment of recurrent major depressive disorder (MDD) in patients who are intolerant of, or who have an inadequate response to alternative therapies.

Generalised anxiety disorder

Treatment of generalised anxiety disorder (GAD).

CONTRAINDICATIONS

SEROQUEL XR is contraindicated in patients who are hypersensitive to any component of this product.

PRECAUTIONS

Concomitant cardiovascular illness

Quetiapine should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease, or other conditions predisposing to hypotension (dehydration, hypovolemia and treatment with antihypertensive medications).

Quetiapine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from pre-marketing clinical studies. Because of the

risk of orthostatic hypotension with quetiapine, caution should be observed in cardiac patients.

Orthostatic hypotension

Quetiapine may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope has been commonly reported (see **ADVERSE EFFECTS**). Orthostatic hypotension, dizziness and syncope may lead to falls (see **ADVERSE EFFECTS**). If hypotension occurs during titration to the target dose, a return to the previous dose in the titration schedule is appropriate.

QT interval

In clinical trials, quetiapine was not associated with a persistent increase in QTc intervals. However, in post marketing experience there were cases reported of QT prolongation with overdose (see **OVERDOSAGE**), in patients with concomitant illness, and in patients taking medicines known to cause electrolyte imbalance or increase QT interval. As with other antipsychotics, caution should be exercised when quetiapine is prescribed in patients, including children and adolescents, with cardiovascular disease or family history of QT prolongation. Particularly in the elderly, the use of quetiapine should be avoided in combination with neuroleptics and drugs that are known to prolong QT_c including Class Ia antiarrhythmics (e.g. disopyramide) or Class III antiarrhythmics (e.g. amiodarone, sotalol), antipsychotic medications (e.g. ziprasidone, chlorpromazine, haloperidol), antibiotics (e.g. moxifloxacin, erythromycin), or any other class of medications known to prolong the QT_c interval (e.g. citalopram, pentamidine, methadone). Quetiapine should also be avoided in circumstances that may increase the risk of occurrence of torsades de pointes and/or sudden death, including (1) a history of cardiac arrhythmias such as bradycardia; (2) hypokalemia or hypomagnesmia; (3) concomitant use of other drugs that prolong the QT_c interval; and (4) presence of congenital prolongation of the QT interval (see **INTERACTIONS WITH OTHER MEDICINES**).

Cardiomyopathy and myocarditis

Cardiomyopathy and myocarditis have been reported in clinical trials and during the post-marketing experience, however, a causal relationship to quetiapine has not been established. Treatment with quetiapine should be reassessed in patients with suspected cardiomyopathy or myocarditis.

Seizures

In controlled clinical trials there was no difference in the incidence of seizures in patients treated with quetiapine or placebo (see **ADVERSE EFFECTS**). As with other antipsychotics, caution is recommended when treating patients with a history of seizures or with conditions that potentially lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Clinical worsening and suicide risk associated with psychiatric disorders

The risk of suicide attempt is inherent in depression and may persist until significant remission occurs. The risk must be considered in all depressed patients.

Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviour (suicidality), whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for clinical worsening and suicidality, especially at the beginning of a course of treatment or at the time of dose changes, either increases or decreases. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset or was not part of the patient's presenting symptoms.

Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition and/or the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present. Patients with comorbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Pooled analysis of 24 short-term (4 to 16 weeks) placebo controlled trials of nine antidepressant medicines (SSRIs and others) in 4,400 children and adolescents with MDD (16 trials), obsessive compulsive disorder (4 trials) or other psychiatric disorders (4 trials) have revealed a greater risk of adverse events representing suicidal behaviour or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients treated with an antidepressant was 4% compared with 2% of patients taking a placebo. There was considerable variation in risk among the antidepressants but there was a tendency towards an increase for almost all antidepressants studied. This meta-analysis did not include trials involving quetiapine.

The risk of suicidality was most consistently observed in the MDD trials but there were signals of risk arising from the trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in these trials. It is unknown whether the suicidality risk in children and adolescent patients extends to use beyond several months. The nine antidepressant medicines in the pooled analyses included five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and four non-SSRIs (bupropion, mirtazepine, nefazodone, venlafaxine).

Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania and mania have been reported in adults, adolescents and children being treated with antidepressants for MDD as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either worsening of depression and/or emergence of suicidal impulses has not been established there is concern that such symptoms may be precursors of emerging suicidality.

Families and caregivers of patients being treated with antidepressants for MDD or for any other condition (psychiatric or nonpsychiatric) should be informed about the need to monitor these patients for the emergence of agitation, irritability, unusual changes in behaviour and other symptoms described above, as well as emergence of suicidality, and to report such symptoms immediately to health care providers. It is particularly important that monitoring be undertaken during the initial few months of antidepressant treatment or at times of dose increase or decrease.

The possibility of a suicide attempt is inherent in schizophrenia; close supervision of high risk patients should accompany drug therapy.

Prescriptions for quetiapine should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Venous thromboembolism

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with quetiapine, and preventative measures undertaken.

Extrapyramidal symptoms (EPS)

In placebo controlled clinical trials of adult patients with schizophrenia, bipolar mania and maintenance treatment of bipolar disorder, the incidence of EPS was no different from that of placebo across the recommended therapeutic dose range. In short-term, placebo-controlled clinical trials for bipolar depression, MDD and GAD, the incidence of EPS was higher in quetiapine treated patients than in placebo treated patients (see **ADVERSE EFFECTS** for rates of EPS observed in all indications and ages).

Class effect: Akathisia has been reported in patients treated with quetiapine. The presentation of akathisia may be variable and comprises subjective complaints of restlessness and an overwhelming urge to move and either distress or motor phenomena such as pacing, swinging of the legs while seated, rocking from foot to foot, or both. Particular attention should be paid to the monitoring for such symptoms and signs as, left untreated, akathisia is associated with poor compliance and an increased risk of relapse.

Tardive dyskinesia

Quetiapine should be prescribed in a manner that is most likely to minimise the occurrence of tardive dyskinesia.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and total cumulative dose of antipsychotic medicines administered to the patient increase. However, tardive dyskinesia can develop, although much less commonly after relatively brief treatment periods at low doses.

If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of quetiapine should be considered. The symptoms of tardive dyskinesia can worsen or even arise after discontinuation of treatment (see **ADVERSE EFFECTS**).

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome has been associated with antipsychotic treatment, including quetiapine. Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatine phosphokinase (see **ADVERSE EFFECTS**). In such an event, quetiapine should be discontinued and appropriate medical treatment given.

Body temperature regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing quetiapine for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, eg, exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Neutropenia and agranulocytosis

Severe neutropenia ($<0.5 \times 10^9$/L) without infection has been uncommonly reported in short term placebo controlled monotherapy clinical trials with quetiapine. There have been reports of agranulocytosis (severe neutropenia with infection) among all patients treated with quetiapine during clinical trials (rare) as well as post-marketing reports (including fatal cases). Most of these cases of severe neutropenia have occurred within the first two months of starting therapy with quetiapine. There was no apparent dose relationship. Possible risk factors for neutropenia include pre-existing low white cell count (WBC), a history of drug induced neutropenia and concomitant use of other medicines that have been associated with neutropenia.

There have been cases of agranulocytosis in patients without pre-existing risk factors. Neutropenia should be considered in patients presenting with infection, particularly in the absence of obvious predisposing factor(s), or in patients with unexplained fever, and should be managed as clinically appropriate.

Quetiapine should be discontinued in patients with a neutrophil count $<1.0 \times 10^9$/L. These patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed 1.5×10^9/L) (see **ADVERSE EFFECTS**).

