Australian Government

Department of Health and Ageing

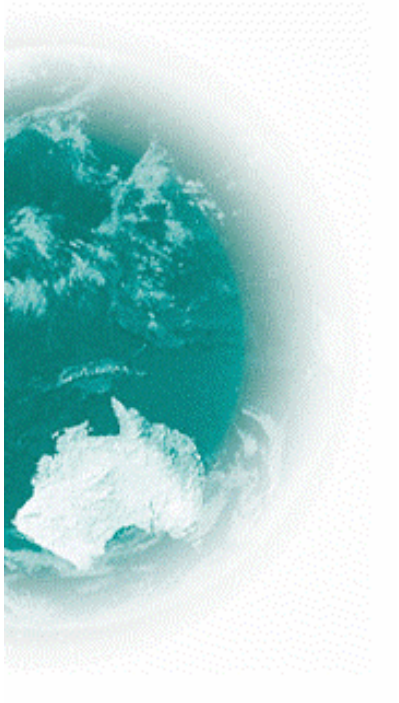
Therapeutic Goods Administration

Australian Public Assessment Report for Quetiapine (as fumarate)

Proprietary Product Name: Seroquel, Seroquel XR

Submission No: PM-2008-03436-1

Sponsor: AstraZeneca Pty Ltd



April 2010

Contents

I. Introduction to Product Submission

Product Details

Type of Submission	Extension of indications
Decision:	Approved
Date of Decision:	3 March 2010
Active ingredient(s):	Quetiapine (fumarate)
Product Name(s):	Seroquel, Seroquel XR
Sponsor's Name and Address:	AstraZeneca Pty Ltd Alma Road North Ryde NSW 2113
Dose form(s):	Seroquel – tablets, Seroquel XR - modified release tablets
Strength(s):	Seroquel - 25 mg, 100 mg, 150 mg, 200 mg and 300 mg Seroquel XR - 50 mg, 150 mg, 200 mg, 300 mg and 400 mg
Container(s):	Seroquel - PVC/aluminium foil blister pack.; Seroquel XR - PVC + PCTFE/aluminium foil blister pack
Pack size(s):	Seroquel: 25 mg: 20s (physician sample only), 60s; 100 mg: 20s (physician sample only), 90s; 150 mg: 60s; 200 mg: 20s (physician sample only), 60s; 300 mg: 20s (physician sample only), 60s and 100s; 4-day starter pack contains 25 mg x 6 tablets; 100 mg x 3 tablets and 200 mg x 1 tablet. Seroquel XR: 50 mg: 10s (physician sample only), 60s and 100s; 150 mg: 10s (physician sample only), 60s and 100s; 200 mg: 10s (physician sample only), 60s and 100s; 300 mg: 10s (physician sample only), 60s and 100s; 400 mg: 10s (physician sample only), 60s and 100s.
Approved Therapeutic use:	Seroquel is indicated for: **Bipolar disorder** *Adults* • 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 *Children/adolescents aged 10 to 17 years* • Monotherapy treatment of acute mania associated with bipolar I disorder **Schizophrenia (adults and adolescents aged 13 to 17 years)** • Treatment of schizophrenia

	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).
Route(s) of administration:	Oral
Dosage:	Depends on age and indication

Product Background

Quetiapine is an atypical antipsychotic agent. The indications for Seroquel (quetiapine) and its extended release form, Seroquel XR have been extensively amended in recent years and with this submission further extensions are proposed. Quetiapine is not currently indicated for use in children or adolescents aged < 18 years.

Seroquel is currently indicated for:

- Treatment of schizophrenia
- Bipolar disorder including:
  - 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;
  - Treatment of acute mania associated with bipolar I disorder as monotherapy or in combination with lithium or sodium valproate.

Seroquel XR is currently indicated for:

- Schizophrenia: Treatment of schizophrenia, prevention of relapse and maintenance of clinical improvement during continuation therapy.
- Bipolar disorder including:
  - 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.
- 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.

- 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.

With this submission the sponsor seeks to extend the patient population for Seroquel (immediate release) to include use in children/ adolescents with schizophrenia or acute mania (as monotherapy) associated with bipolar I disorder. Additionally the sponsor seeks to make other changes to the PI, but these are not the subject of this AusPAR.

The sponsor also seeks to extend the indications of Seroquel XR to include *Treatment of generalised anxiety disorder, including maintenance of the anti-anxiety effect.*

With respect to bipolar disorder in children, the Therapeutic Guidelines – Psychotropic notes that "The diagnosis of juvenile (paediatric) bipolar disorder" in childhood or early adolescence is controversial when made in the absence of elevated mood, and largely premised on chronic irritability.[1] There is little evidence to guide treatment of this presentation, with the symptoms frequently overlapping with attention deficit hyperactivity disorder (ADHD) and oppositional defiant disorder.

None of the atypical antipsychotic medicines currently have indications for treatment of bipolar disorder in children. However risperidone is indicated for use in young children – for children with autism or intellectual impairment with associated conduct and behavioural disorders from 5 years of age. Risperidone and clozapine may be used in adolescents with schizophrenia from 15 years and 16 years of age respectively.

No antipsychotic medication currently has an indication for the treatment of Generalised Anxiety Disorder (GAD). The defining features of GAD are excessive anxiety and worry and the diagnosis can only be made when there is significant social, occupational and functional impairment that has persisted for at least 6 months (functional impairment is not necessary for the diagnosis if clinically significant distress is evident). The recommended treatment for GAD is cognitive behaviour therapy with pharmacological treatments including selective serotonin reuptake inhibitors (SSRIs), benzodiazepines or monoamine oxidase inhibitors (MAOIs) as add on therapy if required.

The following guideline documents, adopted by the TGA, are relevant to this submission:

CPMP/EWP/567/98 *Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment of Bipolar Disorder*

CPMP/EWP/559/95 *Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Schizophrenia*

CPMP/EWP/4284/02 *Guideline on the Clinical Investigation of Medicinal Products Indicated for Generalised Anxiety Disorder*

[1] Psychotropic Expert Group. Therapeutic Guidelines: Psychotropic. Version 6. Melbourne: Therapeutic Guidelines Limited; 2008.

The proposed dosage regimen is as follows:

Seroquel - *Schizophrenia* in children aged 13-17 years: effective dose range 400 to 800 mg daily in divided doses. In adults with schizophrenia the dose may be adjusted within the range 150 to 750 mg daily.

Bipolar mania monotherapy in children aged 10 to 17 years: effective dose range 400 to

600 mg daily in divided doses. In adults with acute mania the dose may be adjusted within the range 200 to 800 mg/ day.

Seroquel XR - *Generalised anxiety disorder*: dose range 50 to 300 mg daily

Regulatory Status

The product is currently registered on the ARTG as Seroquel quetiapine (as fumarate salt) 100 mg tablet blister pack AUST R 58113, 200 mg tablet blister pack AUST R 58114, 150 mg tablet blister pack AUST R 78360, 25 mg tablet blister pack AUST R 58112, 25 mg, 100 mg and 200 mg tablet composite pack AUST R 73350, 300 mg tablet blister pack AUST R 78361, Seroquel XR quetiapine (as fumarate) 50 mg modified release tablet blister pack AUST R 138917, 150 mg modified release tablet blister pack AUST R 153883, 200 mg modified release tablet blister pack AUST R 138920, 300 mg modified release tablet blister pack AUST R 138921, 400 mg modified release tablet blister pack AUST R 138922.

A similar application to extend the indications for Seroquel to include use in children/adolescents with schizophrenia and bipolar mania was lodged in the USA and subsequently approved (2 December 2009). In the European Union (EU), there was a similar application, not seeking indications, but only updating the label with paediatric safety information.

Similar applications to extend the indications for Seroquel XR to include general anxiety disorder (GAD) have been lodged in the US and the EU.

A submission in Canada was withdrawn (26 June 2009) without prejudice.

Product Information

The approved product information current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

Quality Summary and Conclusions

There was no requirement for a quality evaluation for a submission of this type.

III. Nonclinical Findings

Nonclinical Summary and Conclusions

There was no requirement for a nonclinical evaluation for a submission of this type.

IV. Clinical Findings

Introduction

The submission contained data in support of an application to extend the indications for Seroquel XR to include general anxiety disorder (GAD), and for Seroquel to include use in children/adolescents with schizophrenia and bipolar mania. The application also included changes to the Product Information document that were not related to the extension of indications. These changes have not been discussed any further within this AusPAR.

The data submitted in support of use in children and adolescents consisted of:

One study in support of pharmacokinetics (PK), conducted in 27 subjects, all of whom were treated with quetiapine (QTP): ***Study D1441C00028*** (Table 1)

Two studies, conducted in 406 subjects in support of efficacy:

Study D1441C00112, conducted in 222 adolescents with schizophrenia, 147 of whom were treated with QTP (Table 2)

Study D1441C00149 conducted in 284 children and adolescents with bipolar I mania, 195 of whom were treated with QTP (Table 4).

Additional data were submitted from ***Study D1441C00150*** (Table 6) which was an open label extension of ***Studies D1441C00112*** and ***D1441C00149***, conducted in 381 subjects all of whom were treated with QTP.

The data in support of the indication of GAD consisted of five efficacy and safety studies conducted in a total of 4352 subjects, 3028 treated with QTP. The studies were:

Study D1448C00009. 951 subjects, 716 treated with QTP (Table 8).

Study D1448C00010, 854 subjects, 426 treated with QTP (Table 10).

Study D1448C00011, 873 subjects, 439 treated with QTP (Table 13).

Study D1448C00012, 1224 subjects, all treated with QTP (Table 16).

Study D1448C00015, 450 subjects aged 66 years or more, 223 treated with QTP (Table 19).

All the studies were conducted according to Good Clinical Practice and in accordance with the principles of the Declaration of Helsinki.

Pharmacokinetics

Study D1441C00028 was a multicentre (three-centre), open-label, inpatient, steady-state, PK, safety and tolerability study in children and adolescents with confirmed clinical diagnoses of schizophrenia, schizoaffective disorder or bipolar disease (Table 1). Quetiapine was administered over 13 days, with dose titration according to the regimen: Day 1: a single 50-mg dose in the evening), Day 2 (50 mg twice daily), Day 3 (100 mg twice daily), Day 4 (150 mg twice daily), Days 5 to 7 (200 mg twice daily), Day 8 (250 mg twice daily), Day 9 (300 mg twice daily), Day 10 (350 mg twice daily), Days 11 and 12 (400 mg twice daily), and Day 13 (a single 400-mg dose in the morning).

Table 1 Study D1441C00028

Study Design	Medication	No. of Volunteers Entered (M/F) Age range	Pharmacokinetics	Adverse Reactions
Multicentre (three centres), open-label, inpatient, steady-state, PK, safety and tolerability study in children and adolescents with confirmed clinical diagnoses of schizophrenia, schizoaffective disorder or bipolar disease	Day 1: a single 50-mg dose in the evening), Day 2 (50 mg twice daily), Day 3 (100 mg twice daily), Day 4 (150 mg twice daily), Days 5 to 7 (200 mg twice daily), Day 8 (250 mg twice daily), Day 9 (300 mg twice daily), Day 10 (350 mg twice daily), Days 11 and 12 (400 mg twice daily), and Day 13 (a single 400-mg dose in the morning)	28 subjects enrolled, 27 received study medication, 24 evaluable for pharmacokinetics 3 subjects in the 10 to 12 year age group were unable to tolerate daily doses greater than 600 mg Age range 10 to 17 years: Of the 27 subjects in the safety population, 13 were in the 10- to 12-year age range, and 14 were in the 13- to 17-year age range. Thirteen subjects were female and 14 subjects were male. Fourteen subjects were Black, 12 were Caucasian and 1 was Hispanic	Terminal elimination half-life was similar for the two treatment groups. Hence, although AUC and Cmax were higher in the younger age group, this may have been related to lower body weight in the younger subjects. Also for QTP sulfoxide and N-desalkyl quetiapine, terminal elimination half-life was similar, but AUC and Cmax were greater in the younger age group. Exposure to 7-hydroxy quetiapine was similar for the two age groups.	16 (59.3%) subjects experienced 40 AEs. The rate of AEs was similar for the two age groups. The most frequently occurring AEs were: somnolence, dizziness, dyspnoea, headache, increased heart rate, increased appetite and sedation. There were no clinically significant abnormalities in haematology or clinical chemistry parameters. There were no deaths or other serious AEs during study treatment. One subject was inappropriately withdrawn from the study based on an incorrect QTc calculation. One subject discontinued because of a prolonged QTc.

Patient details are shown in Table 1.

Terminal elimination half-life was similar for the two treatment groups. Hence, although the area under the plasma concentration time curve (AUC) and the maximal plasma concentration (Cmax) were higher in the younger age group this may have been related to lower body weight in the younger subjects. Also for quetiapine sulfoxide and N-desalkyl quetiapine terminal elimination half-life was similar, but AUC and Cmax were greater in the younger age group. Exposure to 7-hydroxy quetiapine was similar for the two age groups.

The sponsor performed a comparison of the pharmacokinetic data from this study and data from a study using the same doses in adults (Study D1441C00130). This analysis showed no significant differences in dose normalized exposure (AUC at steady state [AUCss] and Cmax at steady state [Css,max]) between adults and children/adolescents for either quetiapine or 7-hydroxy quetiapine for the same administered dose.

However, for quetiapine sulfoxide and N-desalkyl quetiapine estimates of AUCss were 27% and 45% higher, respectively, in children/adolescents than those in adults. Comparisons of weight-adjusted, dose-normalized exposure (ie, exposure divided by [dose/weight]) showed evidence for statistically significant age-related differences in exposure to quetiapine and 7-hydroxy quetiapine, with lower exposures seen in children/adolescents. However, when normalized for dose and weight

there was no evidence for age-related differences in exposure to the quetiapine sulfoxide or N-desalkyl quetiapine metabolites.

Evaluator's comments: When normalised for weight, the pharmacokinetics of QTP were similar in children and adolescents over the age of 10 years. Dose and weight normalised exposure to QTP was decreased in children and adolescents relative to adults.

Pharmacodynamics

There were no new pharmacodynamic data included in the submission.

Efficacy

Efficacy data in children and adolescents

Study D1441C00112 was a multinational, multicentre, randomised, double blind, parallel group, placebo controlled, efficacy and safety study of quetiapine fumarate in adolescents with schizophrenia (Table 2). The study was sponsored by AstraZeneca and subjects were enrolled from 43 centres. Inclusion and exclusion criteria, and study treatment are summarised in Table 2.

Table 2 Details of Study D1441C00112

Nr. of subjects with age and sex	Diagnosis + criteria for inclusion/exclusion	Test Product Dosage Regimen Route of administration, Formulation, Duration of Treatment	Results (efficacy)	Adverse Reactions
Total 268 enrolled, 222 randomized, 222 treated, age range 13 to 17 years, 129 (58.6%) male, 91 (41.4%) female. 164 patients (73.9% of randomized) completed the study	Male or female, aged 13 to 17 years at randomization, hospitalized or outpatient DSM-IV criteria for schizophrenia confirmed by the K-SADS-PL The social communication questionnaire (SCQ) was administered to assess for pervasive developmental disorders (PDDs) and patients with an SCQ score of ≥15 and who otherwise met entrance criteria must have had a documented history of delusions or hallucinations. Patients with a secondary diagnosis of depression may have continued treatment with an antidepressant if clinically advised by the investigator. PANSS score of ≥60 and a score of 4 or greater on at least 1 of the following items; delusions (P1), conceptual disorganizations (P2), or hallucinations (P3) at both screening and randomization (Day 1)	1. Quetiapine IR 400 mg/day 2. Quetiapine IR 800 mg/day fixed doses (bid or tds); Oral administration Random assignment to treatments in balanced blocks Reference therapy: Placebo 6 weeks	For the primary efficacy outcome variable quetiapine was superior to placebo at both treatment doses. There did not appear to be a difference between the 400 mg per day and the 800 mg per day dose groups. For PANSS total quetiapine was superior to placebo at the 800mg dose at Day 14. For PANSS positive symptom subscale there was superiority for the 800 mg dose. For CGI Severity of Illness there was superiority for the 800 mg dose at Days 14 and 42. For CGAS (Day 42) there was superiority for the 800 mg dose. For CGI Global Improvement Score at Day 42 there was superiority for both doses. For CGSQ there was a significant improvement for the 400 mg dose.	Overall the rate of AEs was higher in the active treatment groups: 58 (79.5%) subjects, 55 (74.3%) and 45 (60.0%) for quetiapine 400 mg, quetiapine 800 mg and placebo respectively. Somnolence was more common in the quetiapine groups. Dizziness and increased appetite were more common in the quetiapine 800 mg group. AEs leading to discontinuation appeared to be dose related. Extrapyramidal symptoms (EPS) were more common in the quetiapine groups. Shifts from normal to low white blood cells (WBC) were observed in 23.2% of patients in the 800 mg/day quetiapine group. Insulin, total cholesterol, LDL-cholesterol and triglyceride plasma concentrations were increased in the quetiapine treated groups

The primary efficacy outcome measure was the change in PANSS total score from baseline to Day 42.[2] The 30-item PANSS was administered at each scheduled visit by a trained and certified rater. The individual-item scores were recorded on a specifically form. The same individual was to administer the PANSS to the patient at each visit to reduce scoring variability. The PANSS total score was calculated as the sum of the 30 individual-item scores (7 positive symptom items, 7 negative symptom items, and 16 general psychopathology items). The supplemental items S1-S3 were not included in the PANSS total score. The secondary efficacy outcome measures were the change from baseline to each corresponding visit in:

- PANSS total (Days 7 and 14)
- PANSS positive symptom and negative symptom subscale (Days 7, 14, and 42)
- CGI Severity of Illness (Days 7, 14, and 42)[3]
- CGAS (Children's Global Assessment Scale) (Day 42)
- sum of PANSS items S1, S2, and S3 (Days 7, 14, and 42)
- sum of PANSS items P4, P7, G8, and G14 scores (aggression/hostility cluster) and depression cluster subscale scores at Day 42
- percentage of patients with response, defined as a ≥30% reduction from baseline in the PANSS total score at Day 42
- CGI Global Improvement Score at Day 42[4]
- Change from baseline to Day 42 in overall caregiver burden, as assessed by the Caregiver Strain Questionnaire (CGSQ)

The safety outcome measures were: adverse events (AEs); clinical laboratory test results (for example, prolactin concentration), electrocardiogram (ECG), vital signs, weight, and body mass index (BMI), Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), and Abnormal Involuntary Movement Scale (AIMS) scores; and the incidence of anticholinergic medication use to treat emergent extrapyramidal symptoms (EPS). Hypothesis tests were performed using mixed model repeated measures (MMRM) analysis, with baseline PANSS total score used as a covariate.

A total of 268 subjects were enrolled in the study, of which 222 were randomized to treatment, and 220 were included in the analysis set: 73 treated with QTP 400 mg/day, 74 with QTP 800 mg/day and 73 with placebo. All randomized subjects received treatment. Two subjects in the placebo group were lost to follow-up. The age range was 13 to 17 years, 129 (58.6%) subjects were male, and 91 (41.4%) were female. A total of 164 subjects (73.9% of randomized) completed the study. The treatment groups were similar in demographic characteristics and in baseline disease characteristics.

For the primary efficacy outcome variable quetiapine was superior to placebo at both treatment doses (Table 3). There did not appear to be a difference between the 400 mg per day and the 800 mg per day dose groups.

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[2] The **Positive and Negative Syndrome Scale (**PANSS) is a 30-item scale that was designed to assess various symptoms of schizophrenia including delusions, grandiosity, blunted affect, poor attention and poor impulse control. The 30 symptoms are rated on a 7-point scale that ranges from 1 (absent) to 7 (extreme psychopathology). This scale has been shown to be sensitive to medication treatment, provide a balanced representation of positive and negative symptoms, and gauge their relationship to one another and to global psychopathology. The PANSS interview process typically takes between 30 and 40 minutes to complete.

[3] The **Clinical Global Impression Severity Scale** (CGI-S) is a 7-point scale that measures the clinician's impression of the severity of illness exhibited by a patient..

[4] The **Clinical Global Impression Improvement Score** (GGI-G) is a 7-point scale measuring the clinician's impression of the change occurring in the illness over a course of treatment, relative to baseline.

Table 3: PANSS total score change from baseline at Day 42 (MMRM, ITT population)

	Descriptive Statistics		MMRM results (N=220)		
	N	**Baseline mean (SD)**	**LS mean change (SE)**	**95% CI**	**p-value**
Quetiapine 400 mg/day	54	96.9 (16.41)	-27.31 (2.644)	-32.52, -22.10	
Quetiapine 400 mg/day	55	98.4 (15.73)	-28.44 (15.73)	-32.04, -24.85	
Placebo	43	97.5 (16.40)	-19.15 (3.040)	-25.14, -13.16	
Quetiapine 400 mg/day vs Placebo			-8.16 (4.008)	-16.06, -0.26	0.043
Quetiapine 800 mg/day vs Placebo			-9.29 (3.518)	-16.22, -2.36	0.009

CI: confidence interval, ITT: Intent to treat, LS: Least squares, MMRM: Mixed model repeated measures, SD: Standard deviation, SE: Standard error

For the secondary efficacy outcome measures the results were:

- PANSS total (Days 7 and 14): quetiapine was superior to placebo at the 800mg dose at Day 14
- PANSS positive symptom and negative symptom subscale (Days 7, 14, and 42): there was superiority for the 800 mg dose at Days 7, 14, and 42 for positive symptoms but no difference between treatments for negative symptoms
- CGI Severity of Illness (Days 7, 14, and 42): there was superiority for the 800 mg dose over placebo at Days 14 and 42
- CGAS (Day 42): superiority for the 800 mg dose compared with placebo
- sum of PANSS items S1, S2, and S3 (Days 7, 14, and 42): there was superiority for both doses at Day 14 but not at Days 7 or 42
- sum of PANSS items P4, P7, G8, and G14 scores (aggression/hostility cluster) and depression cluster subscale scores at Day 42: superiority for both doses compared to placebo for the aggression/hostility subscale but not for the depression symptom subscale
- percentage of patients with response, defined as a ≥30% reduction from baseline in the PANSS total score at Day 42: no significant difference between treatments and placebo
- CGI Global Improvement Score at Day 42: there was superiority for both doses
- Change from baseline to Day 42 in overall caregiver burden, as assessed by the CGSQ: there was a significant improvement compared to placebo for the 400 mg dose, but not for the 800 mg dose

Hence quetiapine had superior efficacy to placebo in decreasing the symptoms of schizophrenia but the benefit was not as clear for relieving caregiver burden.

Study D1441C00149 was a multicentre, double-blind, parallel-group, randomized, placebo-controlled efficacy and safety trial of quetiapine (400 mg/day and 600 mg/day) in patients aged 10 to 17 years with Bipolar I mania (Table 4). The study was sponsored by AstraZeneca Pharmaceuticals and conducted at 34 centres in the US.

Table 4: Details of Study D1441C00149

Nr. of subjects with age and sex	Diagnosis + criteria for inclusion/exclusion	Test Product Dosage Regimen Route of administration Formulation Duration of Treatment	Results (efficacy)	Adverse Reactions
Total 393 enrolled, 284 randomized, 283 treated, mean age 13.2 years, 122 patients in 10-12 age group, 162 in 13-17 age group, overall 56% male. 222 patients (78.2% of randomised) completed the study.	Male or female, aged 10 to 17 years at randomization, hospitalized or outpatient If female and of childbearing potential, must have used a reliable method of contraception All female patients needed to have the absence of pregnancy confirmed by a negative serum β-human chorionic gonadotropin (β-hCG) before randomization DSM-IV criteria for Bipolar I mania confirmed by the K-SADS-PL. Patients with rapid cycling or who experienced a first manic episode were included. Patients could also have had a secondary diagnosis of ADHD	1. Quetiapine 400 mg 2. Quetiapine 600 mg given in divided doses, two or three times daily Oral administration randomly assigned to blinded study treatment in a 1:1:1 ratio and stratified by age group (10 to 12 years and 13 to 17 years) Reference therapy 3. Placebo 3 weeks	For the primary efficacy outcome measure (the change in YMRS total score from baseline to Day 21) quetiapine had superior efficacy to placebo at both doses. For CGI-BP Severity of Illness (Days 4, 7, and 21), CGAS (Day 21), OAS-M (Days 4, 7, and 21), percentage of patients with remission, CGI-BP Global Improvement score (Day 21): both doses of quetiapine were superior to placebo For CDRS-R (Day 21): quetiapine 600 mg was superior to placebo in improving depressive symptoms	AEs and AEs leading to withdrawal from the study were more frequent in the quetiapine groups, but were more frequent in the 400 mg dose group than the 600 mg. Somnolence, sedation and dizziness were the most commonly reported AEs in the quetiapine groups. There were no deaths during the study. SAEs occurred at similar frequencies in the treatment groups. The discontinuations due to AEs in the quetiapine groups were mainly CNS related: somnolence and syncope. Prolongation of QTc was reported in 1 (1.0%) patient in the quetiapine 600 mg group and two (2.2%) in the placebo. Mean fasting glucose concentrations, mean insulin concentration and HOMA-R increased in the quetiapine groups. Mean total cholesterol and LDL-cholesterol concentrations increased in the quetiapine group relative to placebo. Free T4 concentrations decreased and prolactin concentrations increased in the quetiapine groups. There was an increased in pulse rate, a decrease in RR interval and an increase in Bazett's corrected QT interval in the quetiapine groups compared with the placebo group

The inclusion and exclusion criteria, and study treatments are summarised in Table 4.

The primary efficacy outcome measure was the change in YMRS total score from baseline to Day 21.[5] The secondary efficacy outcome measures were changes from baseline to each corresponding visit in:

- YMRS total (Days 4 and 7)
- YMRS individual items (Days 4, 7, and 21)
- CGI-BP Severity of Illness (Days 4, 7, and 21)
- CGAS (Day 21)
- Children's Depression Rating Scale – Revised (CDRS-R) (Day 21)
- Overt Aggression Scale – Modified (OAS-M) (Days 4, 7, and 21)
- percentage of patients with remission, defined as a YMRS total score ≤12 (Day 21)
- percentage of patients with response, defined as a ≥50% reduction from baseline in the YMRS total score (Days 4, 7, and 21)
- CGI-BP Global Improvement score (Day 21)

[5] The **Young Mania Rating Scale (**YMRS) was designed to measure the severity of manic symptoms and to gauge the effect of treatment on mania severity. The YMRS is a checklist of 11 items that are ranked on a scale of 0 to 4 or 0 to 8. Seven of the items are ranked 0 to 4 and have descriptors associated with each severity level (i.e., 0, 1, 2, 3 and 4). Four of the items (irritability, speech, content and disruptive-aggressive behaviour) are scored 0 to 8 and have descriptors for every other increment (i.e., 0, 2, 4, 6 and 8) to allow for the poor cooperation seen in severely ill subjects.