Withdrawal

Acute withdrawal symptoms such as nausea, vomiting and insomnia have been described after abrupt cessation of antipsychotic medicines including quetiapine. Gradual withdrawal over a period of at least one to two weeks is advisable (see **ADVERSE EFFECTS**).

Dependence/ Tolerance

There have been reports of quetiapine misuse, abuse, tolerance, and/or physical dependence. These cases include adult and adolescent patients using quetiapine alone or with other substances of abuse. . Caution is needed when prescribing quetiapine to patients with a history of alcohol or drug abuse. Patients should be observed closely for signs of SEROQUEL XR misuse or abuse (e.g. development of tolerance, increases in dose, drug-seeking behaviour), particularly if they have a history of alcohol or drug abuse.

Hyperglycaemia and diabetes mellitus

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including quetiapine (see **ADVERSE EFFECTS**). Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycaemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycaemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycaemia related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. **Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment.** Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia and weakness. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing.

In some cases, hyperglycaemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Lipids

Increases in triglycerides and cholesterol, and decreases in fasting HDL cholesterol have been observed in clinical trials with quetiapine (see **ADVERSE EFFECTS**). Monitoring is recommended at baseline and periodically during treatment for all patients. Lipid changes should be managed as clinically appropriate.

Metabolic factors

In some patients, a worsening of more than one of the metabolic factors of weight, blood glucose and lipids was observed in clinical studies. All patients taking antipsychotic medications such as quetiapine should be monitored for metabolic

factors at the start of treatment and at intervals during treatment in accordance with current local guidelines. The results of monitoring should be managed as clinically appropriate.

Pancreatitis

Pancreatitis has been reported in clinical trials and during post-marketing experience. Among the post-marketing reports, many patients had factors which are known to be associated with pancreatitis such as increased triglycerides (see **Lipids** section above and in **Effects on laboratory tests**), gallstones and alcohol consumption.

Hepatic

Hepatic failure, including fatalities, has been reported very rarely during the post-marketing period. There have been rare reports of hepatitis in clinical studies. Rare post- marketing reports of hepatitis (with or without jaundice), in patients with or without prior history, have been received. Very rare cases of hepatic steatosis, cholestatic or mixed liver injury have also been reported in the post-marketing period.

For patients who have known or suspected abnormal hepatic function prior to starting quetiapine, standard clinical assessment, including measurement of transaminase levels is recommended. Periodic clinical reassessment with transaminase levels is recommended for such patients, as well as for patients who develop any signs and symptoms suggestive of a new onset liver disorder during quetiapine therapy (see **ADVERSE EFFECTS**).

Increased risk of mortality in elderly patients with dementia-related psychosis

Elderly patients with dementia-related psychosis treated with atypical anti-psychotics are at an increased risk of death compared to placebo. A meta-analysis of seventeen placebo controlled trials with dementia related behavioural disorders showed a risk of death in the drug-treated patients of approximately 1.6 to 1.7 times that seen in placebo-treated patients. The clinical trials included in the meta-analysis were undertaken with olanzapine, aripiprazole, risperidone and quetiapine. Over the course of these trials averaging about 10 weeks in duration, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g. heart failure, sudden death) or infectious (e.g. pneumonia) in nature. Quetiapine is not approved for the treatment of elderly patients with dementia-related psychosis or behavioural disorders.

Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Quetiapine and other antipsychotic medicines should be used cautiously in patients at risk for aspiration pneumonia (e.g. elderly patients).

Constipation and intestinal obstruction

Constipation represents a risk factor for intestinal obstruction. Constipation and intestinal obstruction have been reported with quetiapine (see **ADVERSE EFFECTS**). This includes fatal reports in patients who are at higher risk of intestinal obstruction, including those that are receiving multiple concomitant medications that decrease intestinal motility and/or may not report symptoms of constipation.

Lactose monohydrate

SEROQUEL XR tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

Effects on fertility

Effects related to elevated prolactin levels (marginal reduction in male fertility and pseudopregnancy, protracted periods of diestrus, increased precoital interval and reduced pregnancy rate) were seen in rats, although these are not directly relevant to humans because of species differences in hormonal control of reproduction.

Use in pregnancy – Category C

The safety and efficacy of quetiapine during human pregnancy have not been established.

Non-teratogenic class effect: Neonates exposed to antipsychotic drugs (including quetiapine) during the third trimester of pregnancy are at risk of experiencing extrapyramidal neurological disturbances and/or withdrawal symptoms following delivery. There have been post-market reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required additional medical treatment or monitoring. Quetiapine should be used during pregnancy only if the anticipated benefit outweighs the risk and the administered dose and duration of treatment should be as low and as short as possible.

Teratogenic effects were not observed following administration of quetiapine at oral doses up to 200 mg/kg in rats (less than the exposure to quetiapine at the maximum recommended clinical dose based on AUC) and 100 mg/kg in rabbits (approximately twice the maximum clinical exposure based on BSA).

Use in lactation

There have been published reports of quetiapine excretion into human breast milk, however the degree of excretion was not consistent. In a study in lactating rats the concentration of quetiapine and/or its metabolites was higher in milk than in plasma. Women who are breast-feeding should therefore be advised to avoid breast-feeding while taking quetiapine.

Use in children and adolescents

The safety and efficacy of SEROQUEL XR have not been established in patients under 18 years of age.

Paediatric schizophrenia and bipolar I disorder are serious mental disorders, however, diagnosis can be challenging. For paediatric schizophrenia, symptom profiles can be variable, and for bipolar I disorder, patients may have variable patterns of periodicity of manic or mixed symptoms. It is recommended that medication therapy for paediatric schizophrenia and bipolar I disorder be initiated only after a thorough diagnostic evaluation has been performed and careful consideration given to the potential benefits and risks associated with medication treatment. Medication treatment for both paediatric schizophrenia and bipolar I disorder is indicated as part of a total treatment program that often includes psychological, educational and social interventions.

Efficacy and safety of SEROQUEL have been demonstrated in adolescents aged from 13 years with schizophrenia and in children/adolescents aged from 10 years with bipolar I disorder experiencing acute mania in two clinical trials of 3 and 6 weeks duration, respectively. Safety data was provided for up to 26 weeks in a third open-label safety and tolerability trial [see **CLINICAL TRIALS** – **Children and adolescents (<18 years of age)**]. The safety and efficacy of quetiapine in children and adolescents have not been assessed beyond these time periods.

Although not all adverse reactions that have been identified in adult patients have been observed in clinical trials with quetiapine in children and adolescent patients, the same precautions that appear above for adults should be considered for children and adolescents. As seen in adults, increases in TSH, serum cholesterol, triglycerides, and weight have been observed (see **PRECAUTIONS** – **Effects on laboratory tests** and **ADVERSE EFFECTS**).

The following events were reported more frequently in the short-term studies in children and adolescents than in studies in adults: EPS, increases in appetite and serum prolactin. Increased blood pressure has not been identified in the adult population but was seen in children and adolescents. Blood pressure should be monitored at the beginning of, and periodically during treatment in children and adolescents (see **ADVERSE EFFECTS**).

Long-term safety data including growth, maturation and behavioural development, beyond 26 weeks of treatment with quetiapine, are not available for children and adolescents (10 to 17 years of age).

Genotoxicity

Genetic toxicity studies with quetiapine show that it is not a mutagen or clastogen. Quetiapine showed no evidence of genotoxicity in a series of assays for gene mutation (bacteria and Chinese hamster ovary cells) and chromosomal damage (human lymphocytes and the *in vivo* micronucleus test).

Carcinogenicity

In the rat study (20, 75 and 250 mg/kg/day) the incidence of mammary adenocarcinomas was increased at all doses in female rats, consequential to prolonged hyperprolactinaemia. The incidence of carcinoma of the adrenal cortex was increased in male rats at the highest dose.

In male rat (250 mg/kg/day) and mouse (250 and 750 mg/kg/day), there was an increased incidence of thyroid follicular cell benign adenomas, consistent with known rodent-specific mechanisms resulting from enhanced hepatic thyroxine clearance.

Effects on laboratory tests

Leukopenia and/or neutropenia

As with other antipsychotics transient leukopenia and/or neutropenia have been observed in patients administered quetiapine. Possible risk factors for leukopenia and/or neutropenia include pre-existing low white cell count and history of drug induced leukopenia and/or neutropenia. Occasionally, eosinophilia has been observed (see **ADVERSE EFFECTS**).

Serum transaminase

Asymptomatic elevations in serum transaminase (ALT, AST) or γ-GT levels have been observed in some patients administered quetiapine. These elevations were usually reversible on continued quetiapine treatment (see **ADVERSE EFFECTS**).

Lipids

Increases in triglyceride levels and total cholesterol (predominantly LDL cholesterol) have been observed during treatment with quetiapine. Decreases in fasting HDL cholesterol have also been observed (see **ADVERSE EFFECTS**).

Thyroid hormone levels

Quetiapine treatment was associated with dose-related decreases in thyroid hormone levels. In short term placebo-controlled clinical trials, the incidence of potentially clinically significant shifts in thyroid hormone levels were: total T_4 - 3.4% for quetiapine versus 0.6 % for placebo; free T_4 - 0.7% for quetiapine versus 0.1% for placebo; total T_3 - 0.54% for quetiapine versus 0.0% for placebo and free T_3 - 0.2% for quetiapine versus 0.0% for placebo. The incidence of shifts in TSH was 3.2% for quetiapine versus 2.7 % for placebo. In short term placebo-controlled monotherapy trials, the incidence of reciprocal, potentially clinically significant shifts in T_3 and TSH was 0.0 % for both quetiapine and placebo and 0.1% for quetiapine versus 0.0 % for placebo for shifts in T4 and TSH. As supported by the literature, these changes in thyroid hormone levels are generally not associated with clinically symptomatic hypothyroidism. The reduction in total and free T_4 was maximal within the first 6 weeks of quetiapine treatment, with no further reduction during long-term treatment. In nearly all cases, cessation of quetiapine treatment was associated with a reversal of the effects on total and free T_4, irrespective of the duration of treatment (see **ADVERSE EFFECTS**).

Methadone and tricyclic antidepressant enzyme immunoassays

There have been reports of false positive results in enzyme immunoassays for methadone and tricyclic antidepressants in patients who have taken quetiapine. Confirmation of questionable immunoassay screening results by an appropriate chromatographic technique is recommended.

Effect on ability to drive and use machines

Given its primary central nervous system effects, quetiapine may interfere with activities requiring mental alertness. Patients likely to drive or operate other machines should therefore be cautioned appropriately.

Sleep apnea

In patients who have a history of or are at risk for sleep apnea, and are receiving concomitant central nervous system (CNS) depressants, quetiapine should be used with caution.

Anti-cholinergic (muscarinic) effects

Norquetiapine, an active metabolite of quetiapine, has moderate to strong affinity for several muscarinic receptor subtypes. This contributes to adverse drug reactions reflecting anti-cholinergic effects when quetiapine is used at recommended doses, when used concomitantly with other medications having anti-cholinergic effects, and in the setting of overdose. Quetiapine should be used with caution in patients receiving medications having anti-cholinergic (muscarinic) effects. Quetiapine should be used with caution in patients with a current diagnosis or prior history of urinary retention, clinically significant prostatic hypertrophy, intestinal obstruction or related conditions, increased intraocular pressure or narrow angle glaucoma (see **PHARMACOLOGY – Mechanism of Action**, **INTERACTIONS WITH OTHER MEDICINES**, **ADVERSE EFFECTS** and **OVERDOSAGE**).

INTERACTIONS WITH OTHER MEDICINES

Antipsychotic and other centrally acting medicines

Given the primary central nervous system effects of quetiapine, it should be used with caution in combination with other centrally acting medicines and alcohol.

Thioridazine

Thioridazine (200 mg twice daily) increased the oral clearance of quetiapine (300 mg twice daily) by 65%.

Lorazepam

The mean oral clearance of lorazepam (2 mg, single dose) was reduced by 20 % in the presence of quetiapine administered as 250 mg three times a day. Dosage adjustment is not required.

Levodopa and dopamine agonists

As it exhibits *in vitro* dopamine antagonism, quetiapine may antagonise the effects of levodopa and dopamine agonists.

Potential interactions that have been excluded

Antipsychotics

The pharmacokinetics of quetiapine were not significantly altered following co-administration with the antipsychotics risperidone (3 mg twice daily) or haloperidol

(7.5 mg twice daily). The pharmacokinetics of lithium were not altered when co-administered with quetiapine (250 mg three times a day). The pharmacokinetics of sodium valproate and quetiapine were not altered to a clinically relevant extent when co-administered.

Imipramine and fluoxetine

See CYP inhibitors below.

CYP inhibitors

CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine (see **Pharmacokinetics**).

CYP3A4 inhibitors (e.g. azole antifungals, macrolide antibiotics and protease inhibitors)

During concomitant administration of medicines which are potent CYP3A4 inhibitors (such as azole antifungals, macrolide antibiotics and protease inhibitors), plasma concentrations of quetiapine can be significantly higher than observed in patients in clinical trials (see *Ketoconazole* below). As a consequence of this lower doses of quetiapine should be used. Special consideration should be given in elderly or debilitated patients. The risk-benefit ratio needs to be considered on an individual basis.

It is also not recommended to take quetiapine together with grapefruit juice.

Ketoconazole

In a multiple-dose trial in healthy volunteers to assess the pharmacokinetics of quetiapine given before and during treatment with ketoconazole, co-administration of ketoconazole (200 mg once daily for 4 days) resulted in an increase in mean C_{max} and AUC of quetiapine of 335% and 522%, respectively, with a corresponding decrease in mean oral clearance of 84%. The mean half-life of quetiapine increased from 2.6 to 6.8 hours, but the mean T_{max} was unchanged.

Potential interactions that have been excluded

Cimetidine

The pharmacokinetics of quetiapine (150 mg three times a day) were not significantly altered (20% decrease in clearance) following co-administration with cimetidine (400 mg three times a day for 4 days) a known P450 enzyme inhibitor. Dosage adjustment for quetiapine is not required when it is given with cimetidine.

Imipramine and fluoxetine

The pharmacokinetics of quetiapine were not significantly altered following co-administration with the antidepressants imipramine (75 mg twice daily; a known CYP2D6 inhibitor) or fluoxetine (60 mg once daily; a known CYP3A4 and CYP2D6 inhibitor).

Hepatic enzyme inducers (eg carbamazepine and phenytoin)

Quetiapine (administration of multiple daily doses up to 750 mg/day, on a three times a day dosing schedule) did not induce the hepatic enzyme systems involved in the

metabolism of antipyrine. However, concomitant use of quetiapine with hepatic enzyme inducers such as carbamazepine or phenytoin may substantially decrease systemic exposure to quetiapine (see **Carbamazepine and phenytoin** below). Depending on clinical response, increased doses of quetiapine may be required to maintain control of psychotic symptoms in patients co-administered quetiapine and hepatic enzyme inducers (e.g. carbamazepine, phenytoin, barbiturates, rifampicin, glucocorticoids). The safety of doses above 800 mg/day has not been established in the clinical trials. Continued treatment at higher doses should only be considered as a result of careful consideration of the benefit risk assessment for an individual patient.