- Change from baseline to Day 21 in overall caregiver burden, as assessed by the CGSQ

Hypothesis tests were performed using MMRM. The safety outcome measures were: AEs; the incidence of emergent depression (defined as a CDRS-R total score ≥40); clinical laboratory test results (for example, prolactin concentration) and ECG results; vital signs, weight, and BMI; changes from baseline to each visit in SAS, BARS, and AIMS scores; and the incidence of anticholinergic medication use to treat emergent EPS.

A total of 393 subjects were screened and 284 subjects with Bipolar I disorder were recruited from 34 centres. All 284 subjects were randomised and 95 were treated with QTP 400 mg, 98 with QTP 600 mg and 91 with placebo. The age range was 9 to 17 years. There were 122 subjects in the 10-12 age group, and 162 in the 13-17 age group. A total of 156 (56.3%) subjects were male, and 121 (43.7%) were female. A total of 222 (78.2%) of randomized subjects completed the study.There was a higher proportion of female subjects in the quetiapine 400 mg group and there was also a higher proportion of subjects with prior episodes of self-harm. Other than this, the treatment groups were similar in baseline demographic and disease characteristics.

For the primary efficacy outcome measure (the change in YMRS total score from baseline to Day 21) quetiapine had superior efficacy to placebo at both doses (Table 5).

Table 5: YMRS total score change from baseline at Day 21 (OC, ITT population)

			MMRM results		
	N	**Baseline mean (SD)**	**LS mean change (SE)**	**95% CI**	**p-value**
Quetiapine 400 mg	76	29.2 (5.92)	-14.25 (0.964)	-16.15, -12.35	
Quetiapine 400 mg	81	29.2 (5.96)	-15.60 (0.967)	-17.51, -13.70	
Placebo	67	30.0 (5.45)	-9.04 (1.119)	-11.24, -6.84	
Quetiapine 400 mg vs Placebo			-5.21 (1.475)	-8.11, -2.31	<0.001
Quetiapine 800 mg vs Placebo			-6.56 (1.481)	-9.48, -3.65	<0.001

CI: confidence interval, ITT: Intent to treat, LS: Least squares, MMRM: Mixed model repeated measures, OC: Observed case, SD: Standard deviation, SE: Standard error

The results for the secondary efficacy outcome measures were:

- YMRS total (Days 4 and 7): both doses of quetiapine were superior to placebo at Day 7
- YMRS individual items (Days 4, 7, and 21): both doses of quetiapine were superior to placebo in improving individual item 4 (sleep) at all time points, and for Item 5, irritability, to Day 21 The 600 mg dose was superior to placebo for Item 9, disruptive/aggressive behaviour, to Day 21
- CGI-BP Severity of Illness (Days 4, 7, and 21): both doses of quetiapine were superior to placebo at Days 7 and 21
- CGAS (Day 21): both doses of quetiapine were superior to placebo in improving level of functioning
- CDRS-R (Day 21): quetiapine 600 mg was superior to placebo in improving depressive symptoms
- OAS-M (Days 4, 7, and 21): both doses of quetiapine were superior to placebo at Day 7 in lessening agitation and aggression
- Percentage of patients with remission, defined as a YMRS total score ≤12 (Day 21): both doses of quetiapine were superior to placebo

- Percentage of patients with response, defined as a ≥50% reduction from baseline in the YMRS total score (Days 4, 7, and 21): both doses of quetiapine were superior to placebo at Days 7 and 21
- CGI-BP Global Improvement score (Day 21): both doses of quetiapine were superior to placebo
- Change from baseline to Day 21 in overall caregiver burden, as assessed by the CGSQ: no significant difference between quetiapine and placebo

Study D1441C00150 was a multicentre, open-label, single arm (uncontrolled), flexible dose study to assess the safety and tolerability of quetiapine in children and adolescent patients with Bipolar I disorder and in adolescents with schizophrenia (Table 6). The study was an open label continuation of Study D1441C00112 (Table 2) and Study D1441C00149 (Table 4). The study duration and treatment is shown in Table 6.

Table 6: Details of Study D1441C00150

Nr. of subjects with age and sex	Diagnosis + criteria for inclusion/exclusion	Test Product Dosage Regimen Route of administration, Formulation, Duration of Treatment	Results (efficacy)	Adverse Reactions
381 subjects enrolled, 380 included in the safety population, 205 subjects with bipolar I disorder and 175 subjects with schizophrenia). Mean age 14.4 years, 59.5% male. 125 patients with schizophrenia (71.0% of enrolled) completed the study. 112 patients with bipolar I disorder (54.6% of enrolled) completed the study	The study was an open label continuation of Study D1441C00112 (Table 5-2) and Study D1441C00149 (Table 5-3) Child and adolescent patient (10 to 17 years old, inclusive) with bipolar I disorder, 13 to 17 years old for schizophrenia	Quetiapine IR flexible dosing target of 400 mg/day to 800 mg/day (two or three divided doses per day), dose could be decreased to 200 mg/day based on tolerability Oral administration No comparator 26 weeks	Efficacy as measured by CGAS was maintained to Week 26. For the patients with bipolar disorder, efficacy as measured by YMRS and CGI-BP Severity of Illness score was maintained to Week 26. 110 (56.7%) subjects with bipolar I disorder achieved remission by Week 26. 107 (62.6%) subjects with schizophrenia responded to quetiapine.	AEs were experienced by 321 (84.5%) subjects, SAEs were experienced by 43 (11.3%) subjects and withdrawals due to AEs occurred in 37 (9.7%) subjects. The rate of AEs was not affected by age group. There were no deaths during the study. The most common AEs, n (%) subjects, were: somnolence 87 (22.9%), headache 71 (18.7%), sedation 54 (14.2%), weight increased 51 (13.4%) and vomiting 41 (10.8%) (Table 9-26). SAEs were predominantly psychiatric and appeared to be related to the indication for treatment. AEs leading to discontinuation were predominantly CNS or psychiatric. EPS were reported in 38 (10.0%) subjects. Five (1.3%) subjects experienced six AEs potentially associated with QT prolongation, but for these subjects QTc (Fridericia) intervals ranged from 412 to 445 msec.

A total of 381 subjects were enrolled, 380 were included in the safety population (205 subjects with bipolar I disorder and 175 subjects with schizophrenia). The mean age was 14.4 years, and 59.5% of subjects were male. A total of 125 patients with schizophrenia (71.0% of enrolled) completed the study and 112 patients with bipolar I disorder (54.6% of enrolled) completed the study.

Efficacy as measured by CGAS was maintained to Week 26 (Table 7).

Table 7: CGAS total score change from OL baseline to Week 26 (OC, safety population)

	Bipolar I disorder (N=205)	**Schizophrenia (N=175)**	**Total (N=380)**
OL baseline			
N	203	175	378
Mean (SD)	58.7 (14.08)	54.7 (15.06)	56.9 (14.65)
Change from baseline			
N	162	158	320
Mean (SD)	6.1 (14.92)	8.2 (12.74)	7.1 (13.91)

OC: last observation carried forward, OL: Open-label

For the patients with bipolar disorder, efficacy as measured by YMRS was maintained to Week 26 and CGI-BP Severity of Illness score was maintained to Week 26. As defined by YMRS total score ≤12 at Week 26, for subjects with bipolar I disorder 110 (56.7%) achieved remission by Week 26. From commencement of double blind treatment, to end of Week 26 of open label treatment, 107 (62.6%) subjects with schizophrenia responded to quetiapine, as defined by ≥30% reduction from baseline in the PANSS total score.

Evaluator's comments: QTP at the doses of 400 and 800 mg/day was superior to placebo for the treatment of schizophrenia in children and adolescents age 13 years and over. Efficacy was maintained for 26 weeks.

QTP at the doses of 400 and 600 mg/day was superior to placebo for the treatment of bipolar disorder in children and adolescents aged 10 years and over. Efficacy was maintained for 26 weeks.

Efficacy studies in support of the indication of GAD

Study D1448C00009 was a multicentre, double-blind, randomized, parallel group, placebo-controlled; 2-week post-treatment follow-up period, designed to evaluate the effectiveness of QTP XR compared to placebo in the treatment of anxiety symptoms in patients with GAD as defined by DSM-IV (Table 8). The study was sponsored by AstraZeneca and conducted at 63 centres in the US. The inclusion and exclusion criteria, and study treatments are shown in Table 8.

Table 8: Details of Study D1448C00009

Nr. of subjects with age and sex	Diagnosis + criteria for inclusion/exclusion	Duration of Treatment	Test Product Dosage Regimen Route of administration, Formulation	Results (efficacy)	Adverse Reactions
1364 subjects screened, 951 randomized (876 planned); 618 completed; 894 in MITT analysis set: 219 in the 50 mg group, 226 150 mg, 224 in the 300 mg, and 225 in the placebo	The inclusion criteria included: Male or female aged 18 to 65 years, inclusive A documented clinical diagnosis of GAD according to DSM-IV TR criteria 300.02 as assessed by the MINI HAM-A administered by use of the SIGH-A total score ≥20 with Item 1 (anxious mood) and Item 2 (tension) scores ≥2 at both enrollment and randomization CGI-S score ≥4 at both enrollment and randomization Patients suffering from depressive symptoms, defined as having a MADRS total score ≤16 at both enrollment and randomization Female patients must have had a negative serum pregnancy test at enrollment and had to be willing to use a reliable method of birth control Outpatient status	8 weeks; followed by down-titration to 150 mg/day during the first week of the follow-up period in the 300 mg/day group	QTP XR 50 mg/day, QTP XR 150 mg/day, QTP XR 300 mg/day, Orally once a day Dose was increased from 50 mg/day up to the 300 mg/day dose over a 5 day period Randomised in blocks by centre Reference therapy placebo	For the primary efficacy outcome measure (the change from randomization in the HAM-A total score at Week 88, quetiapine was superior to placebo for the 50 mg/day and 150 mg/day doses. For CGI-I at Week 8 the 50 mg/day and 150 mg/day dose groups were superior to placebo. The 150 mg/day dose group was superior to placebo for the change from randomization in CGI-S score at Week 8. The 50 mg/day and 150 mg/day dose groups were superior to placebo in Change from randomization in HAM-A psychic cluster, HAM-A somatic cluster and HAM-A Response at Week 8	AEs were more common in the quetiapine groups, and AEs leading to discontinuation increased in frequency with increasing dose. The commonest AEs were dry mouth, somnolence and sedation, all of which were more common in the quetiapine groups. SAEs were uncommon and only occurred in the higher dose quetiapine groups: two subjects in the 150 mg/day group and five in the 300 mg/day group. AEs leading to discontinuation were predominantly nervous system, and somnolence and sedation were prominent causes of discontinuation. There were no deaths reported during the study. AEs relating to EPS increased in frequency with increasing dose of quetiapine

The primary efficacy outcome measure was the change from randomization in the HAM-A total score at Week 8.[6] Secondary efficacy outcome measures included:

- Change from randomization in the Q-LES-Q % maximum total score at Week 8[7]
- Change from randomization in the Q-LES-Q Item 16 (Overall quality of life) at Week 8
- Change from randomization in Q-LES-Q Item 15 (Satisfaction with medication) at Week 8
- Change from randomization in the Hamilton Rating Scale for Anxiety (HAM-A) total score at Week 1
- Change from randomization in HAM-A psychic cluster (anxious mood, tension, fears, insomnia, intellectual changes, depressed mood, and behavior at interview) at Week 1

[6] The Hamilton Anxiety Scale (HAMA) is a rating scale developed to quantify the severity of anxiety symptomatology, often used in psychotropic drug evaluation. It consists of 14 items, each defined by a series of symptoms. Each item is rated on a 5-point scale, ranging from 0 (not present) to 4 (severe).

[7] The Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) measures quality-of-life in key domains.

- Change from randomization in HAM-A somatic cluster (somatic muscular, somatic sensory, cardiovascular system, respiratory system, gastrointestinal system, genitourinary system, autonomic system) at Week 1
- Change from randomization in CGI-S score at Week 1
- HAM-A Response (decrease from randomization total score of ≥50%) at Week 1
- Change from randomization in CGI-S score at Week 8
- CGI-I at Week 8 (much or very much improved)
- Change from randomization in HAM-A psychic cluster (anxious mood, tension, fears, insomnia, intellectual changes, depressed mood, and behavior at interview) at Week 8
- Change from randomization in HAM-A somatic cluster (somatic muscular, somatic sensory, cardiovascular system, respiratory system, gastrointestinal system, genitourinary system, autonomic system) at Week 8
- HAM-A Response (decrease from randomization =total score of ≥50%) at Week 8
- HAM-A Remission (HAM-A total score ≤7) at Week 8
- Change from randomization in PSQI score at Week 8[8]

The safety outcome measures were: AEs, vital signs, suicidality (including MADRS Item 10 scores) and results from physical examinations (including weight and waist measurements), laboratory tests, ECGs, SAS, BARS, Changes in Sexual Functioning Questionnaire (CSFQ) and Treatment Discontinuation Signs and Symptoms (TDSS).

Changes in HAM-A total score from randomization were analyzed with analysis of covariance (ANCOVA), with the baseline HAM-A score as covariate and including treatment as a fixed effect and center as a random effect in the model. A Bonferroni-Holm type multiple testing procedure for groups of hypotheses was applied in order to adjust for multiple hypothesis testing.

A total of 1364 subjects were screened, of whom 951 were randomized and 618 completed. There were 894 in the modified intention-to-treat (MITT) analysis set: 219 in the 50 mg group, 226 in the 150 mg, 224 in the 300 mg, and 225 in the placebo group. The treatment groups were similar in demographic characteristics, baseline measures of the efficacy outcome variables and in disease characteristics at baseline.

For the primary efficacy outcome measure (the change from randomization in the HAM-A total score at Week 8), quetiapine was superior to placebo for the 50 mg/day and 150 mg/day doses (Table 9).

[8] The Pittsburg Sleep Quality Index (PSQI) is a self rated questionnaire which assesses sleep quality and disturbances over a one month time interval.

Table 9: Efficacy results at Week 8 (LOCF [last observation carried forward], MITT analysis set)

	PLA N=225	QTP XR 50 N=219	QTP XR 150 N=226	QTP XR 300 N=224
HAM-A total score, LS mean change from randomization	-11.10	-13.31	-13.54	-11.87
Q-LES-Q % maximum total score, LS mean change from randomization	10.96	10.36	11.11	9.27
CGI-S LS mean change from randomization	-1.44	-1.62	-1.70	-1.45
CGI-I, proportion of patients with much/very much improved score	56.89%	66.21%	67.26%	58.04%
HAM-A psychic cluster, mean change from baseline	-6.47	-7.66	-8.14	-7.13
HAM-A somatic cluster mean change from baseline	-4.60	-5.66	-5.41	-4.76
HAM-A response (decrease from randomization total score of ≥50%), proportion of patients	50.7%	60.3%	61.5%	54.9%
HAM-A remission (HAM-A total score ≤7), proportion of patients	27.56%	36.07%	37.17%	28.57%
PSQI	-3.31	-4.07	-4.38	-3.97

For the secondary efficacy outcome measures:

- For CGI-I at Week 8 (much or very much improved) the 50 mg/day and 150 mg/day dose groups were superior to placebo
- The 150 mg/day dose group was superior to placebo for the change from randomization in CGI-S score at Week 8
- The 50 mg/day and 150 mg/day dose groups were superior to placebo in Change from randomization in HAM-A psychic cluster, HAM-A somatic cluster and HAM-A Response at Week 8
- All the quetiapine groups were superior to placebo for the change from randomization in PSQI score at Week 8
- Quetiapine 150 mg/day was superior to placebo for HAM-A Remission (HAM-A total score ≤7) at Week 8
- Quetiapine at all dose levels was superior to placebo for the change from randomization in the HAM-A total score at Week 1
- Quetiapine at all dose levels was superior to placebo for the change from randomization in the HAM-A psychic cluster at Week 1
- The quetiapine 150 mg/dose level was superior to placebo for the change from randomization in HAM-A somatic cluster: estimated difference (95% confidence intervals [CI]) -0.51 (-1.01 to -0.01) p=0.046.
- Quetiapine at all dose levels was superior to placebo for the change from randomization in the CGI-S score at Week 1
- There was no difference between treatments for:
  - Change from randomization in the Q-LES-Q % maximum total score at Week 8
  - Change from randomization in the Q-LES-Q Item 16 (Overall quality of life) at Week 8
  - Change from randomization in Q-LES-Q Item 15 (Satisfaction with medication) at Week 8
  - HAM-A Response at Week 1

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Study D1448C00010 was a multicenter, randomized, parallel-group, double-blind, double dummy, placebo-controlled and active-controlled study to assess the safety and efficacy of QTP XR (150 mg/day and 300 mg/day), and escitalopram compared with placebo in the treatment of patients with GAD (Table 10). The study was sponsored by AstraZeneca and conducted at 64 centres in the US.

The inclusion and exclusion criteria (see Table 10) were the same as for ***Study D1448C00009***, with the addition of the following exclusion criterion: known lack of response to escitalopram in the treatment of anxiety in a dosage of at least 10 mg for 4 weeks, as judged by the investigator. Study treatments are shown in Table 10.

Table 10: Details of D1448C00010

Nr. of subjects with age and sex	Diagnosis + criteria for inclusion/exclusion	Test Product Dosage Regimen Route of administration, Formulation, Duration of Treatment	Results (efficacy)	Adverse Reactions
1344 subjects enrolled, 854 randomised: 215 to placebo, 219 to QTP 150 mg/day, 207 to 300 mg/day and 213 to escitalopram 169 in the placebo group, 156 in the QTP 150 mg/day, 126 in the QTP 300 mg/day and 154 in the escitalopram completed the randomized treatment period Age range 18 to 85 years	The inclusion criteria included: Male or female aged 18 to 65 years, inclusive A documented clinical diagnosis of GAD according to DSM-IV TR criteria 300.02 as assessed by the MINI HAM-A administered by use of the SIGH-A total score ≥20 with Item 1 (anxious mood) and Item 2 (tension) scores ≥2 at both enrollment and randomization CGI-S score ≥4 at both enrollment and randomization Patients suffering from depressive symptoms, defined as having a MADRS total score ≤16 at both enrollment and randomization Female patients must have had a negative serum pregnancy test at enrollment and had to be willing to use a reliable method of birth control Outpatient status	QTP XR 150 mg/day, QTP XR 300 mg/day, Orally once a day Block randomised by centre to treatment group in equal proportions Reference therapy Placebo Escitalopram 10 mg 10 weeks	For the primary efficacy outcome measure both quetiapine doses and escitalopram were superior to placebo, and QTP 150 mg/day was superior to escitalopram. Change from randomization in CGI-S score at Week 8: QTP 150 mg/day and escitalopram were superior to placebo; change from randomization in HAM-A psychic cluster at Week 8: all active treatments superior to placebo; change from randomization in HAM-A somatic cluster at Week 8: QTP 150 mg/day superior to placebo; HAM-A response, HAM-A remission and change from randomization in PSQI score at Week 8: QTP 150 mg/day superior to placebo	AEs and AEs leading to discontinuation were more common in the QTP groups than in the placebo or escitalopram groups. The commonest AEs in the QTP groups were dry mouth, sedation and somnolence. There were no deaths reported during the study. There were few SAEs, with no preponderance for QTP. The commonest reasons for discontinuation due to AEs were nervous system disorders (predominantly somnolence and sedation) which were more common in the QTP groups. With regard to AEs related to EPS, tremor was more common with QTP, but there were similar rates of akathisia and restlessness with QTP and escitalopram. There was one report of neutropenia but this was in a subject in the placebo group. There were no AEs related to QT prolongation.

The primary efficacy outcome measure was the change from randomization in the HAM-A total score at Week 8. The secondary efficacy outcome measures were:

- Change from randomization in the HAM-A total score at Day 4
- Change from randomization in HAM-A psychic cluster (anxious mood, tension, fears, insomnia, intellectual changes, depressed mood, and behavior at interview) at Day 4 and Week 8
- Change from randomization in HAM-A somatic cluster (somatic muscular, somatic sensory, cardiovascular system, respiratory system, gastrointestinal system, genitourinary system, autonomic system) at Day 4 and Week 8
- Change from randomization in CGI-S score at Day 4 and Week 8
- HAM-A response (decrease from randomization total score of ≥50%) at Day 4 and Week 8

- CGI-I at Week 8 (much or very much improved)
- HAM-A remission (HAM-A total score ≤7) at Week 8
- Change from randomization in PSQI score at Week 8
- Change from randomization in Q-LES-Q total score at Week 8
- Change from randomization in Q-LES-Q Item 16 (Overall quality of life) at Week 8
- Change from randomization in Q-LES-Q Item 15 (Satisfaction with medication) at Week 8

Hypothesis tests were performed using ANCOVA with Bonferroni-Holm type multiple testing procedure for groups of hypotheses. The safety outcome measures were the same as for Study ***Study D1448C00009***.

A total of 1344 subjects were enrolled, of whom 854 were randomized to treatment: 215 to placebo, 219 to QTP 150 mg/day, 207 to 300 mg/day and 213 to escitalopram. Of the randomized subjects, 169 in the placebo group, 156 in the QTP 150 mg/day, 126 in the QTP 300 mg/day and 154 in the escitalopram completed the randomized treatment period. The age range was 18 to 85 years. The treatment groups were similar in demographic characteristics, baseline outcome measurements and disease characteristics.

For the primary efficacy outcome measure (the change from randomization in the HAM-A total score at Week 8) both quetiapine doses and escitalopram were superior to placebo, and QTP 150 mg/day was superior to escitalopram (Tables 11 and 12).

Table 11: Efficacy results at Week 8 (LOCF, MITT analysis set)

Outcome variable	**PLA N=212**	**QTP XR 150 N=212**	**QTP XR 300 N=201**	**ESC 10 N=203**
HAM-A total score, LS mean change from randomization	-10.72	-13.92	-12.32	-12.27
Q-LES-Q % maximum total score, LS mean change from randomization	8.36	11.83	7.41	11.50
Q-LES-Q Item 16 score, mean change from randomization	0.5	0.7	0.4	0.6
Q-LES-Q Item 15 score, mean change from randomization	0.0	0.0	-0.4	0.0
CGI-S LS mean change from randomization	-1.29	-1.76	-1.44	-1.51
CGI-I, proportion of patients with much/very much improved score	51.18	65.09	57.21	60.59
HAM-A psychic cluster, mean change from baseline	-6.07	-8.16	-7.30	-7.29
HAM-A somatic cluster mean change from baseline	-4.65	-5.78	-5.03	-5.01
HAM-A response (decrease from randomization total score of ≥50%), proportion of patients	46.2%	62.7%	52.7%	53.7%
HAM-A remission (HAM-A total score ≤7), proportion of patients	27.36%	37.26%	28.36%	31.53%
PSQI	-3.12	-5.06	-3.69	-3.04

Table 12: HAM-A total score change from randomization at Week 8 (LOCF, MITT analysis set)

		PLA N=212	QTP XR 150 N=212	QTP XR 300 N=201	ESC 10 N=203
Randomization	Mean (SD)	25.3 (4.3)	25.0 (4.3)	25.2 (3.9)	24.6 (4.0)
Week 8	Mean (SD)	14.2 (8.3)	11.0 (7.5)	12.6 (7.2)	12.4 (7.7)
Change	Mean (SD)	-11.0 (8.4)	-14.0 (8.1)	-12.6 (7.4)	-12.2 (8.0)
ANCOVA results	LS mean	-10.72	-13.92	-12.32	-12.27
	95% CI	-11.89, -9.55	-15.08, -12.76	-13.51, -11.13	-13.46, -11.08
Difference vs PLA	Est difference		-3.20	-1.60	-1.55
	95% CI		-4.58, -1.82	-3.00, -0.20	-2.95, -0.15
	p-value		<0.001	0.025	0.030
	Level for significance		0.025	0.050	
Difference vs ESC	Est difference		-1.64	-.05	
	95% CI		-3.04, 0.25	-1.47, 1.37	
	p-value		0.021	0.948	

ANCOVA: Analysis of covariance, Est: Estimated

The results for the secondary efficacy outcome measures were:

- Change from randomization in CGI-S score at Week 8: QTP 150 mg/day and escitalopram were superior to placebo
- CGI-I at Week 8 (much or very much improved): no difference between treatments
- Change from randomization in HAM-A psychic cluster at Week 8: all active treatments superior to placebo, and QTP 150 mg/day superior to escitalopram: estimated difference (95% CI) -0.88 (-1.72 to -0.03) p=0.042
- Change from randomization in HAM-A somatic cluster at Week 8: QTP 150 mg/day superior to placebo and escitalopram: estimated difference (95% CI) -0.77 (-1.45 to -0.09) p=0.026
- HAM-A response at Week 8: QTP 150 mg/day superior to placebo
- HAM-A remission at Week 8: QTP 150 mg/day superior to placebo
- Change from randomization in PSQI score at Week 8: QTP 150 mg/day superior to placebo
- Change from randomization in Q-LES-Q total score at Week 8: QTP 150 mg/day and escitalopram were superior to placebo
- Change from randomization in Q-LES-Q Item 16 (Overall quality of life) at Week 8: no difference between treatments
- Change from randomization in Q-LES-Q Item 15 (Satisfaction with medication) at Week 8: no difference between treatments
- Change from randomization in the HAM-A total score at Day 4: both QTP doses superior to placebo
- Change from randomization in HAM-A psychic cluster at Day 4: both QTP doses superior to placebo
- Change from randomization in HAM-A somatic cluster at Day 4: QTP 150 mg/day superior to placebo
- Change from randomization in CGI-S score at Day 4: QTP 150 mg/day superior to placebo
- HAM-A response at Day 4: no difference between treatment groups

Study D1448C00011 was a multicenter, randomised, parallel-group, double-blind, double-dummy, placebo-controlled, active-controlled Phase III study of the efficacy and safety of quetiapine XR 50 mg/day and 150 mg/day and paroxetine 20 mg/day compared with matching placebo in the treatment of GAD (Table 13). The study was coordinated by AstraZeneca and conducted at 113 centres in Europe, Argentina, Canada, Mexico, and South Africa.