The dose of quetiapine may need to be reduced if phenytoin, carbamazepine or other hepatic enzyme inducers are withdrawn and replaced with a non-inducer (e.g. sodium valproate).

Carbamazepine and phenytoin

In a multiple dose trial in patients to assess the pharmacokinetics of quetiapine given before and during treatment with carbamazepine (a known hepatic enzyme inducer), co-administration of carbamazepine significantly increased the clearance of quetiapine. This increase in clearance reduced systemic quetiapine exposure (as measured by AUC) to an average of 13% of the exposure during administration of quetiapine alone; although a greater effect was seen in some patients. As a consequence of this interaction, lower plasma concentrations can occur, and hence, in each patient, consideration for a higher dose of quetiapine, depending on clinical response, should be considered.

Co-administration of quetiapine (250 mg three times a day) and phenytoin (100 mg three times a day; another microsomal enzyme inducer) also caused increases in clearance of quetiapine by 5-fold.

Cardiovascular medicines

Caution should be used when quetiapine is used concomitantly with medicines known to cause electrolyte imbalance or to increase QTc interval (see **PRECAUTIONS** – **QT interval**).

Because of its potential for inducing hypotension, quetiapine may enhance the effects of certain anti-hypertensive medicines.

Medications to manage attention deficit hyperactivity disorder (ADHD)

The data regarding safety and efficacy of SEROQUEL for the treatment of bipolar mania in children and adolescents receiving psychostimulants for co-morbid ADHD are limited. Therefore, concomitant use of ADHD medication and quetiapine is not recommended. If concomitant therapy is considered necessary, patients should be carefully monitored for the effect of the combination of treatments on the signs and symptoms of both ADHD and acute mania. Effects on blood pressure may be cumulative and blood pressure should be carefully monitored.

Anti-cholinergic (muscarinic) effects

Caution should be exercised treating patients receiving other medications having anti-cholinergic (muscarinic) effects (see **PRECAUTIONS**).

ADVERSE EFFECTS

Clinical study experience

Schizophrenia (adults)

The treatment-emergent adverse events that occurred during acute therapy (up to 6 weeks) of schizophrenia in at least 5% of patients treated with SEROQUEL XR in placebo-controlled trials are listed in Table 6 regardless of causality.

Table 6 Adverse events that occurred in at least 5% of patients treated with SEROQUEL XR for acute schizophrenia

	Number (%) of patients	
Preferred term[a]	**Placebo (N=319)**	**Quetiapine XR (N=951)**
Sedation	6.6	12.7
Dry mouth	1.3	12.1
Somnolence	3.8	12.1
Dizziness	3.8	9.8
Headache	14.7	9.7
Insomnia	14.4	7.5
Orthostatic hypotension	4.7	7.4
Constipation	4.7	6.4
Nausea	6.9	5.5

[a] Patients with multiple events falling under the same preferred term are counted only once in that term. N Number of patients in treatment group.

Bipolar disorder (adults)

The treatment-emergent adverse events that occurred during acute therapy of bipolar disorder in at least 5% of patients treated with SEROQUEL XR in placebo-controlled trials are listed in Table 7 regardless of causality.

Table 7 Adverse events that occurred in at least 5% of patients with bipolar disorder treated with SEROQUEL XR for either acute mania or acute depression

	Number (%) of patients			
	Study 002, depression		**Study 004, mania**	
Preferred term	**Quetiapine XR (N=137)**	**Placebo (N=140)**	**Quetiapine XR (N=151)**	**Placebo (N=160)**
Dry mouth	37.2	7.1	33.8	6.9
Somnolence	29.2	5.7	16.6	4.4
Sedation	23.4	7.1	34.4	7.5
Dizziness	13.1	10.7	9.9	4.4
Increased appetite	12.4	5.7	4.0	1.9
Headache	9.5	10.0	11.9	13.8

	Number (%) of patients			
	Study 002, depression		Study 004, mania	
Preferred term	**Quetiapine XR (N=137)**	**Placebo (N=140)**	**Quetiapine XR (N=151)**	**Placebo (N=160)**
Constipation	8.0	6.4	9.9	3.1
Nausea	7.3	7.1	2.0	2.5
Weight increased	7.3	1.4	6.6	0.6
Dyspepsia	6.6	0.7	6.6	3.8
Fatigue	5.8	2.1	6.6	3.8

Major depressive disorder (adults)

The treatment-emergent adverse events that occurred during short-term monotherapy of MDD in at least 5% of patients treated with SEROQUEL XR in placebo-controlled trials are listed in Table 8 regardless of causality.

Table 8 Adverse events that occurred in at least 5% of patients treated with SEROQUEL XR as short-term monotherapy for major depressive disorder

	Number (%) of patients				
Preferred term[a]	**PLA N=648**	**ALL QTP N=1149**	**QTP 50 N=181**	**QTP 150 N=595**	**QTP 300 N=373**
Dry mouth	8.2	34.9	22.1	36.0	39.4
Sedation	4.5	29.2	27.1	28.1	31.9
Somnolence	6.9	24.9	18.2	25.0	27.9
Dizziness	8.6	15.1	8.8	16.6	15.8
Headache	17.3	15.2	12.2	17.5	13.1
Nausea	10.5	11.1	7.7	12.9	9.9
Constipation	3.7	8.4	7.2	8.2	9.1
Fatigue	2.6	7.0	6.1	7.6	6.4
Vomiting	2.2	4.4	1.7	4.5	5.4
Diarrhoea	7.3	6.7	6.6	7.7	5.1
Increased appetite	2.8	5.3	4.4	5.7	5.1
Insomnia	8.2	7.4	5.0	9.6	5.1
Vision blurred	1.5	3.6	1.7	3.2	5.1
Irritability	3.7	4.9	6.1	4.7	4.6
Myalgia	2.0	4.3	4.4	5.0	2.9

[a] Patients with multiple events falling under the same preferred term are counted only once in that term. PLA Placebo. QTP Quetiapine XR. N Number of patients in treatment group

The treatment-emergent adverse events that occurred during adjunct therapy (up to 6 weeks) of MDD in at least 5% of patients treated with SEROQUEL XR in placebo-controlled trials are listed in Table 9 regardless of causality.

Table 9 Adverse events that occurred in at least 5% of patients treated with SEROQUEL XR as adjunctive therapy for major depressive disorder

	Number (%) of patients		
Preferred term[a]	**PLA+AD (N=309)**	**QTP XR 150+AD (N=315)**	**QTP XR 300+AD (N=312)**
Dry mouth	7.8	27.3	39.7
Somnolence	3.6	22.5	26.0
Sedation	4.2	13.0	17.3
Dizziness	6.5	11.4	11.5
Fatigue	3.9	14.3	10.9
Constipation	3.6	5.7	10.6
Headache	11.7	11.4	7.7
Nausea	7.1	7.0	7.7
Weight increased	0.3	3.2	5.1
Insomnia	5.5	6.0	4.5

[a] Patients with multiple events falling under the same preferred term are counted only once in that term. PLA Placebo. QTP Quetiapine. AD Antidepressant. N Number of patients in treatment group.

The pattern of adverse events in the elderly population treated with SEROQUEL XR (short-term monotherapy) was similar to that seen in younger patients, with somnolence, headache, dry mouth and dizziness predominating.

The treatment-emergent adverse events that occurred during maintenance monotherapy of MDD in at least 5% of patients treated with SEROQUEL XR in placebo-controlled trials are listed in Table 10 regardless of causality.

Table 10 Adverse events that occurred in at least 5% of patients treated with SEROQUEL XR as maintenance therapy for major depressive disorder – randomised safety population

	Number (%) of patients	
Preferred term[a]	**Placebo (N=385)**	**Quetiapine XR (N=391)**
Weight increased	1.6	9.7
Nasopharyngitis	6.5	7.2
Headache	11.4	6.9
Dizziness	4.4	6.6
Insomnia	14.8	5.6
Diarrhoea	6.8	5.4

[a] Patients with multiple events falling under the same preferred term are counted only once in that term

Generalised anxiety disorder (adults)

The safety results of five placebo-controlled clinical trials show that SEROQUEL XR is generally safe and well tolerated when used for treatment of GAD. The treatment-emergent adverse events that occurred in at least 5% of patients (regardless of

causality) treated with SEROQUEL XR in non-elderly placebo-controlled trials are listed in Tables 11 (pooled non-elderly short term trials) and 12 (non-elderly maintenance trial). The pattern of adverse events in the elderly population treated with SEROQUEL XR (short-term monotherapy) was similar to that seen in younger patients, with somnolence, dry mouth, dizziness and headache predominating.

Table 11 **Adverse events that occurred in at least 5% of non-elderly patients treated with SEROQUEL XR for the short term treatment of generalised anxiety disorder**

	Number (%) of patients				
Preferred term [a]	**PLA (N=665)**	**ALL QTP XR (N=1569)**	**QTP XR 50 (N=452)**	**QTP XR 150 (N=673)**	**QTP XR 300 (N=444)**
Dry mouth	10.2	31.5	21.5	32.7	39.9
Somnolence	10.5	30.4	25.9	31.8	32.9
Sedation	5.0	20.4	12.4	19.8	29.5
Dizziness	9.0	14.5	13.5	14.1	16.2
Nausea	8.3	11.0	8.0	11.6	13.3
Constipation	3.0	7.1	4.6	6.5	10.6
Headache	18.3	12.6	13.5	13.4	10.6
Fatigue	7.1	11.2	12.2	11.9	9.2
Insomnia	5.6	6.4	5.1	7.0	7.0
Diarrhoea	6.9	5.5	5.1	5.5	6.1
Increased appetite	4.1	5.0	4.4	4.9	5.6
Dyspepsia	0.6	3.1	1.5	2.5	5.4
Vomiting	3.2	3.9	2.2	4.0	5.4

[a] Patients with multiple events falling under the same preferred term are counted only once in that term

Table 12 **Adverse events that occurred in at least 5% of patients treated with SEROQUEL XR as maintenance therapy for generalised anxiety disorder (randomised safety population)**

	Number (%) of patients	
Preferred term	**Placebo (N=216)**	**Quetiapine XR (N=216)**
Dry Mouth	13.0	18.5
Headache	14.8	11.6
Sedation	13.0	9.7
Somnolence	6.5	9.3
Weight increased	3.7	8.3
Nasopharyngitis	3.7	7.9
Constipation	3.2	7.4
Fatigue	7.4	6.5
Insomnia	14.8	5.1
Nausea	15.3	5.1

Other findings observed during clinical studies

Somnolence

Somnolence may occur, usually during the first two weeks of treatment and generally resolves with the continued administration of quetiapine. Somnolence may lead to falls.

Weight Gain (adults)

In schizophrenia trials the proportions of patients meeting a weight gain criterion of ≥7% of body weight from baseline were 10% for SEROQUEL XR compared to 5% for placebo. In SEROQUEL XR mania trials the proportions of patients meeting the same weight gain criterion were 5.1% compared to 0% for placebo. In bipolar depression trials, the proportions of patients meeting the same weight gain criterion were 8.2% for SEROQUEL XR compared to 0.8% for placebo. In MDD monotherapy trials (8 weeks), the proportions of patients meeting the same weight gain criterion were 3.9% for SEROQUEL XR compared to 2.4% for placebo. In MDD adjunctive therapy trials (6 weeks), the proportions of patients meeting the same weight gain criterion were 5.1% for SEROQUEL XR compared to 1.7% for placebo.

In schizophrenia trials the proportions of patients meeting a weight gain criterion of ≥7% of body weight from baseline were compared in a pool of four 3- to 6-week placebo-controlled clinical trials, revealing a statistically significantly greater incidence of weight gain for SEROQUEL (23%) compared to placebo (6%). In SEROQUEL mania monotherapy trials the proportions of patients meeting the same weight gain criterion were 21% compared to 7% for placebo and in mania adjunct therapy trials the proportion of patients meeting the same weight criterion were 13% for SEROQUEL compared to 4% for placebo. In bipolar depression trials, the proportions of patients meeting the same weight gain criterion were 8% for SEROQUEL compared to 2% for placebo.

Withdrawal (discontinuation symptoms)

In acute placebo-controlled monotherapy clinical trials in adults which evaluated discontinuation symptoms, the aggregated incidence of discontinuation symptoms after abrupt cessation was 16.0% for quetiapine and 7.3% for placebo. The aggregated incidence of individual adverse events (e.g. insomnia, nausea, headache, diarrhoea, vomiting, dizziness and irritability) did not exceed 6.7% in any treatment group and usually resolved after 1 week post-discontinuation (see **PRECAUTIONS**).

Leukopenia/Neutropenia

Possible risk factors for leukopenia and/or neutropenia include pre-existing low white cell count and history of drug induced leukopenia and/or neutropenia. Neutrophil count decreases have commonly been observed. In all short-term placebo controlled monotherapy clinical trials, among patients with a baseline neutrophil count ≥1.5 x 10^9/L, the incidence of at least one occurrence of neutrophil count <1.5 x 10^9/L was 1.9% in patients treated with quetiapine, compared to 1.5% in placebo-treated patients. The incidence ≥0.5 - <1.0 x 10^9/L (moderate neutropenia) was 0.2% (uncommon) in patients treated with quetiapine and 0.2% in placebo-

treated patients. In clinical trials conducted prior to a protocol amendment for discontinuation of patients with treatment-emergent neutrophil count <1.0 x 10^9/L, among patients with a baseline neutrophil count ≥1.5 x 10^9/L, the incidence of at least one occurrence of neutrophil count <0.5 x 10^9/L (severe neutropenia) was 0.21% (uncommon) in patients treated with quetiapine and 0% in placebo treated patients (see **PRECAUTIONS**).

Lipid changes (adults)

In schizophrenia trials, the proportions of patients with elevations to levels of cholesterol ≥6.2064 mmol/L and triglycerides ≥2.258 mmol/L were 9% and 18% for SEROQUEL XR treated patients respectively compared to 9% and 5% for placebo treated patients respectively. In bipolar mania trials, the proportion of patients with cholesterol and triglycerides elevations to these levels were 7% and 15% for SEROQUEL XR treated patients respectively, compared to 4% and 6% for placebo treated patients respectively. In bipolar depression trials, the proportion of patients with cholesterol and triglycerides elevations to these levels were 7% and 8% for SEROQUEL XR treated patients respectively, compared to 3% and 8% for placebo treated patients respectively. In MDD monotherapy trials (8 weeks), the proportion of patients with cholesterol and triglycerides elevations to these levels were 5% and 12% for SEROQUEL XR treated patients respectively, compared to 3% and 9% for placebo treated patients respectively. In MDD adjunctive therapy trials (6 weeks), the proportion of patients with cholesterol and triglycerides elevations to these levels were 17% and 16% for SEROQUEL XR treated patients respectively, compared to 6% and 5% for placebo treated patients respectively.