The inclusion and exclusion criteria (see Table 13) were the same as for Study ***Study D1448C00009***, with the addition of the exclusion criteria:

- Use of monoamine oxidase inhibitors (MAOIs), mood stabilizers within 14 days prior to randomization was prohibited
- Use of fluoxetine within 28 days prior to randomization was prohibited
- Known lack of response to paroxetine in the treatment of anxiety in a dosage of at least 20 mg for 4 weeks, as judged by the investigator

The study treatments are shown in Table 13.

Table 13 Details of Study D1448C00011

Nr. of subjects with age and sex	Diagnosis + criteria for inclusion/exclusion	Duration of Treatment	Test Product Dosage Regimen Route of administration, Formulation	Results (efficacy)	Adverse Reactions
1054 screened, 873 randomized (800 planned); 675 completed; 866 in MITT analysis set: 219 in the 50 mg/day, 216 in the 150 mg/day, 214 in the paroxetine, and 217 in the placebo Age range 18 to 65 years	The inclusion criteria included: Male or female aged 18 to 65 years, inclusive A documented clinical diagnosis of GAD according to DSM-IV TR criteria 300.02 as assessed by the MINI HAM-A administered by use of the SIGH-A total score ≥20 with Item 1 (anxious mood) and Item 2 (tension) scores ≥2 at both enrollment and randomization CGI-S score ≥4 at both enrollment and randomization Patients suffering from depressive symptoms, defined as having a MADRS total score ≤16 at both enrollment and randomization Female patients must have had a negative serum pregnancy test at enrollment and had to be willing to use a reliable method of birth control Outpatient status	10 weeks (8 weeks treatment, 2 weeks post-treatment)	QTP XR 50 mg tabs, 50 mg/day QTP XR 50 mg tabs, 150 mg/day Allocation numbers were randomized within blocks to quetiapine XR 50 mg, quetiapine XR 150 mg, paroxetine 20 mg, or placebo in a ratio of 1:1:1:1 Randomisation was neither country nor site specific Reference therapy Placebo Paroxetine 20 mg/day	For the primary efficacy outcome measure all the active treatment groups were superior to placebo but there was no significant difference between the QTP groups and paroxetine. For the change from randomization in Q-LES-Q % maximum total score at Week 8: QTP 150 mg/day and paroxetine were superior to placebo. CGI-I at Week 8: QTP 50 mg/day, QTP 150 mg/day and paroxetine superior to placebo, but no significant difference between QTP and paroxetine. For the change from randomization in HAM-A psychic cluster at Week 8: QTP 50 mg/day, QTP 150 mg/day and paroxetine superior to placebo, and QTP 150 mg/day superior to paroxetine. HAM-A Response at Week 8: QTP 50 mg/day, QTP 150 mg/day and paroxetine superior to placebo. HAM-A Remission at Week 8: QTP 150 mg/day and paroxetine superior to placebo	Adverse events were more common in the active treatment groups: 121 (55.8%) subjects in the placebo group, 156 (70.9%) in the QTP 50 mg/day, 166 (76.1%) in the QTP 150 mg/day and 156 (72.6%) in the paroxetine. Dry mouth, somnolence, fatigue and sedation were more common in the QTP groups than in the placebo or paroxetine groups. SAEs were uncommon overall: two (0.9%) subjects in the placebo group, three (1.4%) in the QTP 50 mg/day and one (0.5%) in the QTP 150 mg/day. There were no deaths reported during treatment. Adverse events leading to discontinuation were more common with QTP: nine (4.1%) subjects in the placebo group, 26 (11.8%) in the QTP 50 mg/day, 35 (16.1%) in the QTP 150 mg/day and 17 (7.9%) in the paroxetine.

The primary efficacy outcome measure was Change from randomization in HAM-A total score at Week 8. Secondary efficacy outcome measures were:

- Change from randomization in Q-LES-Q % maximum total score at Week 8
- Change from randomization in Q-LES-Q Item 16 (Overall quality of life) at Week 8
- Change from randomization in Q-LES-Q Item 15 (Satisfaction with medication) at Week 8
- Change from randomization in the HAM-A total score at Day 4

- Change from randomization in HAM-A psychic cluster (anxious mood, tension, fears, insomnia, intellectual changes, depressed mood, and behavior at interview) at Day 4 and Week 8
- Change from randomization in HAM-A somatic cluster (somatic muscular, somatic sensory, cardiovascular system, respiratory system, gastrointestinal system, genitourinary system, autonomic system) at Day 4 and Week 8
- Change from randomization in CGI-S score at Day 4 and Week 8
- HAM-A Response (decrease from randomization total score of ≥50%) at Day 4 and Week 8
- CGI-I at Week 8 (much or very much improved)
- HAM-A Remission (HAM-A total score ≤7) at Week 8
- Change from randomization in PSQI score at Week 8

Hypothesis tests were performed using ANCOVA with Bonferroni-Holm type multiple testing procedure for groups of hypotheses. The safety outcome measures were the same as for ***Study D1448C00009***.

A total of 1054 subjects were screened, of whom 873 were randomised and 675 completed the study. There were 866 subjects included in the MITT analysis set: 219 in the 50 mg/day group, 216 in the 150 mg/day, 214 in the paroxetine, and 217 in the placebo. The age range was 18 to 65 years. The treatment groups were similar in demographic characteristics, baseline outcome measure scores and baseline disease characteristics.

For the primary efficacy outcome measure (the change from randomization in HAM-A total score at Week 8), all the active treatment groups were superior to placebo but there was no significant difference between the QTP groups and paroxetine (Tables 14 and 15).

Table 14: Efficacy results at Week 8 (LOCF, MITT analysis set)

Outcome variable	**PLA N=217**	**QTP XR 50 N=219**	**QTP XR 150 N=216**	**PAR 20 N=214**
HAM-A total score, LS mean change from randomization	-12.30	-13.95	-15.96	-14.45
Q-LES-Q % maximum total score, LS mean change from randomization	7.44	9.27	13.19	10.85
CGI-S LS mean change from randomization	-1.53	-1.85	-2.10	-1.95
HAM-A psychic cluster, LS mean change from baseline	-6.27	-7.42	-8.64	-7.70
HAM-A somatic cluster, LS mean change from baseline	-6.00	-6.54	-7.37	-6.74
HAM-A response (decrease from randomization total score of ≥50%), proportion of patients	52.1%	62.6%	70.8%	65.9%
HAM-A remission (HAM-A total score ≤7), proportion of patients	27.19%	32.42%	42.59%	38.79%

PAR: Paroxetine

Table 15: HAM-A total score change from randomization at Week 8 (LOCF, MITT analysis set)

		PLA N=217	QTP XR 50 N=219	QTP XR 150 N=216	PAR 20 N=214
Randomization	Mean (SD)	27.3 (4.4)	26.9 (4.2)	26.6 (4.2)	27.1 (4.0)
Week 8	Mean (SD)	14.8 (9.5)	12.8 (8.6)	10.6 (7.8)	12.4 (9.3)
Change	Mean (SD)	-12.5 (9.1)	-14.1 (8.8)	-16.0 (7.9)	-14.7 (9.2)
ANCOVA results	LS mean	-12.30	-13.95	-15.96	-14.45
	95% CI	-13.58, -11.02	-15.22, -12.68	-17.24, -14.68	-15.74, -13.16
Difference vs PLA	Est difference		-1.65	-3.66	-2.15
	95% CI		-3.12, -0.18	-5.13, -2.19	-3.63, -0.68
	p-value		0.027	<0.001	0.004
	Level for significance		0.050	0.025	
Difference vs PAR	Est difference		0.50	-1.51	
	95% CI		-0.97, 1.98	-2.99, -0.03	

The results for the secondary efficacy outcome measures were:

- Change from randomization in Q-LES-Q % maximum total score at Week 8: QTP 150 mg/day and paroxetine were superior to placebo (Table 14)
- Change from randomization in Q-LES-Q Item 16 and Q-LES-Q Item 15 at Week 8: no significant difference between treatment groups
- Change from randomization in CGI-S score at Week 8: QTP 50 mg/day, QTP 150 mg/day and paroxetine superior to placebo (Table 14)
- CGI-I at Week 8 (much or very much improved): QTP 50 mg/day, QTP 150 mg/day and paroxetine superior to placebo (Table 14), but no significant difference between QTP and paroxetine
- Change from randomization in HAM-A psychic cluster at Week 8: QTP 50 mg/day, QTP 150 mg/day and paroxetine superior to placebo, and QTP 150 mg/day superior to paroxetine
- Change from randomization in HAM-A somatic cluster at Week 8: QTP 150 mg/day superior to placebo
- HAM-A Response at Week 8: QTP 50 mg/day, QTP 150 mg/day and paroxetine superior to placebo (Table 14)
- HAM-A Remission at Week 8: QTP 150 mg/day and paroxetine superior to placebo (Table 14)
- Change from randomization in PSQI score at Week 8: QTP 50 mg/day and 150 mg/day superior to placebo
- Change from randomization in the HAM-A total score at Day 4: QTP 50 mg/day and 150 mg/day both superior to placebo
- Change from randomization in HAM-A psychic cluster at Day 4: QTP 50 mg/day and 150 mg/day both superior to placebo Change from randomization in HAM-A somatic cluster at Day 4: QTP 50 mg/day superior to placebo: estimated difference (95% CI) -0.57 (-1.03 to -0.11 p=0.016)
- Change from randomization in CGI-S score at Day 4: QTP 50 mg/day and 150 mg/day both superior to placebo HAM-A Response at Day 4: QTP 50 mg/day superior to placebo: OR (95% CI) 12.84 (1.65 to 99.84) p=0.015

Study D1448C00012 was a multinational, multicenter, double-blind, parallel group, placebo-controlled randomized trial to evaluate the efficacy of QTP XR compared to placebo in decreasing the risk of recurrence of anxiety symptoms in patients with GAD (Table 16). The study was sponsored by AstraZeneca and conducted at 128 centers in Asia, Europe, North America, and Australia.

Table 16: Details of Study D1448C00012

Nr. of subjects with age and sex	Diagnosis + criteria for inclusion/exclusion	Duration of Treatment	Test Product Dosage Regimen Route of administration Formulation	Results (efficacy)	Adverse Reactions
1224 began open-label treatment; 433 randomised; 432 in ITT analysis set: 216 QTP XR, 216 placebo Age range 18 to 65 years	The inclusion criteria included: Male or female aged 18 to 65 years, inclusive A documented clinical diagnosis of GAD according to DSM-IV TR criteria 300.02 as assessed by the MINI HAM-A administered by use of the SIGH-A total score ≥20 with Item 1 (anxious mood) and Item 2 (tension) scores ≥2 at both enrollment and randomization CGI-S score ≥4 at both enrollment and randomization Patients suffering from depressive symptoms, defined as having a MADRS total score ≤16 at both enrollment and randomization Female patients must have had a negative serum pregnancy test at enrollment and had to be willing to use a reliable method of birth control Outpatient status	4-8 weeks of open label run-in treatment with QTP XR; 12-18 weeks of open-label stabilization treatment with QTP XR; up to 52 weeks of double blind treatment with QTP XR or placebo	QTP XR 50 mg/day, 150 mg/day, or 300 mg/day, Orally once a day During open-label run-in treatment patients received quetiapine XR 50 mg/day on Days 1 and 2, and then the dose increased to 150 mg/day on Days 3 and 4, and could be increased to 300 mg thereafter based on the clinical judgment of the investigator. The targeted dose of quetiapine XR was 150 mg/day. Dose adjustment was permitted at any time thereafter (to 50 or 300 mg/day) for efficacy and tolerability, based on the clinical judgment of the investigator. Reference therapy Placebo	QTP was superior to placebo for the primary efficacy outcome measure: the time to an anxiety event from randomization. QTP was superior to placebo for: change from randomization in Q-LES-Q %, Q-LES-Q Item 15 score, Q-LES-Q Item 16 score, HAM-A total score, CGI-S score, PSQI global score, SDS total score, HAM-A psychic anxiety cluster score, and SDS number of unproductive days There was no difference between treatments in the change from randomization in SDS number of under-productive days	There was a similar incidence of AEs in the treatment groups: 111 (51.4%) subjects in the placebo group and 112 (51.9%) in the QTP. AEs occurring to a greater extent in the QTP group were: weight increase, sinusitis and sedation. There were three (1.4%) subjects with SAEs in each group. There were no deaths reported during the study. There were 6 (2.8%) subjects in the placebo group and 5 (2.3%) in the QTP with AEs leading to during the randomization phase. There were no significant differences between the groups in SAS, BARS, or AIMS scores. MADRS total score improved in the QTP group relative to placebo. TDSS scores were higher in the placebo group than the QTP at Day 7 post-randomisation

The inclusion and exclusion criteria (Table 16) for enrolment in the study were the same as for ***Study D1448C00009***, with the addition of the following exclusion criteria:

- Patients suffering from depressive symptoms, defined as having a MADRS total score ≥17 at enrollment
- Treatment with QTP 7 days prior to start of open label run-in treatment

In addition, for inclusion in the open-label stabilization treatment period:

- HAM-A total score of ≤12
- CGI-S score of ≤3 (mild illness)

In addition for inclusion in the Randomized Treatment Period (RTP):

- Prescribed a dose of QTP XR 50 mg, 150 mg, or 300 mg/day for at least 12 weeks during the Open-Label Stabilization Treatment (OLST)
- HAM-A total score of ≤12 at day of randomization
- CGI-S score of ≤3 at day of randomization

- MADRS total score ≤16 at day of randomization

The primary efficacy outcome measure was the time to an anxiety event from randomisation confirmed by at least one of the following:

- Initiation of pharmacological treatment by the investigator to treat anxiety symptoms
- Initiation of pharmacological treatment by the patient for at least 1 week to treat anxiety symptoms
- Hospitalization for anxiety symptoms
- HAM-A total score ≥15 at 2 consecutive assessments 1 week apart or at the final assessment if the patient discontinued
- CGI-S score of ≥5 ("markedly ill")
- Suicide attempt or discontinuation from study due to imminent risk of suicide

Secondary efficacy outcome measures were:

- Change from randomization in Q-LES-Q % maximum total score (Items 1-14)
- Change from randomization in Q-LES-Q Item 15 score
- Change from randomization in Q-LES-Q Item 16 score
- Change from randomization in HAM-A total score
- Change from randomization in CGI-S score
- Change from randomization in HAM-A psychic anxiety cluster score
- Change from randomization in PSQI global score
- Change from randomization in SDS total score (Items 1-3)[9]
- Change from randomization in SDS number of unproductive days
- Change from randomization in SDS number of under-productive days

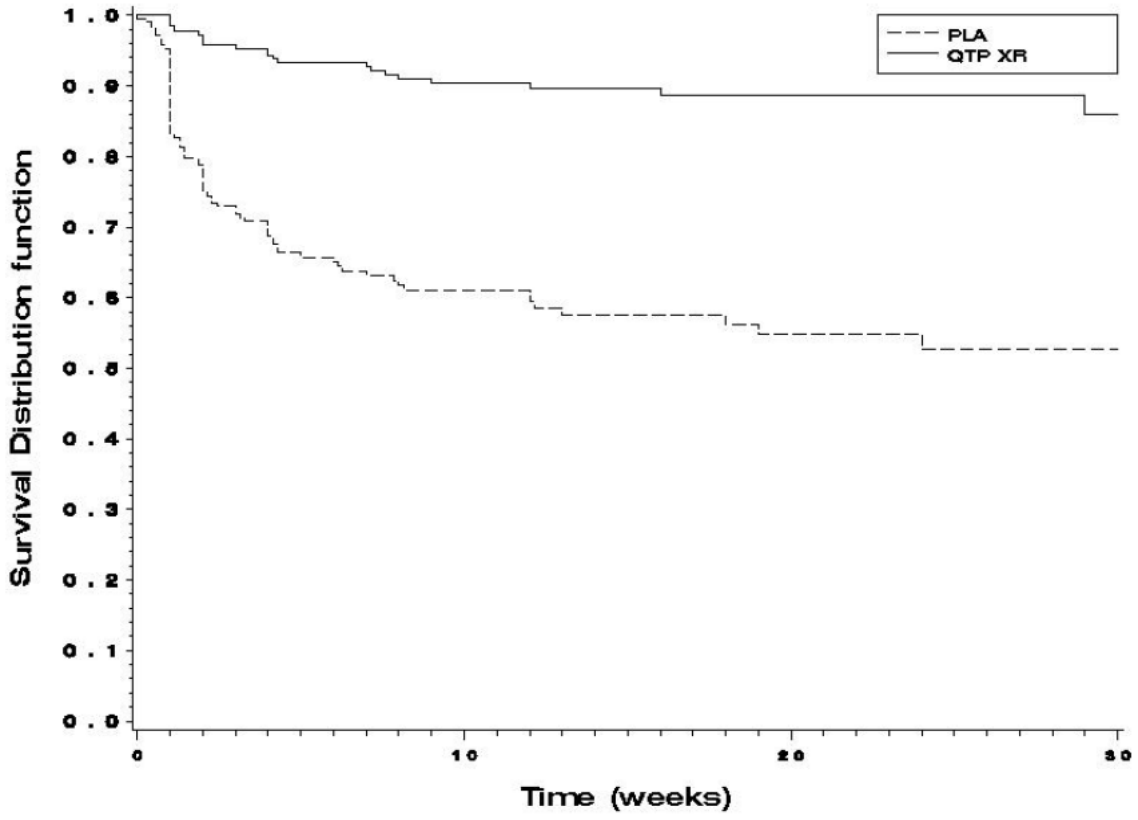
Hypothesis tests were performed using Cox proportional hazards modelling, Kaplan-Meier plots and ANCOVA. The safety outcome measures were: AEs, vital signs, clinical laboratory tests, ECG, EPS assessed using three rating scales: SAS, BARS, and AIMS; MADRS and TDSS.

A total of 1224 subjects began open-label treatment; of which 433 were randomized; and 432 were included in the in ITT analysis set: 216 in the QTP group and 216 in the placebo. The treatment groups were similar in demographic characteristics, baseline outcome measure scores and baseline disease characteristics. Approximately 45% of patients were at a dose of 150 mg/day at randomization, with approximately 28% and 26% at a dose of 50 mg/day and 300 mg/day, respectively.

QTP was superior to placebo for the primary efficacy outcome measure: the time to an anxiety event from randomisation (Figure 1, Table 17).

[9] The Sheehan Disability Scale (SDS), is a three-item instrument for assessing disability in work/school activities, family relationships, and social functioning, and it evaluates the functional impact of psychiatric disorders.

Figure 1 Time to occurrence of an anxiety event, Kaplan-Meier curves (ITT analysis set, randomized period)



Although not stated as outcome measures, QTP was superior to the placebo group in increasing time to occurrence of all-cause discontinuation (p-value <0.0001), with an estimated HR (QTP versus placebo) of 0.32 (95% CI=0.23 to 0.44) and also in increasing time to occurrence of a late onset discontinuation (p-value <0.0001), with an estimated HR of 0.43 (95% CI=0.30 to 0.62).

Table 17: Analysis of time to occurrence of an anxiety event (ITT analysis set, randomized phase)

	Quetiapine XR (N=216) vs Placebo (N=216)
Time to anxiety event	
Hazard ratio (HR)	0.19
95% CI	-0.12, 0.31
p-value	<0.0001
Time to anxiety event censoring events during the first 13 days Quetiapine XR (n=166) vs Placebo (N=210)	
Hazard ratio (HR)	0.27
95% CI	0.15, 0.47
p-value	<0.0001
Analysis of time to recurrence of an anxiety event, last open-label dose: 50 mg Quetiapine XR (n=57) vs Placebo (N=64)	
Hazard ratio (HR)	0.21
95% CI	0.08, 0.51
p-value	0.0006
Analysis of time to recurrence of an anxiety event, last open-label dose: 150 mg Quetiapine XR (n=106) vs Placebo (N=91)	
Hazard ratio (HR)	0.17
95% CI	0.08, 0.36
p-value	<0.0001
Analysis of time to recurrence of an anxiety event, last open-label dose: 300 mg Quetiapine XR (n=53) vs Placebo (N=61)	
Hazard ratio (HR)	0.22
95% CI	0.09, 0.51
p-value	0.0005

For the secondary efficacy outcome measures (Table 18), QTP was superior to placebo for:

- Change from randomization in Q-LES-Q % maximum total score (Table 18)
- Change from randomization in Q-LES-Q Item 15 score (Table 18)
- Change from randomization in Q-LES-Q Item 16 score (Table 18)
- Change from randomization in HAM-A total score (Table 18)
- Change from randomization in CGI-S score (Table 18)
- Change from randomization in PSQI global score (Table 18)
- Change from randomization in SDS total score (Table 18)
- Change from randomization in HAM-A psychic anxiety cluster score: estimated difference (95% CI) 1.45 (1.01 to 1.89) p-value <0.001
- Change from randomization in SDS number of unproductive days: estimated difference (95% CI) 0.16(0.02 to 0.30) p-value = 0.027

Table 18: Efficacy results: secondary variables, RTP (ITT analysis set, randomized phase)

Outcome variable		PLA	QTP XR	Estimated difference (95% CI)	p-value
HAM-A total score	LS mean (SE)	1.90 (0.24)	-0.14 (0.21)	Diff 2.05 (1.43, 2.67)	<0.001
HAM-A psychic anxiety cluster score	LS mean (SE)	1.53 (0.17)	0.08 (0.15)	Diff 1.45 (1.01, 1.89)	<0.001
HAM-A somatic anxiety cluster score	LS mean (SE)	0.38 (0.11)	-0.22 (0.10)	Diff 0.61 (0.30, 0.91)	<0.001
Q-LES-Q % maximum total score	LS mean (SE)	-2.12 (0.73)	0.22 (0.63)	Diff -2.34 (-4.25, -0.43)	0.017
Q-LES-Q 15	LS mean (SE)	-0.39 (0.06)	-0.09 (0.05)	Diff -0.30 (-0.46, -0.14)	<0.001
Q-LES-Q 16	LS mean (SE)	-0.19 (0.05)	-0.01 (0.04)	Diff -0.19 (-0.31, -0.06)	0.003
CGI-S score	LS mean (SE)	0.26 (0.05)	-0.03 (0.05)	Diff 0.30 (0.16, 0.43)	<0.001
PSQI global score	LS mean (SE)	1.60 (0.23)	0.39 (0.20)	Diff 1.21 (0.61, 1.82)	<0.001
SDS total score	LS mean (SE)	1.01 (0.38)	-0.19 (0.33)	Diff 1.19 (0.21, 2.18)	0.017

There was no difference between treatments in the change from randomization in SDS number of under-productive days: estimated difference (95% CI) 0.07(-0.20 to 0.340, p-value= 0.619.

Study D1448C00015 was a multinational, multicenter, double-blind, randomized, parallel-group, placebo controlled 2-week post-treatment follow-up period to evaluate the effectiveness of QTP XR compared to placebo in the treatment of anxiety symptoms in elderly patients with GAD (Table 19). The study was sponsored by AstraZeneca and conducted at 47 centres in Europe and the US.

The inclusion and exclusion criteria (Table 19) were the same as for ***Study D1448C00009***, with the addition of the following inclusion criteria:

- Men and women aged 66 years or older
- Absence of current episode of major depression, defined as having a MADRS total score of ≤16 at both enrollment and randomization

And the following additional exclusion criteria:

- A MMSE score ≤25[10]
- Meeting the DSM-IV Diagnostic Criteria for Dementia of the Alzheimer's type; DSM-IV Diagnostic Criteria for Vascular Dementia; DSM-IV Diagnostic Criteria for Dementia Due to Other General Medical Conditions (eg, head trauma, intracranial structural abnormality, etc.); Practice Parameter for Mild Cognitive Impairment (Neurology 2001;56: 1133-1142); Diagnostic Criteria of The Consortium for Dementia with Lewy Bodies; or the Consensus Diagnostic Criteria for Frontotemporal Dementia
- A DSM-IV Axis II disorder having a major impact on the current psychiatric status
- Prior history of Neuroleptic Malignant Syndrome

The study treatments are shown in Table 19.

[10] The **mini-mental state examination** (**MMSE**) is a brief 30-point questionnaire test that is used to screen for cognitive impairment. It is used to estimate the severity of cognitive impairment at a given point in time and to follow the course of cognitive changes in an individual over time, thus making it an effective way to document an individual's response to treatment.

Table 19 Details of Study D1448C00015

Nr. of subjects with age and sex	Diagnosis + criteria for inclusion/exclusion	Duration of Treatment	Test Product Dosage Regimen Route of administration Formulation	Results (efficacy)	Adverse Reactions
556 subjects were screened, 450 randomized; 346 completed; 448 in MITT analysis set: 222 quetiapine XR, 226 placebo 132 (29.5%) subjects were male, 316 (70.5%) subjects were female, age range was 65 to 87 years	The inclusion criteria included: Male or female aged 66 years and over A documented clinical diagnosis of GAD according to DSM-IV TR criteria 300.02 as assessed by the MINI HAM-A administered by use of the SIGH-A total score ≥20 with Item 1 (anxious mood) and Item 2 (tension) scores ≥2 at both enrollment and randomization CGI-S score ≥4 at both enrollment and randomization Absence of depressive symptoms, defined as having a MADRS total score ≤16 at both enrollment and randomization Female patients must have had a negative serum pregnancy test at enrollment and had to be willing to use a reliable method of birth control Outpatient status	Enrolment period of 28 days, treatment period of 9 weeks, 2 week post treatment period	QTP XR 50 mg/day to 300 mg/day, Orally once a day The dose of quetiapine was titrated up to 300 mg/day over 28 days, and then adjusted in the range 50 to 300 mg/day according to effect and tolerability between Days 29 and 63. There was no down-titration of dose at the end of the study Reference therapy Placebo Treatment allocation was block randomized by study number. Randomisation was neither country nor site specific	QTP was superior to placebo for the primary efficacy outcome measure: the change from randomization in the HAM-A total score at Week 9. QTP was also superior to placebo for the secondary efficacy outcome measures: HAM-A response rate, Q-LES-Q % maximum total score, CGI-S score, CGI-I score, HAM-A psychic cluster, HAM-A somatic cluster, HAM-A remission, MADRS total score, PSQI global score and pain VAS score	AEs were more common in the QTP group, and were reported in 114 (50.2%) subjects in the placebo group and 145 (65.0%) in the QTP. The AEs reported more commonly in the QTP group included somnolence and sedation, dry mouth, nausea and vomiting, extrapyramidal disorders and dysgeusia. SAEs were uncommon, occurring in three (1.3%) subjects in the placebo group and one (0.4%) in the QTP. There was one death in the placebo group from cardiomyopathy/heart failure. AEs leading to discontinuation were more common with QTP, and were reported in three (1.3%) subjects in the placebo group and twelve (5.4%) in the QTP. EPS related symptoms were more common in the QTP group, and these were primarily extrapyramidal disorders, indicating a potential problem in the elderly. One subject in the QTP group was reported with QTc prolongation: 443 msec at randomization increasing to 450 msec with QTP.