In schizophrenia trials, the proportions of patients with elevations to levels of cholesterol ≥6.2064 mmol/L and triglycerides ≥2.258 mmol/L were 16% and 23% for SEROQUEL treated patients respectively compared to 7% and 16% for placebo treated patients respectively. In bipolar depression trials, the proportion of patients with cholesterol and triglycerides elevations to these levels were 9% and 14% for SEROQUEL treated patients respectively, compared to 6% and 9% for placebo treated patients respectively.

In placebo controlled trials decreases in fasting HDL cholesterol have been observed. In short-term placebo-controlled clinical trials the incidence of patients who shifted from ≥1.025 mmol/L to <1.025 mmol/L was slightly higher in the quetiapine group compared to placebo (9.8% and 8.1% respectively). In long-term trials the incidence of patients who shifted from ≥1.025 mmol/L to <1.025 mmol/L was 18.3% in quetiapine and 10.9% in placebo.

Increases in blood glucose levels

In placebo-controlled clinical trials in adults, the percentage of patients who had a shift to a high blood glucose level (fasting blood glucose ≥7 mmol/L or a non-fasting blood glucose ≥11.1 mmol/L on at least one occasion) was 5.1% in patients treated with quetiapine and 4.2% in placebo treated patients (see **PRECAUTIONS**).

Decreases in haemoglobin levels

Decreased haemoglobin to 8.07 mmol/L males, 7.45 mmol/L females on at least one occasion occurred in 11% of quetiapine patients in all trials including open label

extensions. In short-term placebo controlled trials, decreased haemoglobin to 8.07 mmol/L males, 7.45 mmol/L females on at least one occasion in 8.3% of quetiapine patients compared to 6.2% of placebo patients.

Extrapyramidal symptoms (EPS) [adults]

The following clinical trials in adult patients included treatment with SEROQUEL and SEROQUEL XR. In short-term, placebo-controlled clinical trials in schizophrenia and bipolar mania the aggregate incidence of EPS was similar to placebo (schizophrenia: quetiapine 7.8%, placebo 8.0%; bipolar mania quetiapine 11.2%, placebo 11.4%). In short-term, placebo-controlled clinical trials in bipolar depression the aggregate incidence of EPS from the combined data was 8.9% for quetiapine compared to 3.8% for placebo, though the incidence of the individual adverse events (e.g. akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, muscle contractions involuntary, psychomotor hyperactivity and muscle rigidity) were generally low and did not exceed 4% in any treatment group. In short-term, placebo controlled monotherapy clinical trials in MDD the aggregated incidence of extrapyramidal symptoms was 5.4% for SEROQUEL XR and 3.2% for placebo. In a short-term placebo controlled monotherapy trial in elderly patients with MDD, the aggregated incidence of extrapyramidal symptoms was 9.0% for SEROQUEL XR and 2.3% for placebo. In two placebo-controlled short-term adjunct therapy clinical trials for the treatment of MDD utilising between 150 mg and 300 mg of SEROQUEL XR, the incidence of any adverse reactions potentially related to EPS was 5.1% SEROQUEL XR and 4.2% for the placebo group. In short-term, placebo-controlled monotherapy clinical trials in GAD, the aggregated incidence of EPS was 4.9% for SEROQUEL XR and 3.2% for placebo. In a short-term placebo controlled monotherapy trial in elderly patients with GAD, the aggregated incidence of EPS was 5.4% for SEROQUEL XR and 2.2% for placebo. In long-term studies of schizophrenia, bipolar disorder, MDD and GAD the aggregated exposure adjusted incidence of treatment emergent EPS was similar between quetiapine and placebo (see also **PRECAUTIONS** – **Extrapyramidal symptoms** and Table 13 below).

Irritability

In acute placebo-controlled clinical trials in patients ≥18 years of age, the incidence of irritability was 2.3% for quetiapine and 1.7% for placebo.

Dysphagia

An increase in the rate of dysphagia with quetiapine vs placebo was only observed in the adult clinical trials in bipolar depression.

Other adverse drug reactions

In addition to the above, the following adverse drug reactions have also been observed in adult clinical trials (placebo-controlled trials, active-arm controlled trials and open-label uncontrolled trials) with quetiapine.

Table 13

Frequency	System Organ Class	Reaction
Very common (≥10%)	Nervous system disorders	Extrapyramidal symptoms

Frequency	System Organ Class	Reaction
Common	Cardiac disorders	Tachycardia[2] ; palpitations [4]
(≥1% to <10%)	Eye disorders	Vision blurred
	Gastrointestinal disorders	Vomiting [6]
	General disorders and administration site conditions	Mild asthenia; Peripheral oedema; Irritability; Pyrexia
	Investigations	Elevations in serum alanine aminotransferase (ALT) [8]; Elevations in γ-GT levels [8] ; Elevations in serum prolactin[3] ; Decreases in total T_4, free T_4 and total T_3, and increases in TSH [5] Eosinophils increased [7]
	Metabolism & nutritional disorders	Increased appetite
	Nervous system disorders	Dysarthria
	Psychiatric disorders	Abnormal dreams and nightmares
	Respiratory, thoracic and mediastinal disorders	Dyspnoea [4]
	Blood disorder	Leukopenia
Uncommon	Cardiac disorders	Bradycardia [9]
(≥0.1% to <1%)	Gastrointestinal disorders	Dysphagia [2]
	Investigations	Elevations in serum aspartate aminotransferase (AST) [8]; Platelet count decreased[1] ; Decreases in free T_3 [5]
	Immune system disorders	Hypersensitivity
	Nervous system disorders	Syncope[2]; Seizure[2]; Restless legs syndrome; Tardive dyskinesia[2]
	Respiratory, thoracic and mediastinal disorders	Rhinitis
	Renal and urinary disorders	Urinary retention
Rare (≥0.01% to <0.1%)	General disorders and administration site conditions	Neuroleptic malignant syndrome[2]; Hypothermia
	Investigations	Elevations in blood creatine phosphokinase (not associated with neuroleptic malignant syndrome); Agranulocytosis[10]
	Psychiatric disorders	Somnambulism and other related events
	Reproductive system and breast disorders	Priapism
	Gastrointestinal disorders	Intestinal obstruction/Ileus
	Hepatobiliary disorders	Hepatitis (with or without jaundice)
Not known	General disorders and administration site conditions	Neonatal withdrawal[11]

1. Platelets ≤100 x 10^9/L on at least one occasion.
2. See **PRECAUTIONS.**
3. Prolactin levels (patients ≥ 18 years of age): >20µg/L males; >30µg/L females at any time.

4. These reports often occurred in the setting of tachycardia, dizziness, orthostatic hypotension and/or underlying cardiac/respiratory disease.
5. Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in total T_4, free T_4, total T_3 and free T_3 are defined as <0.08x LLN (pmol/L) and shift in TSH is >5mIU/L at any time.
6. Based upon the increased rate of vomiting in elderly patients (≥ 65 years of age).
7. Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in eosinophils are defined as ≥1x10^9 cells/L at any time.
8. Asymptomatic elevations (shift from normal to ≥3 x ULN at any time) in serum transaminases (ALT and AST) or γ-GT levels have been observed in some patients administered quetiapine. These elevations were usually reversible on continued quetiapine treatment.
9. May occur at or near initiation of treatment and be associated with hypotension and/or syncope. Frequency based on adverse event reports of bradycardia and related events in all clinical trials with quetiapine.
10. Based on the frequency of patients during all quetiapine clinical trials with severe neutropenia (<0.5 x 10^9/L) and infection.
11. See **Use in Pregnancy**.

Children and adolescents

The same adverse drug reactions described for adults should be considered for children and adolescents. The following table summarises adverse drug reactions that occur in a higher frequency category in children and adolescents patients (10-17 years of age) than in the adult population, or adverse drug reactions that have not been identified in the adult population.