The primary efficacy outcome variable was Change from randomisation in the HAM-A total score at Week 9.

The secondary efficacy outcome variables were:

- HAM-A response rate, defined as a ≥50% reduction from randomisation in the HAM-A total score at Week 9
- Change from randomisation in Q-LES-Q % maximum total score (Items 1 to 14) at Week 9
- Change from randomisation in Q-LES-Q Item 16 (overall quality of life) at Week 9
- Change from randomisation in the CGI-S score at Week 9
- CGI-I score at Week 9 ("much/very much improved")
- Change from randomisation in HAM-A psychic cluster (anxious mood, tension, fears, insomnia, intellectual changes, depressed mood, and behaviour at interview) at Week 9
- HAM-A remission (HAM-A total score ≤7) at Week 9
- Change from randomisation in MADRS total score at Week 9

- Change from randomisation in HAM-A somatic cluster (somatic muscular, somatic sensory, cardiovascular system, respiratory system, gastrointestinal system, genitourinary system, and autonomic system) at Week 9
- Change from randomisation in the pain VAS score at Week 9
- Change from randomisation in the PSQI global score at Week 9
- Change from randomisation in Q-LES-Q Item 15 (satisfaction with medication) at Week 9

Hypothesis testing was performed using ANCOVA models with baseline measures and centre included as covariates. The safety outcome measures were: AEs, vital signs, clinical laboratory tests, ECG, EPS assessed using three rating scales: SAS, BARS, and AIMS; MADRS and TDSS.

A total of 556 subjects were screened, of which 450 were randomized and 346 completed the study. There were 448 subjects in the MITT analysis set: 222 in the QTP group and 226 in the placebo. There were 132 (29.5%) subjects that were male, 316 (70.5%) subjects that were female, and the age range was 65 to 87 years. The treatment groups were similar in demographic characteristics, baseline outcome measure scores and baseline disease characteristics.

QTP was superior to placebo for the primary efficacy outcome measure: Change from randomization in the HAM-A total score at Week 9 (Table 20).

Table 20: Efficacy results at Week 9 (LOCF, MITT analysis set)

Outcome variable	**PLA**	**QTP XR**
	N=226	**N=222**
HAM-A total score, LS mean change from randomization	-7.21	-14.97
HAM-A response (decrease from randomization total score of ≥50%), proportion of patients	23.9%	68.5%
Q-LES-Q % maximum total score, LS mean change from randomization	4.94	14.82
CGI-S LS mean change from randomization	-0.59	-1.76
HAM-A psychic cluster LS mean change from baseline	-3.81	-8.88
HAM-A somatic cluster LS mean change from baseline	-3.37	-6.05
HAM-A remission (HAM-A total score ≤7), percentage of patients	12.83	40.09
MADRS total score, LS mean change from randomization	-2.22	-6.94
PSQI global score, LS mean change from randomization	-2.09	-6.25

QTP was also superior to placebo for the secondary efficacy outcome measures (Table 20):

- HAM-A response rate, defined as a ≥50% reduction from randomization in the HAM-A total score
- Change from randomization in Q-LES-Q % maximum total score
- Change from randomization in the CGI-S score
- CGI-I score ("much/very much improved")
- Change from randomization in HAM-A psychic cluster
- Change from randomization in HAM-A somatic cluster
- HAM-A remission (HAM-A total score ≤7)
- Change from randomization in MADRS total score
- Change from randomization in the PSQI global score

QTP was also superior to placebo in the change from randomization in the pain visual analog score (VAS): estimated difference (95% CI) -11.76 (-14.87 to -8.66) p-value <0.001. There was no

significant difference between treatments in the change from randomization in Q-LES-Q Item 15 (satisfaction with medication); or in the change from randomization in Q-LES-Q Item 16 (overall quality of life).

Evaluator's comments: For the indication of GAD, QTP was superior to placebo with an optimal target dose of 150 mg/day (**Study D1448C00009, Study D1448C00010, Study D1448C00011, Study D1448C00012)**. Efficacy was maintained over a 52 week period (**Study D1448C00012**). At the 150 mg/day dose, QTP was superior to escitalopram **(Study D1448C00010)** but was only superior to paroxetine for one secondary efficacy outcome measure: HAM-A psychic cluster at Week 8 **(Study D1448C00011).** QTP was superior to placebo in subjects aged 66 years or more **(Study D1448C00015)**.

Safety

Safety data from efficacy studies in children and adolescents

For ***Study D1441C00112,*** summarized in Table 21, exposure to study medication is displayed in Table 25. Overall the rate of AEs was higher in the active treatment groups: 58 (79.5%) subjects, 55 (74.3%) and 45 (60.0%) for quetiapine 400 mg, quetiapine 800 mg and placebo respectively.

Table 21: Overview of exposure in the safety population

		Quetiapine 400 mg/day (N=73)	**Quetiapine 800 mg/day (N=74)**	**Placebo (N=75)**
Days of study participation	n	73	74	75
	Mean (SD)	41.3 (9.33)	41.3 (9.83)	37.7 (12.0)
	Median	44	44	43
	Range	10-54	8-55	4-53
Days on study medication	n	73	74	75
	Mean (SD)	40.1 (10.1)	40.4 (10.1)	36.8 (12.1)
	Median	43	43	43
	Range	4-53	2-51	4-50
Days dosed (%)	n	73	74	75
	Mean (SD)	99.4 (2.57)	99.5 (1.78)	99.8 (0.95)
	Median	100	100	100
	Range	83-100	90-100	93-100
Days dosed in titration (%)	n	73	74	NA
	Mean (SD)	99.5 (3.29)	99.4 (2.53)	NA
	Median	100	100	NA
	Range	80-100	89-100	NA
Days dosed after titration (%)	n	72	72	NA
	Mean (SD)	99.4 (2.56)	99.6 (1.68)	NA
	Median	100	100	NA
	Range	84-100	90-100	NA
Compliance (%)	n	73	74	75
	Mean (SD)	97.3 (6.62)	96.1 (12.3)	98.7 (3.36)
	Median	100	100	100
	Range	67-104	18-110	82-108

Somnolence was more common in the quetiapine groups (Table 22). Dizziness and increased appetite were more common in the quetiapine 800 mg group.

Table 22 AEs reported in 5% or more of subjects in any treatment group (safety population)

Preferred term	**Quetiapine 400 mg/day (N=73)**		**Quetiapine 800 mg/day (N=74)**		**Placebo (N=75)**	
	n	%	n	%	n	%
Somnolence	20	27.4	22	29.7	5	6.7
Headache	6	8.2	16	21.6	14	18.7
Dizziness	6	8.2	11	14.9	4	5.3
Dry mouth	3	4.1	7	9.5	1	1.3
Insomnia	9	12.3	7	9.5	17	22.7
Agitation	6	8.2	6	8.1	10	13.3
Tachycardia	4	5.5	6	8.1	0	
Increased appetite	3	4.1	5	6.8	3	4.0
Fatigue	4	5.5	4	5.4	3	4.0
Irritability	2	2.7	4	5.4	0	
Nausea	3	4.1	4	5.4	13	17.3
Sedation	4	5.5	4	5.4	3	4.0
Vomiting	3	4.1	4	5.4	6	8.0
Anxiety	4	5.5	3	4.1	5	6.7
Diarrhoea	4	5.5	1	1.4	4	5.3

There were no deaths reported during the study. Serious adverse events (SAEs) appear to be mainly related to worsening of schizophrenia symptoms in all three groups. AEs leading to discontinuation were more common in the active treatment groups, and the rate appears to be dose related. CNS disorders leading to withdrawal were more common in the higher dose group. One patient in the quetiapine 800 mg group discontinued because of suicidal ideation. EPS were more common in the quetiapine groups, with similar rates of EPS with the 400 mg and 800 mg doses.

One subject in each of the quetiapine groups had prolongation of corrected QT interval (QTc). One subject in the quetiapine 400 mg group developed neutropenia (absolute neutrophil count (ANC): $1.19x10^3/\mu L$) on Day 38 that returned to normal limits by final visit. Three patients experienced AEs potentially associated with suicidality during the study: one patient in the placebo group (two episodes of intentional self-injury); and two patients in the 800 mg/day quetiapine group (one with intentional self-injury, one with suicidal ideation). A Columbia-style suicidality analysis was performed to further assess the incidence of suicidal behaviour/ideation.[11] The results were reported as: no patients experienced suicidal behaviours and two patients in the 800 mg/day quetiapine group experienced suicidal ideations.

[11] The Columbia Classification Algorithm for Suicide Assessment is a standardized suicidal rating system.

Shifts from normal to low white blood cells (WBC) were observed in 23.2% of patients in the 800 mg/day quetiapine group, compared to 11.1% in the placebo group and 9.8% in the 400 mg/day quetiapine group. Clinical chemistry results were similar for the three treatment groups. Insulin, total cholesterol, LDL-cholesterol and triglyceride plasma concentrations were increased in the quetiapine treated groups compared with the placebo group. A greater number of subjects in the quetiapine groups had elevations in ALT, AST and prolactin during the study. A greater number of subjects in the quetiapine treated groups had decreases in free thyroxine (FT4). Five subjects in the quetiapine 800 mg group had decreased thyroid stimulating hormone (TSH). There was a clinically significant increase in weight in the quetiapine treated groups. QTc increased in a dose dependent manner. There was also an increase in pulse rate. There were no apparent differences between the treatment groups in SAS, AIMS or BARS scores.

For ***Study D1441C00149***, summarized in Table 4, exposure to study medication is summarized in Table 23.

Table 23: Overview of exposure in the safety population

		Quetiapine 400 mg (N=95)	**Quetiapine 600 mg (N=98)**	**Placebo (N=90)**
Days of study participation	n	95	98	90
	Mean (SD)	21.5 (6.61)	22.7 (8.23)	22.0 (7.68)
	Median	22	22	22
	Range	2-37	4-82	4-57
Days on study medication	n	95	98	90
	Mean (SD)	20.6 (6.32)	20.4 (5.63)	20.2 (6.43)
	Median	22	22	22
	Range	2-29	2-29	2-35
Days dosed (%)	n	95	98	90
	Mean (SD)	98.3 (6.64)	99.2 (2.93)	98.8 (4.27)
	Median	100	100	100
	Range	60-100	82-100	71-100
Mean daily dose (mg) over study	n	95	98	NA
	Mean (SD)	287.48 (81.203)	403.77 (115.232)	NA
	Median	306.00	432.63	NA
	Range	10.00 -460.42	15.00 – 585.29	NA
Cumulative dose (mg) over study	n	95	98	NA
	Mean (SD)	7020.8 (2550.60)	9870.2 (3376.82)	NA
	Median	7650.0	10775	NA
	Range	100.00 – 11050.00	150.0 - 15250	NA

AEs and AEs leading to withdrawal from the study were more frequent in the quetiapine groups, but were more frequent in the 400 mg dose group than the 600 mg. Somnolence, sedation and dizziness were the most commonly reported AEs in the quetiapine groups (Table 24).

Table 24: Number (%) of patients with the most commonly reported adverse events, sorted by decreasing order of frequency as summarized over all treatment groups (safety population)

Preferred term	**Quetiapine 400 mg (N=95)**		**Quetiapine 800 mg (N=98)**		**Placebo (N=90)**	
	n	%	n	%	n	%
Somnolence	27	28.4	31	31.6	9	10.0
Sedation	22	23.2	25	25.5	4	4.4
Dizziness	18	18.9	17	17.3	2	2.2
Headache	15	15.8	13	13.3	14	15.6
Nausea	6	6.3	10	10.2	4	4.4
Fatigue	13	13.7	9	9.2	4	4.4
Increased appetite	9	9.5	9	9.2	1	1.1
Tachycardia	5	5.3	8	8.2	0	
Vomiting	8	8.4	7	7.1	3	3.3
Dry mouth	7	7.4	7	7.1	0	
Weight increased	6	6.3	6	6.1	0	
Nasal congestion	3	3.2	6	6.1	2	2.2
Irritability	3	3.2	5	5.1	1	1.1

There was a similar pattern of AEs in both age groups. There were no deaths during the study. SAEs occurred at similar frequencies in the treatment groups, but there was one report of syncope in the quetiapine 400 mg group and one of drug rash in the quetiapine 600 mg group. The discontinuations due to AEs in the quetiapine groups were mainly CNS related: somnolence and syncope. EPS occurred in four (4.2%) subjects in the quetiapine 400mg group and three (3.1%) in the quetiapine 600 mg group, compared with one (1.1%) in the placebo. Prolongation of QTc was reported in 1 (1.0%) patient in the quetiapine 600 mg group and two (2.2%) in the placebo group. Neutropenia was not reported as an AE for any patient in the trial. One patient in each of the quetiapine groups had elevated blood insulin concentration reported as an AE. Suicidal ideation was reported as an AE in one patient in each of the quetiapine treatment groups. A Columbia style suicidality analysis found that two patients in the 400 mg quetiapine group experienced suicidal behaviour and one in the 600 mg QTP group experienced suicidal ideation. Treatment emergent depression, defined as a CDRS-R score of ≥40 in patients with a CDRS-R score <40 at baseline, occurred in two (2.1%) subjects in the QTP 400 mg group, one (1.0%) in the QTP 600 mg and three (3.3%) in the placebo.

There was a shift from normal to low neutrophil count in three (3.6%) subjects in the QTP group, four (4.9%) in the QTP 600 mg and two (2.5%) in the placebo. Mean ALT concentration increased in both QTP groups in a dose dependent manner. Mean fasting glucose concentrations, mean insulin concentration and HOMA-R increased in the QTP groups. Mean total cholesterol and LDL-cholesterol concentrations increased in the QTP group relative to placebo. HDL-cholesterol levels shifted from normal to low in two (2.6%) subjects in the QTP 400 mg group, 13 (16.9%) in the QTP 600 mg group and four (6.6%) in the placebo. Free T4 concentrations decreased and prolactin concentrations increased in the QTP groups. In the QTP 400 mg group, the increase in prolactin levels from baseline, relative to placebo, was statistically significant. The increases in prolactin were assessed as being clinically significant for twelve subjects in the QTP 400 mg group, eleven subjects in the QTP 600 mg group, and two subjects in the placebo group.

There was an increase in pulse rate, a decrease in RR interval and an increase in Bazett's corrected QT interval in the QTP groups compared with the placebo group. However, no subjects were recorded as having shifts from normal to abnormal values in QTc.

For ***Study D1441C00150***, summarised in Table 6, exposure to QTP is summarized in Table 25.

Table 25: Overview of exposure in the safety population

		Acute feeder study treatment				
		Placebo (N=75)	**All QTP (N=251)**	**QTP 400 mg (N=128)**	**QTP 600-800 mg (N=123)**	**Total (N=380)**
Days of study participation	n	129	251	128	123	380
	Mean (SD)	149.3 (67.16)	159.8 (61.68)	163.0 (59.94)	156.5 (63.52)	156.3 (63.69)
	Median	182.0	183.0	183.0	182.0	183.0
	Range	5-318	6-416	12-335	6-416	5-416
Days on study medication	n	129	251	128	123	280
	Mean (SD)	140.7 (63.43)	148.1 (58.71)	151.5 (57.27)	144.6 (60.19)	145.6 (60.37)
	Median	181.0	181.0	182.0	180.0	181.0
	Range	4-267	6-252	12-252	6-229	4-267
Compliance (%)	n	129	251	128	123	380
	Mean (SD)	108.2 (64.01)	105.5 (36.07)	104.2 (27.3)	106.8 (43.48)	106.4 (47.37)
	Median	101.5	101.5	101.4	101.5	101.5
	Range	14-720	33-500	59-351	33-500	14-720
Compliance in titration (%)	n	129	251	128	123	380
	Mean (SD)	91.9 (15.43)	91.5 (12.67)	91.4 (12.61)	91.7 (12.79)	91.6 (13.65)
	Median	100.0	100.0	100.0	100.0	100.0
	Range	7-100	8-100	28-100	8-100	7-100
Mean daily dose (mg) over study	n	125	246	127	119	371
	Mean (SD)	592 (163.9)	603 (153.2)	604 (149.2)	603 (158.0)	599 (156.8)
	Median	598.3	604.0	605.7	601.4	600.0
	Range	200-800	200-800	221-800	200-800	200-800
Cumulative dose (mg) over study	n	125	246	127	119	371
	Mean (SD)	81974 (45922.9)	87732 (41794.7)	88807 (41638.5)	86584 (42106.4)	85792 (43253.5)
	Median	85000.0	97500.0	105300.0	92800.0	92100.0
	Range	3600-189400	0-151600	3000-147200	0-151600	0-189400

AEs were experienced by 321 (84.5%) subjects, SAEs were experienced by 43 (11.3%) subjects and withdrawals due to AEs occurred in 37 (9.7%) subjects. The rate of AEs was not affected by

age group. There were no deaths during the study. The most common AEs, n (%) subjects, were: somnolence 87 (22.9%), headache 71 (18.7%), sedation 54 (14.2%), weight increased 51 (13.4%) and vomiting 41 (10.8%) (Table 26).

Table 26: Number (%) of patients with the most commonly reported adverse events (safety population)

Preferred term	**Bipolar I disorder (N=205)**		**Schizophrenia (N=175)**		**Total (N=380)**	
	n	%	n	%	n	%
Somnolence	45	22.0	42	24.0	87	22.9
Headache	49	23.9	22	12.6	71	18.7
Sedation	42	20.5	12	6.9	54	14.2
Weight increased	35	17.1	16	9.1	51	13.4
Vomiting	23	11.2	18	10.3	41	10.8
Nausea	25	12.2	11	6.3	36	9.5
Dizziness	21	10.2	12	6.9	33	8.7
Fatigue	24	11.7	7	4.0	31	8.2
Insomnia	18	8.8	13	7.4	31	8.2
Increased appetite	18	8.8	9	5.1	27	7.1
Upper respiratory tract infection	14	6.8	12	6.9	26	6.8
Agitation	7	3.4	13	7.4	20	5.3
Irritability	11	5.4	8	4.6	19	5.0
Tachycardia	10	4.9	9	5.1	19	5.0
Abdominal pain upper	13	6.3	4	2.3	17	4.5
Pyrexia	11	5.4	6	3.4	17	4.5
Nasal congestion	11	5.4	4	2.3	15	3.9
Bipolar disorder	11	5.4	0		11	2.9
Anxiety	1	0.5	9	5.1	10	2.6
Schizophrenia	0		9	5.1	9	2.4

SAEs were predominantly psychiatric and appeared to be related to the indication for treatment. AEs leading to discontinuation were predominantly CNS or psychiatric. EPS were reported in 38 (10.0%) subjects. Five (1.3%) subjects experienced six AEs potentially associated with QT prolongation, but for these subjects QTc (Fridericia) intervals ranged from 412 to 445 msec. Five (1.3%) subjects experienced five AEs potentially associated with neutropenia. Five (1.3%) subjects experienced 8 AEs potentially associated with diabetes mellitus: HbA1c increased (2), blood glucose increased (1), blood insulin increased (1), hyperglycemia (1), hyperphagia (1), and thirst (1). Three (0.8%) subjects experienced three AEs potentially associated with syncope. Four (1.1%) subjects experienced six AEs potentially associated with suicidality. A Columbia style suicidality analysis identified one subject who made a suicide attempt, four with suicidal ideation, eight with self-injurious behaviour, one with possible suicide attempt, five with self-injurious behaviour without suicidal intent and 38 subjects with "other" events that could be related to suicidality. Eight (2.3%) subjects had shifts from normal to low neutrophil count. There were no clinically

significant changes in mean biochemical values during the study. Forty (14.9%) subjects had a shift from normal to low HDL-cholesterol during the study. Eight (2.5%) subjects had a shift from normal to low total T4 during the study. Nineteen subjects had a shift from normal to high prolactin concentrations during the study. There was a mean increase in weight of 3.7 kg and of BMI of 0.8 kg/m^2 during the study.

Safety data from pharmacokinetic studies in children and adolescents

In ***Study D1441C00028***, summarised in Table 1, 16 (59.3%) subjects experienced 40 AEs (Table 27). The rate of AEs was similar for the two age groups. The most frequently occurring AEs were: somnolence, dizziness, dyspnoea, headache, increased heart rate, increased appetite and sedation.

Table 27: Adverse events occurring during study treatment in descending order of occurrence in the safety population by preferred term

Preferred term	**Age group**					
	10-12 years		**13-17 years**		**Total**	
	n	%	n	%	n	%
Number of subjects	13	100	14	100	27	100
Somnolence	2	15.4	5	35.7	7	25.9
Dizziness	2	15.4	2	14.3	4	14.8
Dyspnoea	0		2	14.3	2	7.4
Headache	1	7.7	1	7.1	2	7.4
Heart rate increased	0		2	14.3	2	7.4
Sedation	2	15.4	0		2	7.4
Abdominal discomfort	1	7.7	0		1	3.7
Anxiety	1	7.7	0		1	3.7
Bronchospasm	1	7.7	0		1	3.7
Dyskinesia	1	7.7	0		1	3.7
ECG QT corrected interval prolonged	1	7.7	0		1	3.7
Nausea	1	7.7	0		1	3.7
Nervousness	0		1	7.1	1	3.7
Pain	0		1	7.1	1	3.7
Pharyngolaryngeal pain	1	7.7	NA	NA	1	3.7
Pyrexia	1	7.7	NA	NA	1	3.7
Thirst	0		1	7.1	1	3.7
Tooth infection	0		1	7.1	1	3.7
Tremor	1	7.7	0		1	3.7
Schizophrenia	0		9	5.1	9	2.4

There were no deaths or other SAEs during study treatment. One subject was inappropriately withdrawn from the study based on an incorrect QTc calculation. Three subjects could not tolerate a dose greater than 600 mg/day: one because of dyskinesia (involuntary leg movements), one because of dizziness and one because of a prolongation in QTc (stated to have been incorrectly

calculated). There were no clinically significant abnormalities in haematology or clinical chemistry parameters. Two subjects had WBC counts that were within normal limits at screening and below the lower limit of normal at Day 14 (lowest value was $3.2x10^3$/L). Four subjects, two in the 10- to 12-year-old age group and two in the 13- to 17-year-old age group, had treatment-emergent abnormal ALT results (maximum value 69 U/L).

Evaluator's comments: The safety data in children and adolescents identify a number of AEs that occur with greater frequency with QTP than with placebo. These include somnolence, dizziness, increased appetite, weight gain and dizziness. EPS is more common with QTP. In addition fasting glucose, insulin, total cholesterol, LDL-cholesterol and triglyceride plasma concentrations were increased in the quetiapine treated groups. There were elevations in serum prolactin concentrations and decreases in Free T4. QTc increased in a dose dependent manner and there was also an increase in pulse rate. In **Study D1441C00149** there were a greater number of subjects in the QTP group with a shift from normal to low neutrophil count. **Study D1441C00150** indicated that somnolence, headache, sedation, weight increased, and vomiting also occur with long term use of QTP. With long-term use there was a mean increase in BMI of 0.8 kg/m^2.

Safety data for the indication of GAD

For ***Study D1448C00009***, summarized in Table 8, exposure to treatment is summarized in Table 28.

Table 28: Overview of exposure (safety analysis set) in Study D1448C00009

		PLA (N=234)	**QTP XR 50 (N=232)**	**QTP XR 150 (N=238)**	**QTP XR 300 (N=238)**
Days on randomized treatment during the 8-week randomized treatment period	Mean (SD)	50.9 (21.0)	49.4 (22.6)	47.1 (23.4)	43.7 (25.5)
	Median	63.0	63.0	62.0	62.0
	Min to max	1-74	1-72	1-71	1-79
Cumulative dose (mg) over study	Mean	0.0	2210.1	6176.5	11563.7
	Median	0.0	2750.0	8050.0	16300.0
	Min to max	0-0	50-3600	50-10900	50-19900
Mean daily dose	Mean	0.0	46.1	127.6	241.1
	Median	0.0	44.5	130.2	265.9
	Min to max	0	25-100	50-170	25-650
Population cumulative exposure (patient years)		32.6	31.4	30.7	28.5

AEs were more common in the QTP groups, and AEs leading to discontinuation increased in frequency with increasing dose. The commonest AEs were dry mouth, somnolence and sedation, all of which were more common in the QTP groups (Table 29).

Table 29: Adverse events experienced by at least twice as many patients in any quetiapine XR group as in the placebo group and by ≥2% of patients in any group by preferred term (safety analysis set) in Study D1448C00009

Preferred term	**PLA N=234 n (%)**	**QTP XR 50 N=232 n (%)**	**QTP XR 150 N=238 n (%)**	**QTP XR 300 N=238 n (%)**
Any adverse event	168 (71.8)	185 (78.7)	207 (87.0)	198 (83.2)
Dry mouth	30 (12.8)	62 (26.7)	78 (32.8)	81 (34.0)
Somnolence	34 (14.5)	69 (29.7)	73 (30.7)	72 (30.3)
Sedation	20 (8.5)	42 (18.1)	56 (23.5)	59 (24.8)
Constipation	8 (3.4)	11 (4.7)	15 (6.3)	21 (8.8)
Weight increased	3 (1.3)	4 (1.7)	5 (2.1)	8 (3.4)
Dysarthria	1 (0.4)	3 (1.3)	3 (1.3)	8 (3.4)
Disturbance in attention	1 (0.4)	2 (0.9)	7 (2.9)	7 (2.9)
Dyspepsia	0	4 (1.7)	3 (1.3)	7 (2.9)
Abnormal dreams	4 (1.7)	7 (3.0)	8 (3.4)	5 (2.1)
Libido decreased	0	1 (0.4)	2 (0.8)	5 (2.1)
Akathisia	1 (0.4)	0	4 (1.7)	5 (2.1)
Abdominal pain upper	2 (0.9)	6 (2.6)	3 (1.3)	4 (1.7)
Influenza	1 (0.4)	2 (0.9)	6 (2.5)	2 (0.8)
Anxiety	2 (0.9)	1 (0.4)	5 (2.1)	2 (0.8)
Dizziness postural	0	1 (0.4)	5 (2.1)	1 (0.4)

SAEs were uncommon and only occurred in the higher dose QTP groups: two subjects in the 150 mg/day group and five in the 300 mg/day group. AEs leading to discontinuation were predominantly nervous system, and somnolence and sedation were prominent causes of discontinuation. There were no deaths reported during the study. AEs relating to EPS increased in frequency with increasing dose of QTP. There were no AEs potentially related to QT prolongation or neutropenia/ agranulocytosis reported during the study. AEs relating to diabetes mellitus were reported in 4 (1.7%) subjects in the placebo group, one (0.4%) in the QTP 50 mg/day, two (0.8%) in the 150 mg/day and two (0.8%) in the QTP 300 mg/day. Two (0.9%) subjects in the QTP 50 mg/day and three (1.3%) in the QTP 300 mg/day group had AEs relating to syncope. Two (0.9%) subjects in the placebo group, four (1.7%) in the 50 mg/day, four (1.7%) in the 150 mg/day and nine (3.8%) in the 300 mg/day reported sexual dysfunction. There was one (0.4%) subject in the placebo group with an AE related to suicidality, two (0.9%) in the 50 mg/day group and three (1.3%) in the 300 mg/day group. There did not appear to be an excess of AEs related to withdrawal in the QTP groups.

There was a decrease in mean Free T4 and an increase in mean plasma insulin concentrations in the QTP groups. There were no clinically relevant ECG changes. There was no differences between the groups in SAS total score. BARS global assessment score was highest in the QTP 300 mg/day group. The number of patients with MADRS Item 10 score ≥4 (suicidality) was also highest in the QTP 300 mg/day group. There was no difference between the groups in TDSS total score (withdrawal effects).

For ***Study D1448C00010***, summarized in Table 10, exposure to study medication is summarized in Table 30.

Table 30 Overview of exposure (safety analysis set) in Study D1448C00010

		PLA (N=214)	QTP XR 150 (N=217)	QTP XR 300 (N=206)	ESC 10 (N=209)
Days on randomized treatment during the 8-week randomized treatment period	Mean (SD)	48.5 (17.2)	45.8 (18.4)	41.1 (21.2)	47.3 (17.8)
	Median	56.0	56.0	55.0	56.0
	Min to max	1-69	1-65	1-67	1-72
Cumulative dose (mg) over study	Mean	0	6576.7	11310.4	467.1
	Median	0	8050.0	15400.0	550.0
	Min to max	0-0	50-10150	50-19300	10-690
Population cumulative exposure (patient years)		28.4	27.2	23.2	27.1
Mean daily dose (mg)	Mean (SD)	0	142.6 (51.1)	250.7 (63.8)	9.9 (0.9)
	Median	0	144.1	280.2	10.0
	Min to max	0-0	50-850	33-533	5-20

AEs and AEs leading to discontinuation were more common in the QTP groups than in the placebo or escitalopram groups. The most common AEs in the QTP groups were dry mouth, sedation and somnolence (Table 31).

Table 31:Adverse events experienced by at least twice as many patients in any quetiapine XR group as in the placebo group and by ≥2% of patients in any group by preferred term (safety analysis set) in Study D1448C00010

Preferred term	**PLA N=214 n (%)**	**QTP XR 150 N=217 n (%)**	**QTP XR 300 N=206 n (%)**	**ESC 10 N=209 n (%)**
Any adverse event	172 (80.4)	203 (93.5)	193 (93.7)	177 (84.7)
Dry mouth	25 (11.7)	85 (39.2)	96 (46.6)	40 (19.1)
Somnolence	26 (12.1)	85 (39.2)	74 (35.9)	33 (15.8)
Sedation	12 (5.6)	59 (27.2)	72 (35.0)	28 (13.4)
Constipation	9 (4.2)	16 (7.4)	26 (12.6)	14 (6.7)
Dyspepsia	3 (1.4)	9 (4.1)	17 (8.3)	4 (1.9)
Vomiting	8 (3.7)	13 (6.0)	16 (7.8)	9 (4.3)
Irritability	6 (2.8)	15 (6.9)	9 (4.4)	10 (4.8)
Weight increased	1 (0.5)	6 (2.8)	9 (4.4)	2 (1.0)
Asthenia	1 (0.5)	2 (0.9)	8 (3.9)	2 (1.0)
Nasopharyngitis	5 (2.3)	12 (5.5)	7 (3.4)	4 (1.9)
Vision blurred	2 (0.9)	7 (3.2)	7 (3.4)	7 (3.3)
Hyperhidrosis	1 (0.5)	1 (0.5)	6 (2.9)	5 (2.4)
Sluggishness	1 (0.5)	4 (1.8)	6 (2.9)	2 (1.0)
Dysarthria	0	1 (0.5)	5 (2.4)	0
Influenza	2 (0.9)	3 (1.4)	5 (2.4)	5 (2.4)
Myalgia	3 (1.4)	7 (3.2)	5 (2.4)	3 (1.4)
Paraesthesia	2 (0.9)	6 (2.8)	5 (2.4)	3 (1.4)
Restless legs syndrome	0	4 (1.8)	5 (2.4)	3 (1.4)
Restlessness	0	5 (2.3)	5 (2.4)	7 (3.3)
Tachycardia	2 (0.9)	6 (2.8)	4 (1.9)	3 (1.4)
Lethargy	3 (1.4)	6 (2.8)	4 (1.9)	4 (1.8)
Muscle tightness	2 (0.9)	2 (0.9)	4 (1.9)	5 (2.4)
Disturbance in attention	1 (0.5)	6 (2.8)	3 (1.5)	6 (2.9)
Palpitations	3 (1.4)	6 (2.8)	3 (1.5)	2 (1.0)
Urinary tract infection	1 (0.5)	0	2 (1.0)	5 (2.4)
Sinus congestion	1 (0.5)	6 (2.8)	1 (0.5)	2 (1.0)
Nightmare	1 (0.5)	6 (2.8)	0	2 (1.0)

There were no deaths reported during the study. There were few SAEs, with no preponderance for QTP. The commonest reasons for discontinuation due to AEs were nervous system disorders (predominantly somnolence and sedation) which were more common in the QTP groups. With regard to AEs related to EPS, tremor was more common with QTP, but there were similar rates of akathisia and restlessness with QTP and escitalopram. There was one report of neutropenia but this was in a subject in the placebo group. There were no AEs related to QT prolongation. There was one report of impaired glucose tolerance in the QTP 300 mg/day group. Syncope was reported in

one (0.5%) subject in the placebo group, two (0.9%) in the QTP 150 mg/day, three (1.5%) in the QTP 300 mg/day and one (0.5%) in the escitalopram. AEs relating to sexual dysfunction were more common in the escitalopram group: 17 (8.1%) subjects in the escitalopram group, eight (3.7%) in the placebo, nine (4.1%) in the QTP 150 mg/day and eight (3.9%) in the QTP 300 mg/day. Suicidal ideation was reported in one (0.5%) subject in the placebo group and one (0.5%) in the QTP 150 mg/day group. AEs related to withdrawal were more common in the QTP groups, particularly nausea and insomnia.

There were no shifts to low levels of neutrophils. The proportion of subjects shifting to high plasma concentrations of TSH, LDL-cholesterol and glucose was greater in the QTP groups. An increase in QTc of >60 ms was recorded for one subject in the QTP 300 mg/day group and one in the escitalopram group. Weight gain of ≥7% occurred in two (0.9%) subjects in the placebo group, eight (3.8%) in the QTP 150 mg/day, eight (3.9%) in the QTP 300 mg/day and one (0.5%) in the escitalopram.

There was no difference between the treatment groups in SAS total scores and BARS global scores. There was a decrease in depressive symptoms in the QTP 150 mg/day and escitalopram groups. TDSS total scores were higher for QTP than for placebo, indicating some withdrawal effects.

For ***Study D1448C00011***, summarized in Table 13, exposure to study treatment is summarized in Table 32.

Table 32: Overview of exposure (safety analysis set) in Study D1448C00011

		PLA (N=217)	**QTP XR 50 (N=220)**	**QTP XR 150 (N=218)**	**PAR 20 (N=215)**
N		216	218	217	214
Days on randomized treatment during the 8-week randomized treatment period	Mean (SD)	50.4 (14.6)	47.4 (17.9)	47.3 (17.8)	48.2 (17.6)
	Median	56.0	56.0	56.0	56.0
	Min to max	3-73	2-73	1-69	1-67
Cumulative dose (mg) over study	Mean (SD)	0	2345.4 (886.9)	6859.4 (2673.9)	952.9 (354.7)
	Median	0	2800.0	8125.0	1120.0
	Min to max	0-0	100-3250	50-9400	20-1280
Mean daily dose (mg)	Mean (SD)	0	49.5 (3.2)	139.1 (20.9)	19.6 (1.4)
	Median	0	50.0	146.4	20.0
	Min to max	0-0	38-75	13-174	10-23

Adverse events were more common in the active treatment groups: 121 (55.8%) subjects in the placebo group, 156 (70.9%) in the QTP 50 mg/day, 166 (76.1%) in the QTP 150 mg/day and 156 (72.6%) in the paroxetine. Dry mouth, somnolence, fatigue and sedation were more common in the QTP groups than in the placebo or paroxetine groups (Table 33).

Table 33: Adverse events experienced by at least twice as many patients in any quetiapine group as in the placebo group and by ≥2% of patients in any group by preferred term (safety analysis set)

Preferred term	PLA N=217 n (%)	QTP XR 50 N=220 n (%)	QTP XR 150 N=218 n (%)	PAR 20 N=215 n (%)
Any adverse event	121 (55.8)	156 (70.9)	166 (76.1)	156 (72.6)
Dry mouth	13 (6.0)	35 (15.9)	57 (26.1)	21 (9.8)
Somnolence	10 (4.6)	48 (21.8)	56 (25.7)	24 (11.2)
Fatigue	8 (3.7)	34 (15.5)	37 (17.0)	22 (10.2)
Dizziness	15 (6.9)	29 (13.2)	36 (16.5)	46 (21.4)
Sedation	1 (0.5)	14 (6.4)	18 (8.3)	5 (2.3)
Constipation	3 (1.4)	10 (4.5)	13 (6.0)	8 (3.7)
Myalgia	4 (1.8)	4 (1.8)	11 (5.0)	7 (3.3)
Increased appetite	2 (0.9)	9 (4.1)	9 (4.1)	3 (1.4)
Asthenia	1 (0.5)	5 (2.3)	6 (2.8)	4 (1.9)
Back pain	3 (1.4)	5 (2.3)	6 (2.8)	4 (1.9)
Akathisia	0	4 (1.8)	5 (2.3)	2 (0.9)
Dyspepsia	1 (0.5)	3 (1.4)	5 (2.3)	10 (4.7)
Hypersomnia	1 (0.5)	6 (2.7)	5 (2.3)	2 (0.9)
Irritability	2 (0.9)	3 (1.4)	5 (2.3)	1 (0.5)
Nasal congestion	0	1 (0.5)	5 (2.3)	1 (0.5)
Abdominal pain	2 (0.9)	6 (2.7)	0	2 (0.9)
Vision blurred	2 (0.9)	6 (2.7)	3 (1.4)	2 (0.9)

SAEs were uncommon overall: two (0.9%) subjects in the placebo group, three (1.4%) in the QTP 50 mg/day and one (0.5%) in the QTP 150 mg/day. There were no deaths reported during treatment, but one patient died after screening but prior to randomisation. Adverse events leading to discontinuation were more common with QTP: nine (4.1%) subjects in the placebo group, 26 (11.8%) in the QTP 50 mg/day, 35 (16.1%) in the QTP 150 mg/day and 17 (7.9%) in the paroxetine. Nervous system disorders were the commonest reason for AEs leading to discontinuation, with somnolence and sedation being prominent reasons in the QTP groups. AEs relating to EPS occurred more frequently with QTP than placebo, but less frequently than with paroxetine. There were no AEs related to QT prolongation. One subject in the QTP 50 mg/day group had a low neutrophil count at Week 8: (1.55×10^9/L). One subject in the QTP 150 mg/day group had impaired insulin secretion. Two (0.9%) subjects in the QTP 50 mg/day group and one (0.5%) in the QTP 150 mg/day reported syncope as an AE. Sexual dysfunction was reported more commonly in the paroxetine group: 16 (7.4%) subjects, compared with four (1.8%) in the placebo, two (0.9%) in the QTP 50 mg/day and four (1.8%) in the QTP 150 mg/day. Suicidal ideation was reported as an AE in one subject in the QTP 150 mg/day group, and suicide attempt was reported in one subject in the QTP 50 mg/day. Insomnia was reported more commonly as a withdrawal effect with QTP, but dizziness and anxiety were prominent withdrawal effects from paroxetine.

There were few clinically important shifts in haematology or clinical chemistry values. There was no difference between treatments in clinically significant ECG changes. A ≥7% increase in body

weight from baseline occurred in five (2.3%) subjects in the placebo group, ten (4.6%) in the QTP 50 mg/day, 15 (6.9%) in the QTP 150 mg/day and ten (4.7%) in the paroxetine. There was no significant difference between treatment groups in SAS or BARS. All the active treatment groups showed a significant improvement in MADRS total scores compared with placebo. There was no significant difference between QTP and placebo in TDSS total scores.

For ***Study D1448C00012***, summarized in Table 16, exposure to study treatment during open-label phase is summarized in Table 34 and during randomized treatment phase in Table 35.

Table 34: Overview of exposure during open-label treatment in the open label safety analysis set

	PLA (N=216)	**QTP XR (N=216)**	**OL-only QTP XR (N=792)**	**Total (N=1224)**
Mean daily dose (mg)				
Mean (SD)	157.9 (82.2)	155.1 (75.7)	131.6 (72.8)	140.4 (75.9)
Median	148	148	134	143
Min to max	50-295	50-295	20-292	20-295
Median daily dose (mg)				
Mean (SD)	160.6 (90.3)	159.3 (85.9)	133.9 (85.4)	143.1 (87.2)
Median	150	150	150	150
Min to max	50-300	5-300	0-300	0-300
Duration of exposure (days)				
Mean (SD)	130.8 (23.1)	130.5 (21.9)	60.9 (45.2)	85.5 (51.1)
Median	120	123	57	97
Min to max	104-232	98-202	1-211	1-232
Patient years exposure				
Mean (SD)	0.4 (0.1)	0.4 (0.1)	0.2 (0.1)	0.2 (0.1)
Median	0	0	0	0
Min to max	0-1	0-1	0-1	0-1
Total	77	77	132	287

Table 35: Overview of exposure during randomized treatment in the randomized safety analysis set in Study D1448C00012

	PLA (N=216)	**QTP XR (N=216)**
Mean daily dose (mg)		
Mean (SD)	165.1 (95.6)	162.8 (88.3)
Median	15	150
Min to max	50-306	50-300
Median daily dose (mg)		
Mean (SD)	165.3 (97.8)	163.2 (90.0)
Median	150	150
Min to max	50-300	50-300
Duration of exposure (days)		
Mean (SD)	68.6 (72.1)	106.9 (73.7)
Median	37	84
Min to max	1-279	4-296
Patient years exposure		
Mean (SD)	0.2 (0.2)	0.3 (0.2)
Median	0	0
Min to max	0-1	0-1
Total	41	63

There was a similar incidence of AEs in the treatment groups: 111 (51.4%) subjects in the placebo group and 112 (51.9%) in the QTP. AEs occurring to a greater extent (two times the placebo rate) in the QTP group were: weight increased one (0.5%) subjects in the placebo group compared with nine (4.2%) in the QTP, sinusitis one (0.5%) vs six (2.8%) and sedation none vs five (2.3%). Similarly for SAEs there was a similar incidence in both treatment groups: three (1.4%) subjects in each group. There were no deaths reported during the study. AEs leading to discontinuation were uncommon during the randomized treatment phase: six (2.8%) subjects in the placebo group and five (2.3%) in the QTP. In the QTP group the AEs leading to discontinuation were: bladder cancer, epilepsy, glycosylated haemoglobin increased, somnolence and suicidal behaviour. In the open label treatment phase the AEs leading to discontinuation in 1% or more of subjects were: sedation 81 (6.6%) subjects, somnolence 42 (3.4%), fatigue 20 (1.6%), dizziness 17 (1.4%) and irritability 12 (1.0%). During the randomized treatment phase EPS related symptoms occurred in three (1.4%) subjects in the placebo group and seven (3.2%) in the QTP. Neutropenia was reported as an AE in one patient in the QTP group. Blood insulin increase was reported as an AE in one (0.5%) subject in the placebo group and glycosylated hemoglobin increase in two (0.9%) subjects in the QTP group.

An increase in PR of ≥15 bpm from randomisation occurred in 22 (10.4%) subjects in the placebo group and 62 (28.8%) in the QTP. An increase in SBP ≥20 mmHg from randomisation occurred in 30 (14.2%) subjects in the placebo group and (21.9%) in the QTP. There were no clinically significant changes in ECG findings, or differences between the groups in ECG parameters. There were no significant differences between the groups in SAS, BARS, or AIMS scores. MADRS total score improved in the QTP group relative to placebo: estimated difference (95% CI) 1.85 (1.23 to 2.47), p-value <0.001.

TDSS scores were higher in the placebo group than the QTP at Day 7 post-randomisation, indicating the presence of withdrawal effects. These withdrawal effects were insomnia, anxiety/nervousness, agitation and irritability.

For ***Study D1448C00015,*** summarized in Table 19, exposure to study medication is summarized in Table 36.

Table 36: Overview of exposure (safety analysis set) in Study D1448C00015

		PLA (N=227)	**QTP XR (N=223)**
Days on randomized treatment	Mean (SD)	56.0 (15.7)	57.4 (15.1)
	Median	63.0	63.0
	Min to max	1-87	2-72
Cumulative dose (mg) over study	Mean (SD)	11795.4 (4784.9)	10036.5 (4700.6)
	Median	14100.0	10200.0
	Min to max	50-19250	150-18050
Mean daily dose (mg)	Mean (SD)	202.6 (54.4)	167.6 (62.7)
	Median	233.3	167.7
	Min to max	50-256	25-254
Median daily dose (mg)	Mean (SD)	233.1 (77.6)	185.7 (83.4)
	Median	300.0	150.0
	Min to max	50-300	25-300
Total exposure (patient years)		34.80	35.02
Mean daily dose (mg) by category			
<100	n (%)	12 (5.3)	38 (17.0)
100 to 200	n (%)	83 (36.6)	112 (50.2)
>200	n (%)	132 (58.1)	73 (32.7)
Maximum daily dose (mg)			
25	n (%)	0	1 (0.4)
50	n (%)	1 (0.4)	5 (2.2)
100	n (%)	10 (4.4)	21 (9.4)
150	n (%)	21 (9.3)	54 (24.2)
200	n (%)	31 (13.7)	49 (22.0)
250	n (%)	9 (4.0)	6 (2.7)
300	n (%)	155 (68.3)	87 (39.0)

Adverse events were more common in the QTP group, and were reported in 114 (50.2%) subjects in the placebo group and 145 (65.0%) in the QTP. The AEs reported more commonly in the QTP group included somnolence and sedation, dry mouth, nausea and vomiting, extrapyramidal disorders and dysgeusia (Table 37).

Table 37: Adverse events experienced by at least twice as many patients in the quetiapine XR group as in the placebo group and by ≥2% of patients in any group by preferred term (safety analysis set) in Study D1448C00015

Preferred term	**PLA N=227 n (%)**	**QTP XR N=223 n (%)**
Any adverse event	114 (50.2)	145 (65.0)
Somnolence	19 (8.4)	58 (26.0)
Dry mouth	16 (7.0)	37 (16.6)
Nausea	9 (4.0)	20 (9.0)
Dysgeusia	0	7 (3.1)
Extrapyramidal disorder	1 (0.4)	7 (3.1)
Sedation	3 (1.3)	7 (3.1)
Vomiting	1 (0.4)	7 (3.1)
Disturbance in attention	1 (0.4)	6 (2.7)
Sluggishness	0	6 (2.7)

SAEs were uncommon, occurring in three (1.3%) subjects in the placebo group and one (0.4%) in the QTP. There was one death in the placebo group from cardiomyopathy/heart failure. AEs leading to discontinuation were more common with QTP, and were reported in three (1.3%) subjects in the placebo group and twelve (5.4%) in the QTP. EPS related symptoms were more common in the QTP group.

One subject in the QTP group was reported with QTc prolongation: 443 msec at randomization increasing to 450 msec with QTP. Neutropenia and/or agranulocytosis were not reported in any subjects as AEs. AEs relating to diabetes mellitus were not more common in the QTP group. There were no subjects with AEs potentially related to suicidality. Withdrawal related AEs were more common in the QTP group and primarily related to insomnia and poor sleep quality. There were no subjects with reports of falls or fractures as AEs.

The proportions of subjects with clinically significant shifts in haematology and clinical chemistry parameters was similar for the two treatment groups, except for a higher proportion of patients shifting to a high T4 in the QTP group. Two (0.9%) subjects in the QTP group and none in the placebo had an increase in SBP ≥20 mmHg. Two (1.0%) subjects in the placebo group and one (0.5%) in the QTP had an increase in QTc ≥60 msec. One (0.5%) subject in the QTP group had an increase in body weight of ≥7%. There was a mean increase in waist circumference of 0.7 cm in the QTP group and a mean decrease of 0.2 cm in the placebo group.

There were no significant differences between the groups in SAS and BARS scores. There was a worsening of AIMS score for 16 (7.1%) subjects in the placebo group and 23 (10.4%) in the QTP. TDSS scores were similar for the two treatment groups.

Evaluator's comments: In subjects with GAD treated with QTP, dry mouth, somnolence, fatigue and sedation were the most common AEs. Weight gain was more common with QTP than placebo. EPS were associated with QTP in a dose dependent manner. Withdrawal effects included insomnia, anxiety/nervousness, agitation, nausea and irritability. EPS were a more prominent AE in subjects aged 66 years and over. QTc prolongation was not as prominent in adults treated with QTP as in children and adolescents. SAEs were uncommon and there were no deaths during treatment with QTP or during the follow-up phase.

Data from pooled analyses of safety data in GAD

Pooled Safety Data Tables was a series of tables of pooled safety data from Studies 9, 10 and 11. These studies were all of similar design, except for some differences in the doses used. Somnolence, dry mouth and sedation were prominent dose-related AEs of QTP. SAEs were uncommon with no clear associations of particular SAEs with QTP.

Suicidality Report was a pooled analysis of data relating to suicidal ideation and suicide related behaviour from Studies 9, 10 and 11. The rates of suicidal ideation and suicide related behaviour were similar for QTP and placebo. The report did not identify any additional concerns relating to suicidality with QTP.

Evaluator's comments: The analysis of the pooled data did not demonstrate any additional rare adverse events associated with QTP.

Clinical Summary and Conclusions

Conclusions

With regard to the pharmacokinetics of QTP in children and adolescents, when normalised for weight, the pharmacokinetics of QTP were similar in children and adolescents over the age of 10 years. Dose and weight normalised exposure to QTP was decreased in children and adolescents relative to adults. It is not clear how the pharmacokinetic data were used to guide the choice of doses used in the efficacy trials in children and adolescents.

QTP at the doses of 400 and 800 mg/day was superior to placebo for the treatment of schizophrenia in children and adolescents age 13 years and over. Efficacy was maintained for 26 weeks.

QTP at the doses of 400 and 600 mg/day was superior to placebo for the treatment of bipolar disorder in children and adolescents aged 10 years and over. Efficacy was maintained for 26 weeks.

For the indication of GAD, QTP was superior to placebo with an optimal target dose of 150 mg/day (**Study D1448C00009, Study D1448C00010, Study D1448C00011, Study D1448C00012)**. Efficacy was maintained over a 52 week period **Study D1448C00012**. At the 150 mg/day dose, QTP was superior to escitalopram **(Study D1448C00010)** but was only superior to paroxetine for one secondary efficacy outcome measure: HAM-A psychic cluster at Week 8 **(Study D1448C00011).** QTP was superior to placebo in subjects aged 66 years or more **(Study D1448C00015)**.

The safety data in children and adolescents identify a number of AEs that occur with greater frequency with QTP than with placebo. These include somnolence, dizziness, increased appetite, weight gain and dizziness. EPS were more common with QTP. In addition, fasting glucose, insulin, total cholesterol, LDL-cholesterol and triglyceride plasma concentrations were increased in the quetiapine treated groups. There were elevations in serum prolactin concentrations and decreases in Free T4. QTc increased in a dose dependent manner and there was also an increase in pulse rate. In **Study D1441C00149** there were a greater number of subjects in the QTP group with a shift from normal to low neutrophil count. **Study D1441C00150** indicated that somnolence, headache, sedation, weight increased, and vomiting also occur with long term use of QTP. With long-term use there was a mean increase in BMI of 0.8 kg/m^2.

In subjects with GAD treated with QTP, dry mouth, somnolence, fatigue and sedation were the most common AEs. Weight gain was more common with QTP than placebo. EPS were associated with QTP in a dose dependent manner. Withdrawal effects included insomnia, anxiety/nervousness, agitation, nausea and irritability. EPS were a more prominent AE in subjects aged 66 years and over. QTc prolongation was not as prominent in adults treated with QTP than in children and adolescents. SAEs were uncommon and there were no deaths during treatment with QTP or during the follow-up phase. The analysis of the pooled data did not demonstrate any additional rare adverse events associated with QTP.

Deficiencies in the Submission

Long-term safety data including effects upon growth, maturational, behavioural and cognitive development are not available. Similarly, effects on metabolism in children, including the risk of developing metabolic syndrome have not been studied over a prolonged period.

The dosing regimens in the efficacy trials conducted in children and adolescents appear to have been derived empirically, rather than from the pharmacokinetic studies, and do not appear to have been individualised for body size. This is contrary to the way most paediatric doses are calculated. Hence, although the doses recommended for children and adolescents are supported by the results of the clinical trials, there remains considerable scope for further optimising the dose in this population.

All the studies used ECGs in determining eligibility for inclusion criteria. This limits the safety data for those patients with ECG abnormalities, especially long QT syndrome. This also means that an ECG prior to commencing QTP would be mandatory, and that long QT syndrome would be a contraindication to QTP.