Table 14

Frequency	System Organ Class	Reaction
Very common (≥10%)	Metabolism & nutrition disorders	Increased appetite
	Investigations	Elevations in serum prolactin [1]; Increases in blood pressure [2]
	Gastrointestinal disorders	Vomiting
Common (≥1%-<10%)	Respiratory, thoracic & mediastinal disorders	Rhinitis
	Nervous system disorders	Syncope

1 Prolactin levels (patients < 18 years of age): >20 µg/L males; > 26 µg/L females at any time. Less than 1% of patients had an increase to a prolactin level >100 µg/L

2 Based on shifts above clinically significant thresholds (adapted from the National Institutes of Health criteria) or increases >20 mmHg for systolic or >10 mmHg for diastolic blood pressure at any time in two acute (3-6 weeks) placebo-controlled trials in children and adolescents

Weight Gain (children and adolescents)

In one 6-week, placebo-controlled trial in adolescent patients (13-17 years of age) with schizophrenia, the mean increase in body weight, was 2.0 kg in the quetiapine group and -0.4 kg in the placebo group. 21% of quetiapine-treated patients and 7% of placebo-treated patients gained ≥7% of their body weight.

In one 3-week, placebo-controlled trial in children and adolescent patients (10-17 years of age) with bipolar mania, the mean increase in body weight was 1.7 kg in the quetiapine group and 0.4 kg in the placebo group. 12% of quetiapine-treated patients and 0% of placebo-treated patients gained ≥7% of their body weight.

In the open-label study that enrolled patients from the above two trials, 63% of patients (241/380) completed 26 weeks of therapy with quetiapine. After 26 weeks of treatment, the mean increases in body weight and BMI were 4.4 kg and 1.1 kg/m^2 respectively. 45% of the patients gained ≥7% of their body weight (not adjusted for

normal growth). 18.3% of the patients had a clinically significant change in BMI (adjusted for growth).

In one 8-week, placebo-controlled trial in children and adolescent patients (10-17 years of age) with bipolar depression, in which efficacy was not established, the mean increase in body weight was 1.4 kg in the quetiapine modified release group and 0.6 kg in the placebo group. For children and adolescents who completed the 8 weeks of quetiapine therapy 13.7% of SEROQUEL XR-treated patients and 6.8% of placebo-treated patients gained ≥7% of their body weight.

Extrapyramidal Symptoms (EPS) [children and adolescents]

In a short-term placebo-controlled monotherapy trial in adolescent patients (13-17 years of age) with schizophrenia, the aggregated incidence of EPS was 12.9% for quetiapine and 5.3% for placebo, though the incidence of the individual adverse events (e.g. akathisia, tremor, extrapyramidal disorder, hypokinesia, restlessness, psychomotor hyperactivity, muscle rigidity, dyskinesia) was generally low and did not exceed 4.1% in any treatment group. In a short-term placebo-controlled monotherapy trial in children and adolescent patients (10-17 years of age) with bipolar mania, the aggregated incidence of EPS was 3.6% for quetiapine and 1.1% for placebo.

In a short-term placebo-controlled monotherapy trial in children and adolescent patients (10-17 years of age) with bipolar depression in which efficacy was not established, the aggregated incidence of extrapyramidal symptoms was 1.1% for SEROQUEL XR and 0.0% for placebo.

Suicide/suicidal thoughts or clinical worsening (all ages)

In short-term placebo-controlled clinical trials across all indications and ages, the incidence of suicide-related events was 0.8% for both quetiapine (76/9327) and placebo (37/4845).

In these trials of patients with schizophrenia the incidence of suicide related events was 1.4% (3/212) for quetiapine and 1.6% (1/62) for placebo in patients 18-24 years of age, 0.8% (13/1663) for quetiapine and 1.1% (5/463) for placebo in patients ≥25 years of age, and 1.4% (2/147) for quetiapine and 1.3% (1/75) for placebo in patients <18 years of age. There has been one trial conducted in patients 10-17 years of age in which efficacy was not established. The incidence of suicide related events was 1.0% (1/92) for quetiapine and 0% (0/100) for placebo. In this study there were two additional events in two patients that occurred during an extended post-treatment follow-up phase of the study; one of these patients was on quetiapine at the time of the event (see **PRECAUTIONS**).

In these trials of patients with bipolar mania the incidence of suicide related events was 0% for both quetiapine (0/60) and placebo (0/58) in patients 18-24 years of age, 1.2% for both quetiapine (6/496) and placebo (6/503) in patients ≥25 years of age, and 1.0% (2/193) for quetiapine and 0% (0/90) for placebo in patients <18 years of age.

In these trials of patients with bipolar depression the incidence of suicide related events was 3.0% (7/233) for quetiapine and 0% (0/120) for placebo in patients 18-24

and 1.8% for both quetiapine (19/1616) and placebo (11/622) in patients ≥25 years of age. There have been no trials conducted in patients <18 years of age with bipolar depression.

In these trials of patients with MDD the incidence of suicide related events was 2.1% (3/144) for quetiapine and 1.3% (1/75) for placebo in patients 18-24 and 0.6% (11/1798) for quetiapine and 0.7% for placebo (7/1054) in patients ≥25 years of age. There have been no trials conducted in patients <18 years of age with MDD.

In these trials of patients with GAD the incidence of suicide related events was 0.5% for quetiapine (1/194) and 0.9% for placebo (1/109) in patients 18-24 years of age and 0.4% for quetiapine (7/1810) and 0.1% for placebo (1/983) in patients ≥25 years of age.

Cataracts/lens opacities

In a clinical trial to evaluate the cataractogenic potential of SEROQUEL (200-800 mg/day) versus risperidone (2-8 mg/day) in patients with schizophrenia or schizoaffective disorder, the percentage of patients with increased lens opacity grade was not higher in SEROQUEL compared with risperidone for patients with at least 21 months of exposure.

Post-marketing experience

In addition to the above, the following post-marketing adverse drug reactions have been observed with quetiapine.

Table 15

Frequency	System Organ Class	Reaction
Rare (≥0.01 - <1%)	Reproductive system & breast disorders	galactorrhea
Very rare (<0.01%)	Immune system disorders	anaphylactic reaction

Very rare cases of cataract and urinary retention have been reported in the post-marketing data, but no causal link between these reports and quetiapine has been established.

There have been rare post-marketing reports of pancreatitis. Among the post-marketing reports, many patients had factors which are known to be associated with pancreatitis such as increased triglycerides (see discussion on **Lipids** and **Effects on laboratory tests** in the **PRECAUTIONS** section, above), gallstones and alcohol consumption.

Very rare cases of exacerbation of pre-existing diabetes have been reported.

Hepatic failure, including fatalities, has been reported very rarely during the post-marketing period. Rare post-marketing reports of hepatitis (with or without jaundice), in patients with or without prior history, have been received. Very rare cases of

hepatic steatosis, cholestatic or mixed liver injury have also been reported in the post-marketing period (see **PRECAUTIONS**).

Other adverse events reported since market introduction, which were temporally related to quetiapine therapy, but not necessarily causally related, include: cardiomyopathy, myocarditis, syndrome of inappropriate antidiuretic hormone secretion (SIADH), hyponatraemia, cerebrovascular accident, Stevens-Johnson Syndrome, and drug reaction with eosinophilia and systemic symptoms (DRESS).

DOSAGE AND ADMINISTRATION

Chronic antipsychotic treatment should generally be reserved for patients who appear to suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative equally effective but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory response should be sought. The need for continued treatment should be reassessed periodically.

SEROQUEL XR should be administered once daily, without food.