Clinical Evaluator Recommendations

The application to extend the indications for Seroquel XR to include general anxiety disorder (GAD), and for Seroquel to include use in children/adolescents with schizophrenia and bipolar mania should be approved. The following indications should be approved for Seroquel XR and Seroquel:

Seroquel XR is indicated for:

Schizophrenia

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

Generalised anxiety disorder (GAD)

Treatment of generalised anxiety disorder, including maintenance of the anti-anxiety effect

Seroquel is indicated for:

Bipolar disorder

- *Maintenance treatment of bipolar I disorder, in combination with lithium or sodium valproate, for the prevention of recurrence of manic, depressive or mixed episodes*
- *Treatment of acute mania associated with bipolar I disorder as monotherapy or in combination with lithium or sodium valproate*

Schizophrenia

- *Treatment of schizophrenia*

V. Pharmacovigilance Findings

There was no Risk Management Plan submitted with this application as it was not a requirement at the time of submission.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation for a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation for a submission of this type.

Clinical

Pharmacology

AUC_{ss} ,C_{ss} max for quetiapine and its metabolites were higher in the 10 to 12 years group compared with the 13 to 17 year group. Compared with adults (without adjusting for differences in body weight) exposure to quetiapine in children aged 10 to 17 years was slightly lower than for adults - the ratio (10 – 17 year olds: adults) of least squares means for AUC_{ss} was 0.88 (90% CI: 0.76, 1.03) and for C_{ss} was 0.92 (90%CI: 0.79, 1.06). Exposure to the metabolites was slightly higher for children and adolescents compared with adults.

The clinical evaluator commented that the dosing regimens for efficacy trials in children and adolescents appear to have been derived empirically rather than from the pharmacokinetic studies and noted that doses have not been individualised for body size. The sponsor, in a response to the clinical evaluation, stated that there was high inter-individual variability in response and safety profile to the same dose of Seroquel and therefore it recommends optimisation of dose based on an individual patient's tolerability and response.

Efficacy

Schizophrenia in children and adolescents

Study 112 was the pivotal study for this indication. Mean PANSS score at baseline was 98.1, 97.7 and 97.2 in the quetiapine 400 mg, 800 mg and placebo groups respectively. Mean PANSS score at Day 42 (primary analysis) reduced by 27.31 for the quetiapine 400 mg group, 28.44 for the 800 mg group and by 19.15 for the placebo group. Differences in reduction in PANSS were: quetiapine 400 mg vs. placebo -8.16 (95%CI: -16.06, 00.26) and quetiapine 800 mg vs. placebo -9.29 (95%CI: -16.22, -2.36). Thus both doses were statistically significantly superior to placebo for the primary outcome variable. Of note in the secondary efficacy outcomes, were the responder rates (≥ 30% reduction in PANSS from baseline to Day 42) which were: 51.9%, 40.0% and 39.5% for quetiapine 400 mg, 800 mg and placebo respectively. The responder rates are considerably lower for the primary analysis at 38.4%, 36.5% and 19% for the 400 mg, 800 mg and placebo groups respectively. Neither dose of quetiapine was statistically superior to placebo with respect to responder rates for the LOCF dataset. The % of subjects with a Clinical Global Impression – Global Improvement (CGI-GI) assessment of "improvement" or better at Day 42, was 49.3%, 52.7% and 27.4% for the 400 mg, 800 mg and placebo groups respectively. The odds ratio quetiapine 400 mg vs. placebo was 2.81 (95% CI 1.29, 6.10) and for quetiapine 800 mg vs. placebo was 2.71 (95% CI 1.23, 5.99).

Study 150 was a 26-week, open-label extension study that included subjects from study 112 and from study 149 (monotherapy of mania). At Week 26 the mean PANSS score had decreased by 9.8 points. The mean decrease in PANSS score from beginning of the double-blind period to end of open treatment was 34 points. 17.4% of subjects in the open-label treatment period achieved a response (≥ 30% reduction in PANSS score) from open-label baseline to end of week 26. From the beginning of the double-blind period to end of open treatment 62.6% of subjects achieved a response.

Bipolar 1 mania in children

The pivotal study for this proposed indication was Study 149. Mean YMRS score at baseline was 31.3 in the quetiapine 400 mg group, 30.6 in the quetiapine 600 mg group and 31.7 in the placebo group. Mean time since first known manic or mixed episode was 4.3 years. Mean YMRS score changes from baseline to Day 21 were -14.25 for quetiapine 400 mg, -15.60 for quetiapine 600 mg and -9.04 for placebo. Both doses of quetiapine were statistically significantly superior to placebo for reduction from baseline in mean YMRS scores. The secondary endpoints CGI-BP severity of illness, remission rate, response rate and CGI-BP Global improvement all demonstrated superiority of both doses of quetiapine over placebo at Day 21. There was a difference (favouring the 600 mg dose) of 1.35 in mean change from baseline in YMRS at Day 21 between the 400 mg and 600 mg doses of quetiapine. A dose response was not consistently seen with similar responder rates and remission rates with both doses of quetiapine.

In study 150 a total of 205 subjects had bipolar 1 disorder and were enrolled from study 149. The mean baseline YMRS score at commencement of open-label treatment for that population was 16.3. Mean duration on study treatment was 151 days. By week 26 the mean decrease was -3.5 points. 56.7% of bipolar 1 subjects achieved remission during open label treatment.

Generalised Anxiety Disorder (GAD)

Five studies were submitted for this proposed indication. In each of these studies the 150 mg quetiapine XR dose demonstrated statistical superiority to placebo for the primary endpoint and also for the more clinically relevant secondary endpoints of response rate and remission rate. Quetiapine XR 300 mg daily was given only in studies 9 and 10. It was superior to placebo for the primary endpoint in study 10 only. It was not superior to placebo in either study for remission or response rates. Escitalopram 10 mg daily and paroxetine 20 mg daily were superior to placebo for the primary efficacy endpoint.

Study 15 examined GAD treatment in patients aged ≥ 66 years. Mean reduction in HAM-A scores from randomisation, response and remission rates for quetiapine XR were superior to placebo and similar to results in studies in younger subjects.

Study 12 was a randomised withdrawal study to evaluate efficacy of quetiapine XR compared with placebo in decreasing the risk of recurrence of anxiety symptoms in adult patients aged to 65 years with GAD. Quetiapine XR was superior to placebo for time to an anxiety event from randomisation. 84 (39%) of the placebo group and 22 (10%) of the quetiapine XR group had an anxiety event during the double-blind period. The risk of an anxiety event was reduced by 81% in the quetiapine XR group compared to the placebo group (HR 0.19; 95%CI 0.12; 0.31; p< 0.0001). A secondary analysis which excluded events occurring in the first 13 days of randomised treatment (to account for possible withdrawal effects) also showed statistical superiority of quetiapine XR over placebo.

Safety

Children and adolescents

Adverse events occurring more frequently with quetiapine XR in children and adolescents are consistent with those seen in adults: somnolence, dizziness, increased appetite, and weight gain. Fasting glucose, insulin, total cholesterol, LDL-cholesterol and triglyceride plasma concentrations were all increased in quetiapine treated groups. Serum prolactin was elevated and Free T4 was reduced, also consistent with known side effects in adults. QTc interval was increased in a dose-dependent manner. Of particular note 44.8% of children and adolescents given quetiapine for 26 weeks had weight gain of ≥ 7%. The sponsor also reported that 18.3 % of children had at least 0.5 standard deviation from baseline in BMI.

Extrapyramidal symptoms were more frequent than in the adult studies of Seroquel.

Adults:

The most frequently reported events were dry mouth, somnolence/ sedation, dizziness and nausea. These were all dose related, with increasing incidences with increasing dose of quetiapine XR. Safety data on the effects of long term use of quetiapine in subjects with GAD are limited because the maintenance study (study 12) was terminated after meeting pre-specified efficacy criteria.

The clinical evaluator noted that all studies used ECGs in determining exclusion criteria and that this limits the safety data for those patients with CEG abnormalities, especially long QT syndrome. The evaluator recommended that an ECG be mandatory prior to commencing quetiapine and that long QT syndrome be a contraindication to use of quetiapine. The sponsor noted that baseline ECG and exclusion criteria related to ECG are a complement to the general exclusion of patients with unstable medical conditions in the clinical trial program.

A safety review of QT prolongation was conducted by the sponsor in April 2009 and included data from 26454 patients exposed to Seroquel/ Seroquel XR in the clinical trials and safety database. Following that review the PIs for Seroquel and Seroquel XR were amended to include a precautionary statement concerning QT prolongation however QT prolongation is not a contraindication to use of quetiapine and a baseline ECG is not mandatory prior to commending quetiapine

Risk-Benefit Analysis

The PK study showed that exposure to quetiapine and its metabolites is similar in children aged from 10 to 17 years and adults given the same dose. It provides a basis for the dose regimens used in subsequent efficacy and safety studies in children and adolescents.

Schizophrenia

In the assessment of quetiapine for treatment of schizophrenia, Study 112 enrolled subjects who were at least mildly ill and with mean PANSS score consistent with markedly ill with symptoms of schizophrenia. While a statistically significant improvement relative to placebo for the primary efficacy parameter was demonstrated in the pivotal study for both the 400 mg daily and 800 mg daily doses of quetiapine, there was no evidence of dose response and the responder rate was similar in the quetiapine 800 mg daily group and placebo for the primary analysis.

The Delegate considered that the LOCF analysis is more appropriate for this study than the primary analysis presented as it allows inclusion of those subjects who may have withdrawn due to poorly documented inadequate efficacy or unacceptable side effects. The efficacy measures that best reflect clinical significance are response rates at Day 42 ($\geq$ 30% reduction from baseline in PANSS score) and CGI-GI at Day 42, using the MITT population with LOCF. These measures showed either a trend towards efficacy (for response rates) or statistical superiority for both doses of quetiapine. Again there was no convincing evidence of a dose response relationship. These results, together with evidence of increasing response over time from the open extension of study 112 are sufficient to support treatment of schizophrenia in children and adolescents aged from 13 years.

There was little evidence for increased efficacy of the 800 mg daily dose over the 400 mg daily dose of quetiapine. The CGI-CI was better for the 400 mg dose than the 800 mg dose. For the LOCF analysis there were very small differences in response rates and CGI-CI rates between the 400 mg and 800 mg doses. Weight gain and changes in laboratory parameters which are associated with increased risk of cardiovascular disease were seen in the longer term study in children and adolescents with schizophrenia. These side effects are dose dependent.

The Delegate noted that given the known side effects of quetiapine the sponsor should justify the proposed maximum dose of 800 mg daily for children and adolescents with schizophrenia.

In its pre-ADEC response, although the sponsor agreed with the Delegate that there is no unequivocal dose response, a greater change from baseline in efficacy of the 800 mg/day dose than

for the 400 mg/day dose was observed for the primary endpoint. The Delegate implied that the 400 mg/day dose was better than 800 mg/day in regards to the Clinical Global Impression - Global Improvement (CGI-GI); both doses were superior to placebo. In contrast, statistically significant improvements in 2 secondary efficacy measures, CGI - Severity of Illness (CGI-S) and Children's Global Assessment Score (CGAS) total score, were only observed during treatment with the 800 mg/day dose. The CGI-S score provides an overall clinical psychiatric impression about the severity of illness. At baseline patients had a mean CGI-S score of markedly ill, which significantly improved after treatment with Seroquel 800 mg/day to a moderately ill state at Day 42. Improvement in C-GAS demonstrated that on average patients started with moderate interference of functioning in most areas or severe interference in one area, which changed to sporadic difficulties or symptoms during Seroquel treatment. Therefore, the efficacy shown in the disease-specific primary variable, PANSS, is accompanied by a clinically meaningful improvement in general functioning that is greater during treatment with 800 mg/day. There is also a clear indication that both 400 and 800 mg/day doses led to a significantly greater number of patients with improvement (CGI-GI). There were no secondary efficacy measures where statistically significant improvements were observed with the 400 mg/day dose, but not observed with the 800 mg/day dose.

The sponsor noted that the Delegate commented that the last observation carried forward (LOCF) analysis of the primary efficacy endpoint would be more appropriate then the mixed model repeated measures (MMRM; primary analysis) as it allows inclusion of those subjects who may have withdrawn due to poorly documented inadequate efficacy or unacceptable side-effects. The sponsor wished to clarify that the entire intent-to-treat ITT population was included in the MMRM analysis of primary endpoint in both the schizophrenia and bipolar studies and not only those who completed the study. The use of MMRM is preferable as this is less sensitive for bias introduced by uneven drop-out rates than the last observation carried forward (LOCF) approach.

In summary, the sponsor maintained that Seroquel is effective over the dose range proposed for the treatment of schizophrenia (400 and 800 mg/day). While AstraZeneca acknowledges that there is no unequivocal dose response, clinically significant improvements have been shown by doses greater than 400 mg/day. Therefore, the proposed dose range provides clinicians appropriate flexibility to individualise patient treatment and increase the likelihood for a positive clinical outcome for a greater number of patients. However, in light of the Delegate's comments, the sponsor proposed to include a statement within the Dosage and Administration section of the Product Information (PI) to emphasise that the lowest effective dose should be used.

Bipolar 1 mania

There is a difference in acceptance of bipolar 1 disorder between the DSM-IV and the CPMP/EWP/567/98 *Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment of Bipolar Disorder*. The diagnostic criteria for mania in DSM-IV are the same for children and adults, however, the guidance document adopted by the TGA notes that bipolar disorder develops in early adulthood therefore specific studies in younger children do not seem to be relevant. The Therapeutic Guidelines – psychotropic states that the diagnosis of "juvenile (paediatric) bipolar disorder" in childhood or early adolescence is controversial when made in the absence of elevated mood, and largely premised on chronic irritability.

Study 149 demonstrated efficacy of quetiapine in the treatment of bipolar 1 mania in children and adolescents but, as with treatment of schizophrenia, there was little indication of greater efficacy of the higher dose compared with the lower dose of quetiapine. This study enrolled a substantial proportion of children aged from 10 to 12 years who were evenly distributed in the 3 treatment arms. Efficacy results were comparable in the two age subgroups but no statistical analysis of these efficacy results was presented. Over 44% of children in this study had comorbid ADHD with 21% of subjects taking psychostimulants - 28% in the quetiapine 400 mg group and 17-18% in the

quetiapine 600 mg and placebo groups. Hyperactivity and psychosis are known adverse effects of psychostimulants. It is possible these effects could be misdiagnosed as acute mania, however, this possibility was reduced because subjects were required to be stable on psychostimulants prior to commencing the study.

No separate analysis of efficacy in subjects with comorbid ADHD taking psychostimulants was presented. The Delegate requested that the sponsor comment on the diagnosis of bipolar 1 disorder in children, to provide information on efficacy for the subgroup of children and adolescents with comorbid ADHD taking psychostimulants and to justify the proposed maximum quetiapine dose of 600 mg daily.

The sponsor responded by noting that the Delegate raised concerns on the diagnosis of bipolar I disorder in children. The sponsor indicated that globally accepted standard methods were used in Study 149 by appropriately trained physicians to diagnose bipolar mania according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) as confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children Present and Lifetime Version (K-SADS-PL). Although clinical practice may vary from country to country, use of these diagnostic tools ensures that international standards have been applied. Hence, in the opinion of the sponsor, there is an unmet medical need for alternative treatments for children and adolescents diagnosed with bipolar mania.

The sponsor also responded on the issue that the Delegate had raised concerning the use of Seroquel in children younger than 13 years. As noted by the Delegate, no statistical analysis was provided in the dossier for the 2 age-range subgroups: children (10 to 12 years) and adolescents (13 to 17 years). This study was not powered to test effects in these small subgroups for statistically significant differences; therefore, p values greater than 0.05 do not overrule clinically significant observations. The sponsor provided the requested analysis in relation to the primary outcome measure. The subgroups were well-matched at baseline. Clinically significant efficacy was shown in both children and adolescents by observed decreases in YMRS total score. The sponsor acknowledged that the diagnosis of bipolar mania patients aged 10 to 12 years is rare but considers that treatment with Seroquel offers significant long-term benefit for these children. Onset of mania during childhood or adolescence is a serious manifestation of bipolar disorder, a psychiatric condition that typically has a recurrent course, and severe long-term implications if left untreated.

The sponsor also noted that the Delegate had raised concerns on the use of Seroquel in children/adolescents with co-morbid ADHD taking psychostimulant medications, and made a request for further information on the efficacy of Seroquel in this subgroup. The sponsor noted that the Delegate considered that the requirement that patients used stable doses, taken for at least 30 days before study treatment began, reduced the possibility that psychostimulant side-effects could be misdiagnosed as mania. In addition, the sponsor considers that the diagnostic methods used in this study exclude this possibility. While this study was not powered to test effects in these small subgroups for statistically significant effects, the sponsor provided the requested analysis in relation to the primary outcome measure. The subgroups were well-matched at baseline. In each case, the efficacy outcomes favouring Seroquel over placebo were similar in the sub-populations (whether analysed by presence of ADHD or presence of psychostimulant use). The change in YMRS score was slightly greater for patients who received the 600 mg/day dose compared with those who received the 400 mg/day dose. This difference was most evident in the subgroup with co-morbid ADHD. It should be noted that due to the small sample size, p values greater than 0.05 do not overrule clinically significant observations. Hence, the sponsor considers that the clinical data fully support the use of Seroquel in patients with co-morbid ADHD whether or not they are taking psychostimulants.

The sponsor responded that the Delegate acknowledged that Study 149 demonstrated that both doses of Seroquel (400 and 600 mg/day) were statistically significantly superior to placebo for the

primary, as well as the majority of secondary efficacy endpoints, in the treatment of bipolar mania in children and adolescents aged 10 to 17 years of age. While the sponsor agrees with the Delegate that there is no unequivocal dose response in the primary and secondary efficacy measures, the study was not designed to demonstrate statistical superiority of the 600 mg/day versus 400 mg/day dose. However, as stated by the Delegate, there was a difference in the primary efficacy variable between the 400 and 600 mg/day doses (favouring the 600 mg/day dose) of 1.35 in mean YMRS results at Day 21 compared with baseline. Consequently, there may be need for individuals to receive doses greater than 400 mg/day to achieve optimal benefit. This point is further supported by subgroup analyses. However, in light of the Delegate's comments, the sponsor proposed to include a statement similar to that stated above for schizophrenia within the Dosage and Administration section of PI to emphasise that the lowest effective dose should be used.

There has been no formal assessment of efficacy of Seroquel in prevention of relapse or recurrence of acute mania in children and adolescents who received quetiapine for treatment of an episode of acute mania. Study 150 enrolled subjects without regard to their therapeutic response to Seroquel for treatment of acute mania and there was no placebo arm which would be required to determine the extent of benefit of continued treatment with Seroquel in both subjects who initially responded and in those who did not initially respond.

The proposed indications for Seroquel do not differentiate indications which are specific to children and adolescents. The indications for Seroquel applicable to children and adolescents should be limited to those in which efficacy has been demonstrated.

The sponsor noted that the Delegate has also raised concerns regarding the known safety profile of Seroquel in relation to justifying the proposed maximum doses for paediatric patients of 600 mg/day in bipolar mania and 800 mg/day in schizophrenia. The sponsor agreed with the Delegate's comments that the frequently reported adverse events (AEs) that occurred in children and adolescents were consistent with those seen in adults, with the exception of blood pressure increases observed in paediatric patients. Furthermore, both the short-term and long-term data show that in general there are no dose-related safety concerns in the proposed population. The sponsor considers that the safety profile of Seroquel is consistent over the dose range of 400 to 800 mg/day. As proposed within the PI, the dose prescribed for each patient would be adjusted within the tolerability shown by the individual.

The sponsor considers that in cases where a patient requires a dose greater than 400 mg/day to achieve a therapeutic response, it is safe to permit increases to a maximum of 600 or 800 mg/day for paediatric patients with bipolar mania or schizophrenia, respectively. There were no changes in safety parameters in the short-term studies that showed a relationship with dose. In the 2 short-term studies, there was no apparent dose-relationship over the dose range of 400 to 800 mg/day Seroquel with respect to the overall incidence of AEs, discontinuations due to AEs, and serious AEs. However, a trend for dose response was seen for dry mouth and irritability that occurred at low incidences (<10% of patients). In the longer-term (up to 26 weeks) study in patients with schizophrenia and bipolar mania (Study 150), the safety profile of Seroquel was generally consistent with that seen in the acute paediatric studies and revealed no new safety concerns associated with longer-term treatment. The safety profile from this study was acceptable and supports that adjustment of the dose given to individual patients where required would be safe up to a maximum daily dose of 800 mg. As the study had a flexible dose design (400 to 800 mg/day, with the option to reduce to 200 mg/day) and no placebo control, any of the safety observations cannot be considered in relationship with dose. This includes the two specific issues raised by the Delegate: effects on body weight and laboratory results related to cardiovascular safety. Analysis of the increase in Body Mass Index (BMI) observed in the long-term study showed that the largest changes from baseline to final visit in weight and BMI were in the underweight subgroup, and the smallest changes were in the overweight subgroup. Mean changes and shifts in lipid parameters

were examined to identify any differences. Changes in lipid parameters did not appear to be dose dependent and were similar when examined by indication and age subgroups. Appropriate precautions are provided within the current PI, and in clinical practice changes in body weight, blood glucose, and lipids can be managed as clinically appropriate.

Generalised Anxiety Disorder

The short term studies for generalised anxiety disorder were well designed and showed statistically significant superiority of all doses of quetiapine XR over placebo for clinically relevant endpoints. Escitalopram and paroxetine were appropriate active controls, both having indications for GAD in Australia. Though there was no formal statistical comparison, quetiapine XR showed similar efficacy to escitalopram and paroxetine. There was no increase in efficacy with the doubling of dose of quetiapine from 150 mg to 300 mg. The Delegate noted that given the known adverse effects of quetiapine, the sponsor should comment on the proposed maximum dose of 300 mg daily for this indication. The sponsor acknowledged the Delegate's comment that there was no increase in efficacy with the doubling of dose of Seroquel XR from 150 mg/day to 300 mg/day, and accepted the Delegate's recommendation to approve the dose range of 50 to 150 mg/day for use in GAD patients.

The maintenance study for GAD showed that flexibly dosed quetiapine XR reduced the incidence of relapse/ recurrence of anxiety events associated with GAD. This study did not differentiate between relapses and recurrences of anxiety events. The optimum dose range for prevention of recurrence of GAD symptoms was not determined, the dose range in the maintenance study was based on the doses required for treatment of acute mania. Because the maintenance study was terminated early, longer term safety data, including the extent of weight gain with long term use, cannot be determined for subjects given quetiapine XR for treatment of GAD. Weight gain, and other long term adverse effects are however, likely to be similar to those seen in patients given quetiapine for other indications.

The Delegate proposed to:

1. Approve Seroquel for the treatment of schizophrenia in patients aged from 13 to 17 years with a recommended dose of 400 mg daily in divided doses.

2. Approve Seroquel as monotherapy for treatment of acute mania in patients aged from 13 to 17 years with a recommended dose of 400 mg daily in divided doses. Whether quetiapine should be approved for children with comorbid ADHD taking psychostimulant medication and for children aged from 10 to 12 years requires further consideration of the sponsor's response. The Delegate did not propose to approve quetiapine for those patient groups.

3. Approve Seroquel XR for the treatment of generalised anxiety disorder in adults with a recommended dose of 50 to 150 mg daily.

The advice of the ADEC was requested specifically on use of quetiapine in children younger than 13 years with acute mania and in children and adolescents taking psychostimulants.

The Australian Drug Evaluation Committee (ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

ADEC recommended partial approval of the submission with the revised indications and proposed dosage as follows:

> *Seroquel:*
>
> *Treatment of schizophrenia in patients aged from 13 to 17 years with a recommended dose of 400 mg daily in divided doses.*
>
> *Monotherapy treatment of acute mania associated with bipolar 1 disorder in patients aged from 10 to 17 years with a recommended dose of 400 mg daily in divided dose. This may be increased to 600 mg daily in divided doses depending on clinical response.*
>
> *Seroquel XR:*
>
> *Treatment of generalised anxiety disorder in adults who are intolerant to, or had an inadequate response to alternative drug therapies with a recommended dose of 50 to 150 mg daily.*

In making this recommendation, ADEC agreed with the Delegate that there was little evidence for increased efficacy of the 800 mg daily dose over the 400 mg daily dose of quetiapine for the treatment of schizophrenia. Therefore, the proposed dosage should be restricted to the lower dose.

The Committee considered that the evidence presented at pre-ADEC response was supportive of efficacy in children aged 10-12 years for bipolar 1 mania. Although study 149 demonstrated efficacy of quetiapine in the treatment of bipolar 1 mania in children and adolescents, the dose response was noted to be inconsistent. The mean changes in the Young Mania Rating Scale (YMRS) were significant for both dose groups in patients aged 13-17 years. However, in children age 10-12 years, it was only significant for the 600 mg dose group. The Committee considered that there is insufficient efficacy and safety data to recommend use in patients receiving concomitant psychostimulants for co-morbid ADHD. Additionally, it was commented that there is a potential risk of worsening mood stability as well as possible drug efficacy interaction between Seroquel and psychostimulants, where Seroquel may decrease the effectiveness of the psychostimulants.

The ADEC also noted that the short term studies for generalised anxiety disorder showed statistically significant superiority of all doses of quetiapine modified release over placebo for clinically relevant points. However, there was no increase in efficacy with the doubling of dose of quetiapine modified release from 150 mg to 300 mg. The Committee concluded that the benefit to risk ratio is against an atypical antipsychotic as a first line treatment in GAD, therefore Seroquel XR should be restricted to patients who are intolerant of, or who have had an inadequate response to alternative therapies.

The Committee raised concerns regarding the half life of Seroquel doubling across both age groups, which is indicative of cumulative effect and encourages greater monitoring for potential adverse effects.

The specific conditions of registration should include the provision of a dosing schedule based on body weight in children and adolescents.

Outcome

Based on review of quality, safety and efficacy data, TGA approved the registration of Seroquel immediate release tablets containing quetiapine fumarate 25mg, 100mg, 150mg, 200mg and 300mg for the indication:

to include use in children/adolescents with schizophrenia and bipolar mania as described in the Product Information (PI) document.

The TGA also approved the registration of Seroquel XR modified release tablets containing quetiapine 50mg, 150mg, 200mg, 300mg and 400mg for the indication:

Treatment of generalised anxiety disorder (GAD)

Attachment 1. Product Information

Seroquel®

quetiapine fumarate

PRODUCT INFORMATION

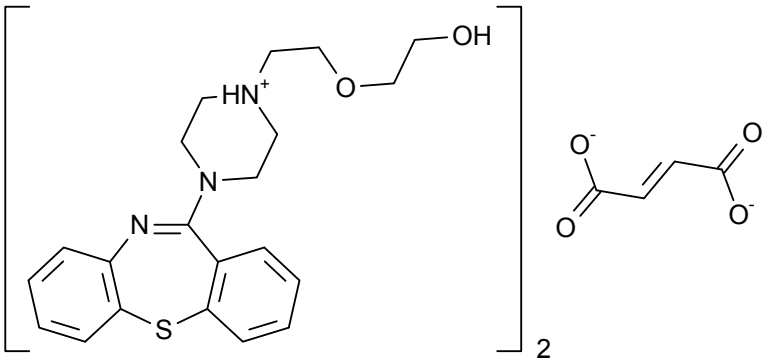
NAME OF THE MEDICINE

Quetiapine fumarate

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

Quetiapine fumarate has no chiral centres and only one morphological entity has been detected throughout development.

Structural Formula:



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 displays good solid state stability, has an aqueous solubility of 3.29 mg/mL at 25°C and exhibits suitable tableting properties when combined with appropriate excipients.

SEROQUEL 25 mg, 100 mg, 150 mg and 200 mg are round, biconvex, film-coated tablets. SEROQUEL 300 mg are capsoid, film-coated tablets.

SEROQUEL 25 mg, 100 mg, 150 mg, 200 mg and 300 mg tablets contain quetiapine fumarate equivalent to 25 mg, 100 mg, 150 mg, 200 mg and 300 mg quetiapine free base respectively. The inactive ingredients are: povidone, calcium hydrogen phosphate, microcrystalline cellulose, lactose, sodium starch glycollate, magnesium stearate, hypromellose, macrogol 400, titanium dioxide, iron oxide yellow CI77492 (25 mg, 100 mg and 150 mg) and iron oxide red CI77491 (25 mg).

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. Additionally, norquetiapine has high affinity (higher than quetiapine) for the noradrenaline transporter, $5HT_{1B}$ and muscarinic receptors. Quetiapine and norquetiapine also have high affinity at histaminergic H_1 and adrenergic α_{1B} and $_{1A}$ receptors, with a lower affinity at adrenergic α_2 and $5HT_{1A}$ receptors. Quetiapine has no appreciable affinity at cholinergic, muscarinic or benzodiazepine receptors. 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.

It has been demonstrated that SEROQUEL is effective when given once or twice a day, although quetiapine has a pharmacokinetic half-life of approximately 7 hours. This is further supported by the data from a positron emission tomography (PET) study which identified that for quetiapine, $5HT_2$ and D_2 receptor occupancy are maintained for up to 12 hours. The safety and efficacy of doses greater than 800 mg/day have not been evaluated.

Pharmacokinetics

Absorption

Quetiapine is well absorbed and the bioavailability of quetiapine is not significantly affected by administration with food.

Distribution

The elimination half-lives of quetiapine and norquetiapine are approximately 7 and 12 hours respectively. Quetiapine is approximately 83% bound to plasma proteins. 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. The kinetics of quetiapine do not differ between men and women.

Metabolism

Quetiapine is extensively metabolised by the liver following oral administration, with parent compound accounting for less than 5% of unchanged drug related material in the urine or faeces, following the administration of radiolabelled quetiapine. The average molar dose fraction of free quetiapine and the active human plasma metabolite norquetiapine is <5% excreted in the urine.

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 coadministration 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.

The mean clearance of quetiapine in the elderly is approximately 30 to 50% lower than that seen in adults aged 18 to 65 years.

Excretion

Approximately 73% of the radioactivity is excreted in the urine and 21% in the faeces.

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 30 mL/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 administration).

Use in children and adolescents (10 to 17 years of age)

At steady-state the pharmacokinetics of the parent compound in children and adolescents (10-17 years of age) were similar to adults, while AUC and C_{max} of the active metabolite, norquetiapine, were higher in children and adolescents than in adults, 45% and 31%, respectively. However, when adjusted for weight AUC and C_{max} of the parent compound in children and adolescents were lower than in adults, 41% and 39%, respectively, while the pharmacokinetics of the metabolite, norquetiapine, was similar (see Dosage and administration).

Pre-clinical data

Acute toxicity studies

Quetiapine has low acute toxicity. Findings in mice (median lethal dose > 500 mg/kg PO; 100 mg/kg IP), rats (median lethal dose > 500 mg/kg PO; 100 mg/kg IP) and dogs (dose limit study 10-75 mg/kg PO) were typical of neuroleptic agents and included decreased motor activity, ptosis, loss of righting reflex, prostration, fluid around the mouth and convulsions.

Repeat-dose toxicity studies

In multiple-dose studies in rats, dogs and monkeys, anticipated central nervous system effects of an antipsychotic drug were observed with quetiapine (eg sedation at lower doses and tremor, convulsions or prostration at higher exposures).

Hyperprolactinaemia, induced through the dopamine D_2 receptor antagonist activity of quetiapine or its metabolites, varied between species but was most marked in the rat, and a range of effects consequent to this were seen in the 12-month study, including mammary hyperplasia, increased pituitary weight, decreased uterine weight and enhanced growth of females.

Reversible morphological and functional effects on the liver, consistent with hepatic enzyme induction, were seen in mouse, rat and monkey.

Thyroid follicular cell hypertrophy was seen in mice, rats and monkeys. This hypertrophy was secondary to compensatory elevations of circulating Thyroid Stimulating Hormone (TSH) brought about by increased hepatic metabolism of thyroid hormones.

Pigmentation of a number of tissues, particularly the thyroid, was not associated with any morphological or functional effects.

Transient increases in heart rate were not accompanied by consistent effects on blood pressure in dogs.

Posterior triangular cataracts seen after 6 months in dogs at 100 mg/kg/day were consistent with inhibition of cholesterol biosynthesis in the lens. No cataracts were observed in Cynomolgus monkeys dosed up to 225 mg/kg/day, although an increase in lens relucency was seen at the highest dose. No effects on the lens were seen in rodents. Monitoring in clinical studies did not reveal drug-related corneal opacities in man.

No evidence of neutrophil reduction or agranulocytosis was seen in any of the toxicity studies, however there was evidence for reduced lymphocytes in the bone marrow of dogs and in the circulation of monkeys.

CLINICAL TRIALS

Bipolar disorder (adults)

Maintenance treatment in combination with lithium or sodium valproate

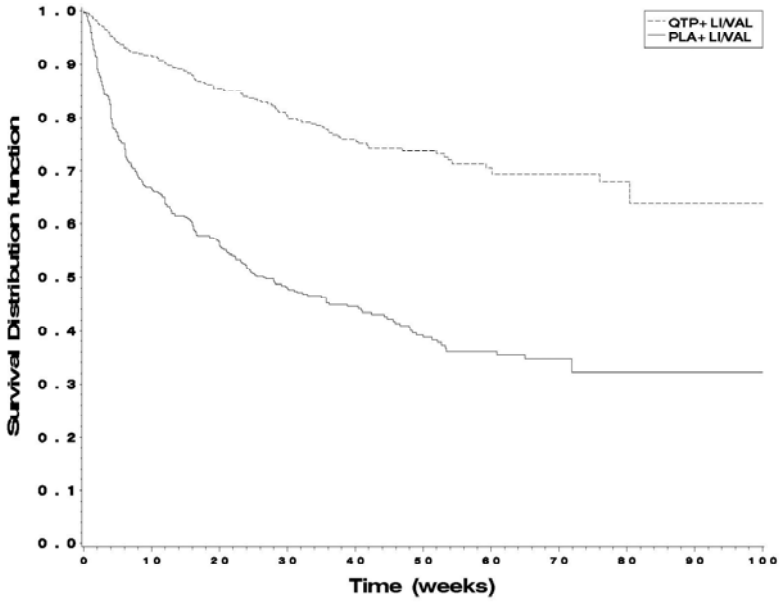
The efficacy of SEROQUEL in the maintenance treatment of bipolar disorder was established in two similarly designed placebo-controlled trials in patients who met DSM-IV criteria for bipolar I disorder. These trials included patients whose most recent mood episode was mania (approximately 36%), depression (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 first recurrence as 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 first recurrence as a depression 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**

	Kaplan Meier survival estimate of event rates (%)		
Time to event	**QTP + LI/VAL (N=646)**	**PLA + LI/VAL (N=680)**	**p value**
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 to Table 2).

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

Maintenance treatment as monotherapy

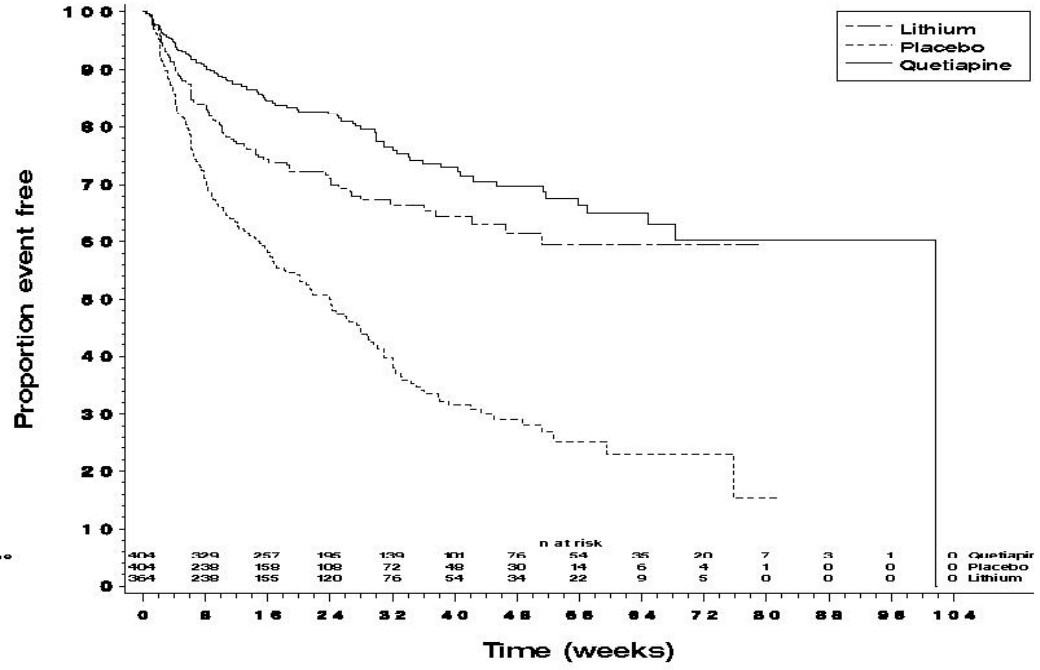
The efficacy of SEROQUEL in the maintenance treatment of bipolar disorder as monotherapy was established in a placebo-controlled trial in 1172 patients who met DSM-IV criteria for bipolar I disorder. Approximately 50% of the 2438 patients initially treated with quetiapine for their index episode achieved 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 depressed events (refer Table 3). Efficacy was demonstrated to be independent of the nature of the most recent episode (manic, mixed or depressed), rapid cycling course, gender, age or ethnicity.

Figure 2 **Time to relapse/recurrence of a mood event, manic event and depressed 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 depressed 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.

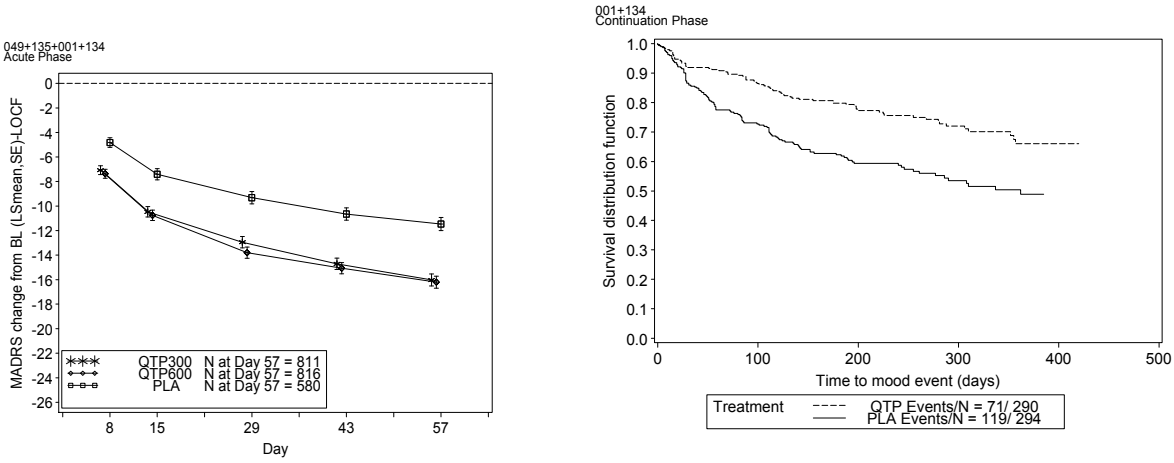
Bipolar depression

The safety and efficacy of SEROQUEL 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. Patients met the DSM-IV criteria for bipolar I or II disorder, with or without rapid cycling courses. In the 8-week study period approximately 35% of patients met the criteria for bipolar II disorder.

Anti-depressant activity was assessed by the change from baseline for MADRS total score (primary endpoint), at 8 weeks (day 57). In all 4 studies SEROQUEL doses of 300 mg/day and 600 mg/day demonstrated clinical and statistical superiority to placebo in the treatment of depression at 8 weeks (refer Figure 3A). The anti-depressant effect of SEROQUEL was superior compared to placebo as early as day 8 (week 1) and was maintained through to week 8 (refer Figure 3A).

Figure 3 Treatment (A) and maintenance of effect (B) of SEROQUEL in bipolar depression (combined intention to treat population)

A MADRS total score change from baseline over time by treatment (LOCF) **B Time to recurrence of a mood event (Kaplan Meier curves)**



BL baseline. ITT Intention-to-treat. LOCF Last observation carried forward. LS Least squares. MADRS Montgomery-Asberg Depression Rating Scale. N Number of patients in treatment group. PLA Placebo. QTP Quetiapine. SE standard error.

The magnitude of the anti-depressant effect was supported by the secondary outcome variables [Hamilton Rating Scale for Depression (HAM-D) total score, the item analyses of the MADRS and HAM-D item 1 (depressed mood) score]. Response rates (defined as (≥50% reduction in MADRS total score) and remission rates (defined as MADRS total score of 12 or less) were superior for SEROQUEL compared to placebo at week 8. The Clinical Global Impression – Severity of Illness (CGI-S) and Clinical Global Impression – Improvement (CGI-I), measures of the clinicians impression of the severity of the patients overall illness and improvement from baseline, were also assessed with SEROQUEL superior to placebo at week 8 in all 4 studies.

Alleviation of anxiety symptoms by SEROQUEL 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.

The change from baseline for total MADRS score for SEROQUEL vs placebo was statistically significant for patients with bipolar I or bipolar II disorder. Efficacy was also demonstrated to be independent of cycling frequency, gender, or age.

Quality of life assessments as measured by Q-LES-Q (Quality of Life Enjoyment and Satisfaction Scale) total score revealed superior improvement with SEROQUEL 300 mg treatment and improvement was also seen with SEROQUEL 600 mg compared to placebo.

Maintenance of the SEROQUEL effect in bipolar depression was demonstrated during the continuation phase with patients treated with SEROQUEL 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 3B. SEROQUEL patients had a lower risk of experiencing a mood event at weeks 26 and 52 compared to patients on placebo. Patients on SEROQUEL 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 SEROQUEL versus placebo was reduced by 41% for the 300 mg dose and by 55% for the 600 mg dose.

SEROQUEL patients also had a lower risk of experiencing a depressed event at weeks 26 and 52 compared to patients on placebo. The analysis of time to a depressed event mirrored the overall mood event results with patients on SEROQUEL having a 57% less risk of experiencing a depressed event compared with patients treated with placebo (HR 0.43, 95% CI 0.30, 0.62, p<0.001). The risk of a depressed event for SEROQUEL 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. SEROQUEL treatment of a depressed 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 SEROQUEL treatment, compared to 156 days for placebo treatment.

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

In the majority of studies in the acute phase statistically significant improvements over placebo were seen in reductions in suicidal thinking as measured by MADRS item 10. There was also no increased risk of suicidal behaviour or ideation associated with SEROQUEL treatment for bipolar depression in either the acute or continuation phase.

Acute mania

The efficacy of SEROQUEL in the treatment of manic episodes was established in three short-term placebo-controlled trials in patients who met DSM-IV criteria for bipolar I disorder. These trials included patients with or without psychotic features and excluded patients with rapid-cycling or mixed episodes.

The primary outcome variable for these trials was change from baseline to Day 21 in the YMRS total score, an instrument used to assess manic symptoms. Various secondary outcomes were also assessed. The CGI-Bipolar Version reflects the clinician's impression of the severity of the patient's overall bipolar illness and improvement from baseline (CGI-BP Severity and CGI-BP Improvement). In addition, MADRS was used to assess depressive symptoms, and the Positive and Negative Symptoms Scale (PANSS) was used to assess the efficacy in psychosis, agitation and aggression. The Global Assessment Scale (GAS) was used to assess improvement in functional status.

The results of the trials follow:

In two 12-week trials (n=300, n=299) comparing SEROQUEL to placebo, SEROQUEL was superior to placebo in reducing manic symptoms. Of those patients with a clinical response, 87% received doses of SEROQUEL between 400 and 800 mg per day. The mean last week median dose of SEROQUEL in responders was approximately 600 mg/day.

The majority of patients who responded at day 21 maintained responses to day 84. On secondary endpoints, SEROQUEL was also clinically and statistically superior to placebo. Improvements were observed in CGI-BP Severity and Improvement, MADRS total score, PANSS total score, PANSS activation subscale and in the GAS score. The effectiveness of SEROQUEL was unaffected by age, gender, ethnicity or the presence of psychotic symptoms at baseline.

In a 3-week placebo controlled trial (n=170) comparing SEROQUEL to placebo in patients on a mood stabiliser (lithium or valproate), SEROQUEL was superior to placebo in reducing manic symptoms. Improvements were observed in CGI-BP Severity and Improvement and PANSS total score. Of those patients with a clinical response, 91% received doses of SEROQUEL between 400 and 800 mg per day. The mean last week median dose of SEROQUEL in responders was approximately 600 mg/day. In a similarly designed 6-week placebo controlled trial (n=200) SEROQUEL demonstrated a similar improvement in YMRS scores but did not demonstrate superiority to placebo at either day 21 or day 42, possibly due to a higher placebo effect.

Schizophrenia (adults)

The efficacy of SEROQUEL was established in short-term controlled trials of psychotic inpatients who met DSM III-R criteria for schizophrenia. Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), CGI and Scale for Assessing Negative Symptoms (SANS).

The main trials were:

1. A 6-week placebo-controlled trial (n=361) involving 5 fixed doses of SEROQUEL (75, 150, 300, 600 and 750 mg/day on a three times a day dosing schedule).

2. A 6-week placebo-controlled trial (n=109) involving titration of SEROQUEL in doses up to 750 mg/day on a three times a day dosing schedule.

3. A 6-week placebo-controlled (n=286) involving titration of SEROQUEL in high (up to 750 mg/day on a three times a day dosing schedule) and low (up to 250 mg/day on a three times a day dosing schedule) doses.

4. A 6-week dose and dose regimen comparison trial (n=618) involving 2 fixed doses of SEROQUEL (450 mg/day on both twice a day and three times a day dosing schedules and 50 mg/day on a twice a day dosing schedule).

SEROQUEL has been shown to be effective in the treatment of both positive and negative symptoms of schizophrenia. In a comparative clinical trial of 10 weeks duration, SEROQUEL has been shown to be as effective as risperidone, using a 40% or more decline in the baseline PANSS score as a definition of response; although statistically comparative efficacy was not demonstrated when using a 30% decline in PANSS score, the differences between treatments were modest in absolute terms and in all probability not clinically meaningful.

Children and adolescents (10 to 17 years of age)

Three clinical trials have been conducted with SEROQUEL in children and adolescents; two short-term randomised placebo-controlled trials – a 3 week trial in schizophrenia (patients aged 13-17 years) and a 6 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.

Acute mania (monotherapy)

The efficacy of SEROQUEL in the treatment of acute manic episodes associated with bipolar I disorder in children and adolescents (10 to 17 years of age) was demonstrated in a 3-week, double-blind, placebo-controlled, multicentre trial. Patients who met DSM-IV diagnostic criteria for a manic episode were randomized into one of three treatment groups: SEROQUEL 400 mg/day, SEROQUEL

600 mg/day, or placebo. Approximately 45% (n=124) of patients (n=277) had co-morbid attention deficit hyperactivity disorder (ADHD), with 59 (21%) of patients receiving concomitant psychostimulants (see Interaction with other medicines).

Study medication was initiated at 50 mg/day and on Day 2 increased to 100 mg/day. Subsequently, the dose was titrated to a target dose of 400 or 600 mg using increments of 100 mg/day, given two or three times daily. Results of the study demonstrated superior efficacy of SEROQUEL 400 mg/day and 600 mg/day compared with placebo (see Table 4).

Table 4 Summary of YMRS efficacy results (ITT population) for treatment of acute mania (monotherapy) in children/adolescents

YMRS endpoint	QTP 400mg vs PLA QTP N=93 / PLA N=89	QTP 600mg vs PLA QTP N=95 / PLA N=89
Total score – LS mean change from baseline to Day 21 (primary endpoint)	-14.25 vs -9.04; p<0.001	-15.60 vs -9.04; p<0.001
Response [a] (% patients) at Day 21	63 vs 37%; p=0.001	58 vs 37%; p=0.005
Remission [b] (% patients)	53 vs 30%; p=0.010	54 vs 30%; p=0.003

YMRS – Young Mania Rating Scale, ITT Intent-to-treat. LS – Least square, PLA Placebo. QTP Quetiapine. N Number of patients in treatment group, [a] ≥50% reduction for YMRS total score, [b] ≤12 YMRS total score

Schizophrenia

The efficacy of SEROQUEL in the treatment of schizophrenia in adolescents (13 to 17 years of age) was demonstrated in a 6-week, double-blind, placebo-controlled trial. Patients who met DSM-IV diagnostic criteria for schizophrenia were randomized into one of three treatment groups: SEROQUEL 400 mg/day, SEROQUEL 800 mg/day, or placebo. Study medication was initiated at 50 mg/day and on Day 2 increased to 100 mg/per day. Subsequently, the dose was titrated to the a target dose of 400 or 800 mg using increments of 100 mg/day, given two or three times daily. Results of the study demonstrated superior efficacy of SEROQUEL 400 mg/day and 800 mg/day compared to placebo (see Table 5).

Table 5 Summary of key efficacy results (ITT population) for treatment of schizophrenia in adolescents

Endpoint at Day 42	QTP 400mg vs PLA QTP N=73 / PLA N=73	QTP 800mg vs PLA QTP N=74 / PLA N=73
PANSS total score (MMRM) – LS mean change from baseline (primary endpoint)	-27.31 vs -19.15; p=0.043	-28.44 vs -19.15; p=0.009
PANSS response [a] (LOCF; % patients)	38.4 v 26.0; NS [b]	36.5 v 26.0; NS [b]
CGI - Global Improvement (LOCF; % patients with improvement)	49.3 v 27.4; p=0.009 [c]	52.7 v 27.4; p=0.014 [c]

MMRM - mixed model repeated measures; LOCF - last observation carried forward; ITT Intent-to-treat. PANSS – Positive and Negative Syndrome Scale; CGI - Clinical Global Impression; LS – Least square, PLA Placebo. QTP Quetiapine. N Number of patients in treatment group, [a] ≥30% reduction for PANSS total score; [b] Generalised estimating equation for statistics (N=220); [c] Generalised estimating equation for statistics (N=219)

INDICATIONS

SEROQUEL is indicated for:

Bipolar disorder

Adults

- 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

Children/adolescents aged 10 to 17 years

- Monotherapy treatment of acute mania associated with bipolar I disorder

Schizophrenia (adults and adolescents aged 13 to 17 years)

- Treatment of schizophrenia

CONTRAINDICATIONS

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

PRECAUTIONS

Concomitant cardiovascular illness

SEROQUEL 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).

SEROQUEL 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 SEROQUEL, 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 QT_c intervals. However, in post marketing experience there were cases reported of QT prolongation with overdose (see Overdosage). 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. Also caution should be exercised when quetiapine is prescribed with medicines known to prolong the QT_c interval, and concomitant neuroleptics, especially the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia.

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 major depressant disorder (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 major depressive disorder 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 major depressive disorder 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 major depressive disorder 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 SEROQUEL should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

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 of adult patients with bipolar

depression, the incidence of EPS was higher in SEROQUEL treated patients than in placebo treated patients (see Adverse Effects for rates of EPS observed in all indications).

Tardive dyskinesia

SEROQUEL 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 SEROQUEL 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 SEROQUEL. Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatine phosphokinase. In such an event, SEROQUEL 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 SEROQUEL 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

Severe neutropenia ($<0.5 \times 10^9$/L) has been uncommonly reported in SEROQUEL clinical trials. Most cases of severe neutropenia have occurred within the first two months of starting therapy with SEROQUEL. There was no apparent dose relationship. Possible risk factors for neutropenia include pre-existing low white cell count (WBC) and history of drug induced neutropenia. 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.

Hepatic enzyme inducers

Concomitant use of SEROQUEL with hepatic enzyme inducers such as carbamazepine may substantially decrease systemic exposure to quetiapine. Depending on clinical response, higher doses of SEROQUEL may need to be considered if SEROQUEL is used concomitantly with a hepatic enzyme inducer.

CYP3A4 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. As a consequence of this, lower doses of SEROQUEL should be used. Special consideration should be given in elderly and debilitated patients. The risk-benefit ratio needs to be considered on an individual basis in all patients (see Interactions with other medicines).

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 SEROQUEL (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.

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 Zyprexa (olanzapine), Abilify (aripiprazole), Risperdal (risperidone), and SEROQUEL (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 (eg heart failure, sudden death) or infectious (eg pneumonia) in nature. SEROQUEL is not approved for the treatment of elderly patients with dementia-related psychosis or behavioural disorders.

Withdrawal

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

Dysphagia

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

Lipids

Increases in triglycerides and 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 increases should be managed as clinically appropriate.

Lactose

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

Use in pregnancy (Category B3)

The safety and efficacy of quetiapine during human pregnancy have not been established. Therefore, SEROQUEL should only be used during pregnancy if the benefits justify the potential risks.

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.

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

The degree to which quetiapine is excreted into human milk is unknown, however 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 SEROQUEL.