The tablets should be swallowed whole and not split, chewed or crushed.

Adults

Bipolar Disorder

Maintenance treatment

Patients who have responded to SEROQUEL XR for acute treatment of bipolar disorder should continue therapy at the same dose. It is generally recommended that responding patients be continued beyond the acute response, but at the lowest possible dose needed to maintain remission.

For prevention of relapse/ recurrence of manic, depressive and mixed episodes in bipolar disorder, the usual effective dose is within the range of 300 to 800 mg/day (see **CLINICAL TRIALS**).

The dose of SEROQUEL XR can be re-adjusted depending on the clinical response and tolerability of the individual patient. Patients should be periodically reassessed to determine the need for maintenance treatment.

Bipolar Depression

When treating depressive episodes in bipolar disorder, treatment should be initiated either by the treating psychiatrist or by the general practitioner after consultation with the psychiatrist.

SEROQUEL XR should be titrated as follows: 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). SEROQUEL XR can be titrated to 400 mg on Day 5 and up to 600 mg by Day 8.

Acute mania

SEROQUEL XR should be titrated as follows: 300 mg on Day 1, 600 mg on Day 2 and up to 800 mg after Day 2, alone or in combination with a mood stabiliser.

The dose should be adjusted within the usual effective dose range of 400 to 800 mg/day, depending on the clinical response and tolerability of the individual patient.

Schizophrenia

The daily dose at the start of therapy is 300 mg on Day 1, 600 mg on Day 2 and up to 800 mg after Day 2. The dose should be adjusted within the usual effective dose range of 400 to 800 mg/day, depending on the clinical response and tolerability of the individual patient. For maintenance therapy in schizophrenia no dosage adjustment is necessary. The safety of doses above 800 mg/day has not been evaluated.

Recurrent major depressive disorder

When treating recurrent MDD in patients who are intolerant of, or who have an inadequate response to alternative therapies, treatment should be initiated either by the treating psychiatrist or by the general practitioner after consultation with the psychiatrist.

SEROQUEL XR should be administered once daily in the evening.

Initial dosing should begin at 50 mg on Day 1 and 2, increased to 150 mg on Day 3 and 4. The usual effective dose in MDD is 150 mg (see **CLINICAL TRIALS**). Further adjustments can be made upwards or downwards within the recommended dose range of 50 mg to 300 mg depending upon the clinical response and tolerability of the patient.

Patients who have not responded to SEROQUEL XR after 6 weeks treatment for MDD should have treatment re-evaluated (see **CLINICAL TRIALS**).

For maintenance therapy in MDD in patients who have responded to acute treatment, the effective dose during initial treatment should be continued. It is generally recommended that responding patients be continued beyond the acute response, but at the lowest possible dose needed to maintain remission. The dose can be adjusted within the recommended dose range depending upon the clinical response and tolerability of the patient. Patients should be periodically reassessed to determine the need for maintenance treatment.

Generalised anxiety disorder

Initial dosing should begin at 50 mg on Day 1 and 2, increased to 150 mg on Day 3 and 4. Further adjustments can be made within the recommended dose range of 50 mg to 150 mg depending upon the clinical response and tolerability of the patient. Efficacy was demonstrated with SEROQUEL XR at doses ranging from 50 to 300 mg/day, however no additional benefit was seen with the 300 mg group compared to the 150 mg group (see **CLINICAL TRIALS**). Doses above 150 mg/day are not recommended.

For maintenance therapy in GAD the effective dose during initial treatment should be continued. The dose can be adjusted within the recommended dose range depending upon the clinical response and tolerability of the individual patient.

Switching from SEROQUEL immediate release tablets

For more convenient dosing, patients who are currently being treated with divided doses of SEROQUEL immediate release tablets may be switched to SEROQUEL XR at the equivalent total daily dose taken once daily (see **CLINICAL TRIALS**). For example - patients administered SEROQUEL immediate release 300 mg twice daily (total daily dose of 600 mg) would be switched to a dose of SEROQUEL XR 600 mg once daily on the next calendar day. Individual dosage adjustments may be necessary.

Elderly

As with other antipsychotics, SEROQUEL XR should be used with caution in the elderly, especially during the initial dosing period. The rate of dose titration may need to be slower, and the daily therapeutic dose lower, than that used in younger patients. The mean plasma clearance of quetiapine was reduced by 30% to 50% in elderly subjects when compared with younger patients. Elderly patients should be started on 50 mg/day. The dose can be increased in increments of 50 mg/day to an effective dose, depending on the clinical response and tolerability of the individual patient.

In elderly patients with MDD, initial dosing should begin at 50 mg on Days 1-3, the dose can be increased to 100 mg on Day 4, 150 mg on Day 8 and then up to 300 mg depending on clinical response and tolerability.

In elderly patients with GAD, initial dosing should begin at 50 mg on Days 1-3, the dose can be increased to 100 mg on Day 4, 150 mg on Day 8. Further adjustments can be made within the recommended dose range of 50 mg to 150 mg depending on clinical response and tolerability.

Children and adolescents (<18 years of age)

The safety and efficacy of SEROQUEL XR was evaluated in an 8-week study of children and adolescent patients (10-17 years of age) with bipolar depression. Efficacy in this study was not established (see **ADVERSE EFFECTS**). However, clinical trials have been conducted with SEROQUEL in children and adolescents 10 to 17 years of age with bipolar mania (as monotherapy), and 13 to 17 years of age with schizophrenia (see **CLINICAL TRIALS**).

Renal impairment

Dosage adjustment is not necessary.

Hepatic impairment

Quetiapine is extensively metabolised by the liver. Therefore, SEROQUEL XR should be used with caution in patients with known hepatic impairment, especially during the initial dosing period. Patients with hepatic impairment should be started on 50 mg/day. The dose can be increased in increments of 50 mg/day to an

effective dose, depending on the clinical response and tolerability of the individual patient.

OVERDOSAGE

In clinical trials, experience with quetiapine in overdosage is limited. Survival has been reported in acute overdoses of up to 30 grams of quetiapine. Most patients who overdosed reported no adverse events or recovered fully from the reported events. Death has been reported in a clinical trial following an overdose of 13.6 grams of quetiapine alone. In post marketing experience, there have been very rare reports of overdose of quetiapine alone resulting in death or coma.

In post marketing experience there were cases reported of QT prolongation with overdose.

Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose (see **PRECAUTIONS** – **Concomitant cardiovascular illness**).

In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e. drowsiness and sedation, tachycardia, hypotension and anti-cholinergic effects.

Management of overdose

There is no specific antidote to quetiapine. In cases of severe signs, the possibility of multiple drug involvement should be considered, and intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system. Whilst the prevention of absorption in overdose has not been investigated, administration of activated charcoal together with a laxative should be considered.

In cases of quetiapine overdose, refractory hypotension should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (adrenaline and dopamine should be avoided, since β-stimulation may worsen hypotension in the setting of quetiapine-induced α-blockade).

Close medical supervision and monitoring should be continued until the patient recovers.

Contact the Poisons Information Centre on 131126 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

SEROQUEL XR 50 mg, 150 mg, 200 mg, 300 mg and 400 mg tablets are registered in blister packs [PVC + PCTFE (polychlorotrifluoroethylene) / aluminium] of 10s (physician sample only), 30s[##], 60s and 100s[#].

[#] not supplied in Australia

150 mg strength only. Not supplied in Australia

Store below 30°C.

NAME AND ADDRESS OF THE SPONSOR

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POISONS SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

30 January 2008 (50, 200, 300 and 400 mg tablets)

15 June 2009 (150 mg tablet)

DATE OF MOST RECENT AMENDMENT

15 August 2017