Use in children and adolescents (10 to 17 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 for adolescents aged from 13 years with schizophrenia and for 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). The safety and efficacy of SEROQUEL 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 SEROQUEL 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 SEROQUEL, are not available for children and adolescents (10 to 17 years of age).

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.

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).

Interactions with other medicines

Antipsychotic and other centrally acting medicines

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

Thioridazine

Thioridazine (200 mg twice a day) increased the oral clearance of quetiapine (300 mg twice a day) 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 dosing. Dosage adjustment is not required.

Levodopa and dopamine agonists

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

Carbamazepine and phenytoin

See Hepatic enzyme inducers below

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 a day) or haloperidol (7.5 mg twice a day). 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 Metabolism section). CYP2D6 and CYP2C9 are also involved.

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 (refer Ketoconazole below). As a consequence of this lower doses of SEROQUEL 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 SEROQUEL 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 a day; a known CYP2D6 inhibitor) or fluoxetine (60 mg once daily; a known CYP3A4 and CYP2D6 inhibitor).

Hepatic enzyme inducers (e.g. 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 SEROQUEL may be required to maintain control of psychotic symptoms in patients co-administered SEROQUEL and hepatic enzyme inducers (eg 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 SEROQUEL may need to be reduced if phenytoin, carbamazepine or other hepatic enzyme inducers are withdrawn and replaced with a non-inducer (eg 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 SEROQUEL, 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 SEROQUEL is used concomitantly with medicines known to cause electrolyte imbalance or to increase QTc interval.

Because of it's potential for inducing hypotension, SEROQUEL 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 SEROQUEL 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.

Effects on laboratory tests

Leukopenia and/or neutropenia

As with other antipsychotics transient leukopenia and/or neutropenia have been observed in patients administered SEROQUEL. 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 SEROQUEL. These elevations were usually reversible on continued SEROQUEL treatment (see Adverse effects).

Triglycerides and cholesterol

Small elevations in non-fasting serum triglyceride levels and total cholesterol (predominantly LDL cholesterol) have been observed during treatment with SEROQUEL (see Adverse effects).

Thyroid hormone levels

SEROQUEL treatment was associated with small dose-related decreases in thyroid hormone levels, particularly total T_4 and free T_4. The reduction in total and free T_4 was maximal within the first 2 to 4 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. About 0.7% (26/3489) of SEROQUEL adult patients experienced TSH increases in monotherapy studies. Six of the patients with TSH increases needed replacement thyroid treatment. In the adult mania adjunct studies, 12% (24/196) of the SEROQUEL treated patients compared to 7% (15/203) placebo treated patients had elevated TSH levels.

In acute placebo-controlled studies in children and adolescent patients with schizophrenia or bipolar mania the incidence of shifts to potentially clinically important thyroid function values at any time for SEROQUEL and placebo treated patients for elevated TSH was 2.9% vs 0.7% respectively, and for decreased total thyroxine was 2.8% vs 0% respectively. Of the SEROQUEL treated patients with elevated TSH levels, 1 had a simultaneous low free T4 level at the end of treatment.

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

Somnolence has been very commonly reported in patients treated with quetiapine. Given its primary central nervous system effects, quetiapine has the potential to impair judgement, thinking or motor skills. Patients likely to drive or operate other machines should therefore be cautioned appropriately.

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 1% [rounded to the nearest percent] of patients treated with SEROQUEL in placebo-controlled Phase-II/III trials where the incidence in patients treated with quetiapine was greater than the incidence in placebo-treated patients are listed in Table 6 regardless of causality.

Table 6 Adverse events that occurred in at least 1% of patients treated with SEROQUEL for schizophrenia in placebo-controlled Phase-II/III trials[1]

Body system/Adverse event[2]	Number (%) of patients with adverse events	
	Quetiapine [n=510]	Placebo [n=206]
Body as a whole		
Headache	19%	18%
Asthenia	4%	3%
Abdominal pain	3%	1%
Back pain	2%	1%
Fever	2%	1%
Nervous system		
Somnolence	18%	11%
Dizziness	10%	4%
Digestive system		
Constipation	9%	5%
Dry mouth	7%	3%
Dyspepsia	6%	2%
γ-GT increased	2%	1%
Cardiovascular system		
Postural hypotension	7%	2%
Tachycardia	7%	5%
Metabolic and nutritional disorders		
ALT increased	6%	2%
AST increased	4%	1%
Weight gain	2%	0%
Skin and appendages		
Rash	4%	3%
Respiratory system		
Rhinitis	3%	1%
Haemic and lymphatic system		
Leukopenia	2%	0%

Body system/Adverse event[2]	Number (%) of patients with adverse events	
	Quetiapine [n=510]	Placebo [n=206]
Special senses		
Ear pain	1%	0%

n=number of patients in treatment group

[1] Events for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: pain, infection, chest pain, hostility, accidental injury, hypertension, hypotension, nausea, vomiting, diarrhoea, myalgia, agitation, insomnia, anxiety, nervousness, akathisia, hypertonia, tremor, depression, paresthesia, pharyngitis, dry skin, amblyopia and urinary tract infection.

[2] Adverse events recorded where the incidence in patients treated with quetiapine was greater than the incidence in placebo-treated patients.

Bipolar I Disorder – Acute Mania (adults)

Adverse events that occurred during the treatment of acute mania in 5% or more of patients treated with SEROQUEL in either the monotherapy or adjunct therapy, placebo controlled trials and observed at a rate of at least twice that of placebo are listed in Table 7 regardless of causality.

Table 7 Adverse events observed in at least 5% of patients treated with SEROQUEL as monotherapy or in combination with a mood stabiliser (lithium or valproate) for acute mania in bipolar I disorder

	Quetiapine monotherapy		Quetiapine adjunct therapy					
			Randomised treatment		Assigned mood stabilizer			
	Number (%) of patients with adverse events							
Event	**QTP N=209**	**PLA N=198**	**QTP+ LI/VAL N=196**	**PLA+ LI/VAL N=203**	**QTP+ LI N=122**	**PLA+ LI N=128**	**QTP+ VAL N=74**	**PLA+ VAL N=75**
Somnolence	16.3%	4.0%	33.7%	9.4%	30.3%	5.5%	39.2%	16.0%
Dry mouth	15.8%	3.0%	19.4%	3.0%	17.2%	3.1%	23.0%	2.7%
Weight gain	9.1%	1.5%	6.1%	2.5%	4.9%	2.3%	8.1%	2.7%
Dizziness	6.7%	2.5%	9.2%	6.4%	4.9%	3.9%	16.2%	10.7%
Asthenia	5.3%	2.0%	9.7%	3.9%	4.9%	3.1%	17.6%	5.3%
Pharyngitis	2.4%	2.0%	5.6%	2.5%	4.1%	2.3%	8.1%	2.7%
Postural hypotension	4.3%	1.5%	6.6%	1.5%	3.3%	0.8%	12.2%	2.7%

PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group.

Bipolar I Disorder – Maintenance (adults)

The safety results of two clinical trials show that SEROQUEL is generally safe and well tolerated when used in combination with lithium or valproate in long-term treatment. Adverse events occurring at an incidence of 5% or more in any randomised treatment group from placebo-controlled clinical trials in patients with

bipolar I disorder treated with SEROQUEL in combination with lithium or valproate as maintenance therapy is summarised by randomised treatment and by assigned mood stabiliser for the combined studies in Table 8 regardless of causality.

Table 8 **Adverse events observed in at least 5%of patients (randomised safety population) treated with SEROQUEL in adjunctive maintenance trials for bipolar I disorder**

	Number (%) of patients with adverse events					
	Randomized treatment		Assigned mood stabilizer			
MedDRA preferred term[a]	QTP+LI/VAL (N=646)	PLA +LI/VAL (N=680)	QTP+LI (N=274)	PLA+LI (N=287)	QTP+VAL (N=372)	PLA+VAL (N=393)
Headache	7.4%	9.3%	9.1%	10.5%	6.2%	8.4%
Nasopharyngitis	7.1%	7.2%	6.6%	7.3%	7.5%	7.1%
Upper respiratory tract infection	6.7%	4.0%	7.7%	4.9%	5.9%	3.3%
Insomnia	6.5%	16.6%	8.0%	19.5%	5.4%	14.5%
Tremor	6.0%	5.0%	5.1%	6.3%	6.7%	4.1%
Nausea	5.9%	7.6%	8.8%	11.8%	3.8%	4.6%
Diarrhoea	2.9%	6.0%	3.3%	8.0%	2.7%	4.6%

[a] Patients with multiple events falling under the same preferred term are counted only once in that term. PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group. MedDRA Medical Dictionary of Regulatory Activities.

Adverse events occurring at an incidence of 5% or more in any randomised treatment group from placebo-controlled clinical trials in patients with bipolar I disorder treated with SEROQUEL as monotherapy maintenance therapy is summarised by randomised treatment in Table 9 regardless of causality.

Table 9 **Adverse events observed in at least 5%of patients (randomised safety population) treated with SEROQUEL in monotherapy maintenance trials for bipolar I disorder**

	Number [n (%)] of patients with adverse events		
MedDRA preferred term [a]	Quetiapine (N=404)	Placebo (N=404)	Lithium (N=418)
Headache	36 (8.9)	32 (7.9)	48 (11.5)
Somnolence	27 (6.7)	17 (4.2)	11 (2.6)
Insomnia	26 (6.4)	69 (17.1)	52 (12.4)
Nausea	18 (4.5)	33 (8.2)	53 (12.7)
Tremor	12 (3.0)	8 (2.0)	31 (7.4)
Diarrhoea	11 (2.7)	21 (5.2)	26 (6.2)
Vomiting	8 (2.0)	12 (3.0)	47 (11.2)

[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. n Number of patients. MedDRA Medical Dictionary of Regulatory Activities

Bipolar Depression (adults)

The safety results of four placebo controlled clinical trials show that SEROQUEL is generally safe and well tolerated when used for treatment of bipolar depression. All four studies contained an 8 week acute phase with 2 of these studies containing a continuation phase of an additional 52 weeks. Adverse events occurring at an incidence of 5% or more in any treatment group in the acute phase for the combined studies are summarised in Table 10 regardless of causality.

Adverse events occurring at an incidence of 5% or more in any treatment group in the continuation phase for the combined studies are summarised in Table 11 regardless of causality.

Table 10 Adverse events observed in at least 5% of patients (safety population) in any treatment group in the acute phase of bipolar depression trials

MedDRA preferred term[a]	Number (%) of patients with adverse events		
	Quetiapine 300 mg N = 853	Quetiapine 600 mg N = 859	Placebo N = 602
Dry mouth	28.4%	29.8%	8.8%
Somnolence	22.6%	21.4%	6.3%
Sedation	18.2%	18.3%	6.0%
Dizziness	12.5%	15.4%	6.3%
Headache	9.4%	9.2%	16.3%
Constipation	7.2%	9.3%	3.0%
Fatigue	6.4%	8.1%	5.5%
Nausea	6.0%	8.3%	10.3%

[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. MedDRA Medical Dictionary of Regulatory Activities.

Table 11 Adverse events (treatment emergent only [b]) observed in at least 5% of patients (safety population) in any treatment group in the continuation phase of bipolar depression trials

MedDRA preferred term[a]	Number (%) of patients with adverse events		
	Quetiapine 300 mg N = 141	Quetiapine 600 mg N = 150	Placebo N = 294
Headache	13.5%	11.3%	9.5%
Nasopharyngitis	9.9%	2.7%	5.4%
Nausea	7.1%	2.0%	3.7%
Diarrhoea	5.7%	0.7%	1.7%
Dry mouth	3.5%	6.0%	1.4%

[a] Patients with multiple events falling under the same preferred term are counted only once in that term.
[b] Events first reported or worsened intensity during continuation phase. N Number of patients in treatment group. MedDRA Medical Dictionary of Regulatory Activities.

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 SEROQUEL. 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 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 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% compared to 4% for placebo. In bipolar depression trials, the proportions of patients meeting the same weight gain criterion were 8% 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 (eg, 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 placebo controlled monotherapy clinical trials in adults, 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 1.72% in patients treated with quetiapine, compared to 0.73% 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 and the incidence ≥0.5 - <1.0 x 10^9/L (moderate neutropenia) was 0.75% (uncommon) in patients treated with quetiapine and 0.11% in placebo-treated patients (see Precautions).

Cholesterol and triglyceride elevations (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 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.

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 (adults)

The following clinical trials 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 long-term studies of schizophrenia and bipolar disorder the aggregated exposure adjusted incidence of treatment-emergent extrapyramidal symptoms was similar between quetiapine and placebo. See Precautions - Extrapyramidal symptoms.

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 12

Frequency	System Organ Class	Reaction
Common	Eye disorders	Vision blurred
(≥1% to <10%)	General disorders and administration site conditions	Peripheral oedema; irritability
	Investigations	Elevations in serum prolactin [3]
	Metabolism & nutritional disorders	Increased appetite
	Nervous system disorders	Syncope [2]; Dysarthria
	Psychiatric disorders	Abnormal dreams and nightmares
Uncommon (≥0.1% to <1%)	Blood and lymphatic system disorders	Eosinophilia
	Gastrointestinal disorders	Dysphagia
	Investigations	Platelet count decreased [1]
	Immune system disorders	Hypersensitivity
	Nervous system disorders	Seizure [2]; Restless legs syndrome; Tardive dyskinesia [2]
Rare (≥0.01% to <0.1%)	General disorders and administration site conditions	Neuroleptic malignant syndrome [2]
	Investigations	Elevations in blood creatine phosphokinase (not associated with neuroleptic malignant syndrome)
	Reproductive system and breast disorders	Priapism

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

Children and adolescents (schizophrenia and acute mania)

The incidence of common (≥5%) adverse events that occurred in children and adolescent (10-17 years) in two short-term treatment placebo-controlled trials in schizophrenia and bipolar mania is listed below in Table 13 regardless of causality.

Table 13 Adverse events that occurred in at least 5% of child/adolescent patients treated with SEROQUEL in short-term schizophrenia and bipolar mania studies (pooled safety analysis set)

	Number (%) of patients with adverse events	
Preferred term	**Quetiapine * (N=340)**	**Placebo (N=165)**
Somnolence	29.4%	8.5%
Sedation	16.2%	4.2%
Dizziness	15.3%	3.6%
Headache	14.7%	17.0%
Fatigue	8.8%	4.2%
Increased appetite	7.6%	2.4%

	Number (%) of patients with adverse events	
Preferred term	**Quetiapine * (N=340)**	**Placebo (N=165)**
Dry mouth	7.1%	0.6%
Insomnia	6.8%	14.5%
Nausea	6.8%	10.3%
Tachycardia	6.8%	0%
Vomiting	6.5%	5.5%
Agitation	5.6%	9.7%
Weight increased	5.0%	1.2%

*400-800 mg/day; N – number of patients

The adverse events ≥5% reported in a 26-week, open-label clinical trial with SEROQUEL in children and adolescents with schizophrenia and bipolar mania were: somnolence (22.9%), headache (18.7%), sedation (14.2%), weight increased (13.4%), vomiting (10.8%), nausea (9.5%), dizziness (8.7%), fatigue (8.2%), insomnia (8.2%), increased appetite (7.1%), upper respiratory tract infection (6.8%), agitation (5.3%), irritability (5.0%), tachycardia (5.0%).

Comparison to adult adverse drug reactions

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	Metabolism & nutrition disorders	Increased appetite
(≥10%)	Investigations	Elevations in serum prolactin [1]; Increases in blood pressure [2]
	Nervous system disorders	Extrapyramidal symptoms [3]

[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

[3] Refer text below

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 SEROQUEL group and -0.4 kg in the placebo group. 21% of SEROQUEL-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 SEROQUEL group and 0.4 kg in the placebo group. 12% of SEROQUEL-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 SEROQUEL. 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).

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 SEROQUEL and 5.3% for placebo, though the incidence of the individual adverse events (eg, 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 SEROQUEL and 1.1% 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 0.9% for both quetiapine (61/6270) and placebo (27/3047).

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.

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 (see Precautions).

Post-marketing experience

Very rare post-marketing cases of anaphylactic reaction and rare post-marketing cases of galactorrhea have been received.

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.

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

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 can be administered with or without food.

Adults

Bipolar disorder

Maintenance treatment

SEROQUEL should be administered twice daily.

Patients who have responded to SEROQUEL 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 (refer Clinical Trials).

The dose of SEROQUEL 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 should be administered once daily at bedtime.

SEROQUEL should be titrated as follows: 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). The dose may be adjusted up to 600 mg/day in increments of 100 mg/day depending on the clinical response and tolerability of the individual patient.

Acute mania

SEROQUEL should be administered twice daily. The total daily dose for the first four days of therapy is 100 mg (Day 1), 200 mg (Day 2), 300 mg (Day 3) and 400 mg (Day 4), alone or in combination with a mood stabiliser. Further dosage adjustments up to 800 mg/day by Day 6 should be in increments of no greater than 200 mg/day.

The dose may be adjusted depending on clinical response and tolerability of the individual patient, within the range of 200 to 800 mg/day. The usual effective dose is in the range of 400 to 800 mg/day.

Schizophrenia

SEROQUEL should be administered twice daily. The total daily dose for the first four days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4).

From Day 4 onwards, the dose should be titrated to the usual effective dose of 300 to 450 mg/day. Depending on the clinical response and tolerability of the individual patient, the dose may be adjusted within the range 150 to 750 mg/day.

Elderly

As with other antipsychotics, SEROQUEL 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, depending on the clinical response and tolerability of the individual patient. The mean plasma clearance of quetiapine was reduced by 30% to 50% in elderly subjects when compared with younger patients.

Children and adolescents

The safety and efficacy of SEROQUEL have been evaluated in children and adolescents 10 to 17 years of age with bipolar mania (as monotherapy), and 13 to 17 years of age with schizophrenia.

SEROQUEL should be administered twice daily. However, SEROQUEL may be administered three times daily based on response and tolerability.

Acute mania - monotherapy (10 to 17 years of age)

The total daily dose for the first five days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3), 300 mg (Day 4) and 400 mg (Day 5). After Day 5, the dose should be adjusted within the effective dose range of 400 to 600 mg/day depending upon the clinical response and tolerability of the patient. Patients should be administered the lowest effective dose. Dosage adjustments should be in increments of no greater than 100 mg/day.

Schizophrenia (13 to 17 years of age)

The total daily dose for the first five days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3), 300 mg (Day 4) and 400 mg (Day 5). After Day 5, the dose should be adjusted within the effective dose range of 400 to 800 mg/day depending upon the clinical response and tolerability of the patient. Patients should be administered the lowest effective dose. Dosage adjustments should be in increments of no greater than 100 mg/day.

Renal impairment

Dosage adjustment is not necessary.

Hepatic impairment

Quetiapine is extensively metabolised by the liver. Therefore, SEROQUEL 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 25 mg/day. The dose should be increased in increments of 25 to 50 mg/day to an effective dose, depending on the clinical response and tolerability of the individual patient.

OVERDOSAGE

In clinical trials, experience with SEROQUEL in overdosage is limited. Estimated doses of quetiapine up to 30 g have been taken, without fatal consequences, and with patients recovering without sequelae, however, death has been reported in a clinical trial following an overdose of 13.6 g of quetiapine alone. In postmarketing experience, there have been very rare reports of overdose of SEROQUEL 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, ie drowsiness and sedation, tachycardia and hypotension.

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.

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 4-Day STARTER PACK contains 25 mg x 6 tablets; 100 mg x 3 tablets and 200 mg x 1 tablet.φ

SEROQUEL 25 mg is presented as a peach coloured round, biconvex, film-coated tablet; 20sφ, 60s

SEROQUEL 100 mg is presented as a yellow coloured round, biconvex, film-coated tablet; 20sφ, 90s

SEROQUEL 150 mgφ is presented as a pale yellow coloured, round, biconvex, film-coated tablet; 60s.

SEROQUEL 200 mg is presented as a white coloured round, biconvex, film-coated tablet; 20sφ, 60s.

SEROQUEL 300 mg is presented as a white coloured, capsoid, film-coated tablet; 20sφ, 60s, 100sφ.

For all strengths except 300 mg, ‘SEROQUEL’ and the strength are impressed on one side and the tablet is plain on the other. The 300 mg tablet has 'SEROQUEL' impressed on one side and '300' on the other. SEROQUEL tablets are presented in a PVC/aluminium foil blister pack.

φ Not marketed

Storage conditions

Store below 30°C

NAME AND ADDRESS OF THE SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road
NORTH RYDE NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Medicine

DATE OF APPROVAL

Date of TGA approval: 3rd March 2010

SEROQUEL and SEROQUEL XR are trademarks of the AstraZeneca group of companies.

Seroquel XR®

quetiapine fumarate

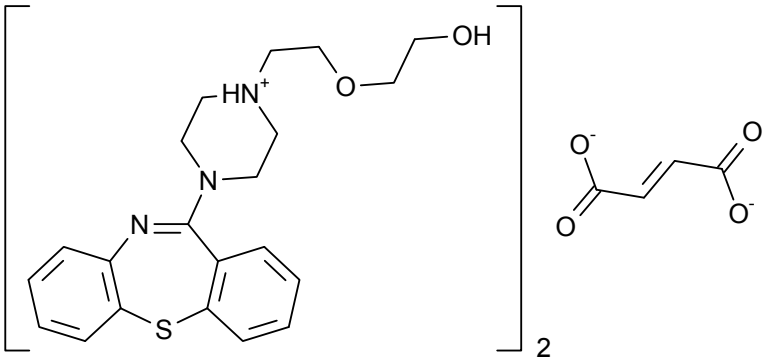
PRODUCT INFORMATION

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, lactose, 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. Additionally, norquetiapine has high affinity (higher than quetiapine) for the noradrenaline transporter, $5HT_{1B}$ and muscarinic receptors. Quetiapine and norquetiapine also have high affinity at histaminergic H_1 and adrenergic α_{1B} and $_{1A}$ receptors, with a lower affinity at adrenergic α_2 and $5HT_{1A}$ receptors. Quetiapine has no appreciable affinity at cholinergic, muscarinic or benzodiazepine receptors. 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.

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 30 mL/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 Administration).

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.

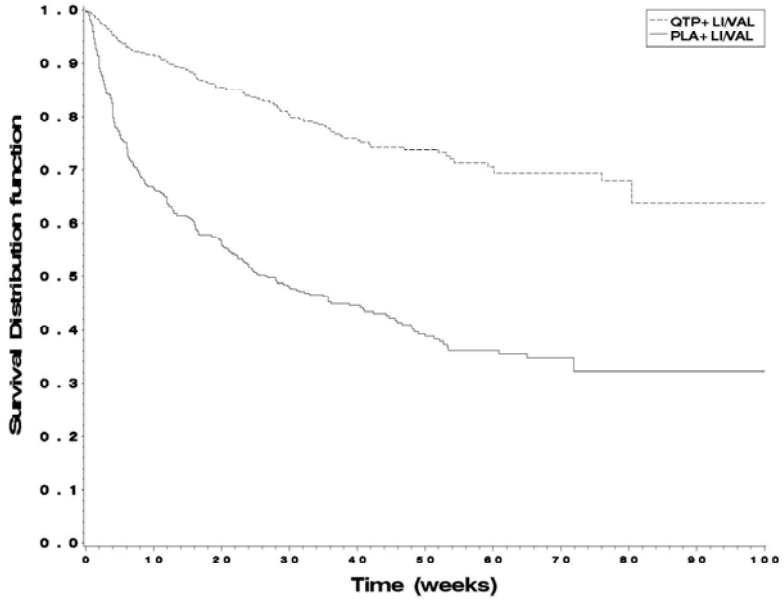
Maintenance treatment in combination with lithium or sodium valproate

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 first recurrence as 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 first recurrence as a depression 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

	Kaplan Meier survival estimate of event rates (%)		
Time to event	**QTP + LI/VAL (N=646)**	**PLA + LI/VAL (N=680)**	**p value**
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 to Table 2).

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

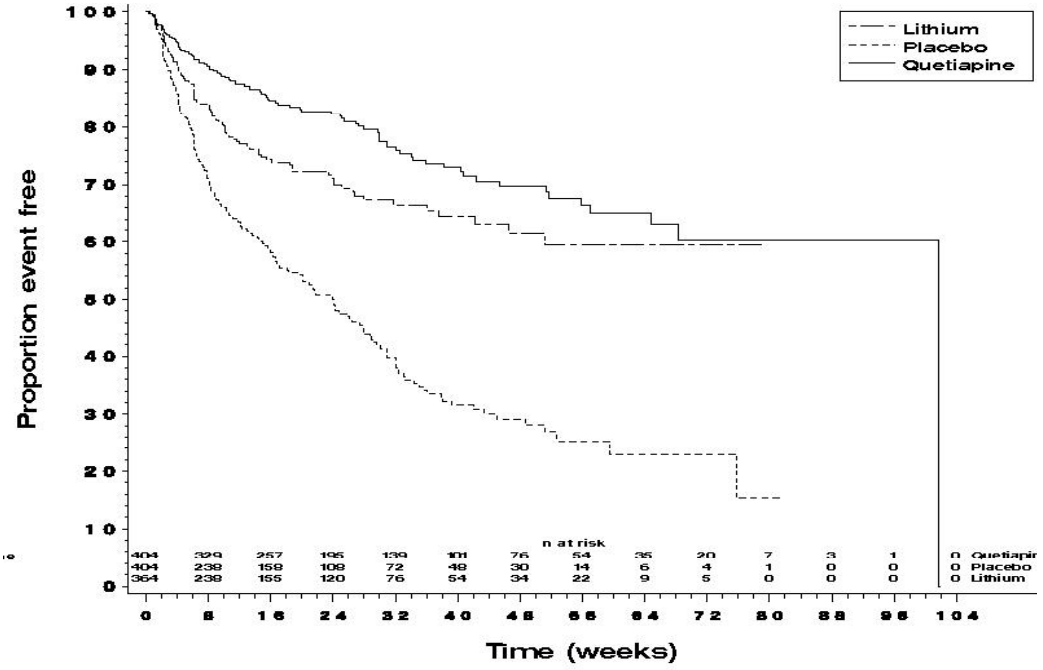
Maintenance treatment as monotherapy

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 depressed events (refer Table 3). Efficacy was demonstrated to be independent of the nature of the most recent episode (manic, mixed or depressed), rapid cycling course, gender, age or ethnicity.

Figure 2 Time to relapse/recurrence of a mood event, manic event and depressed 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 depressed 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

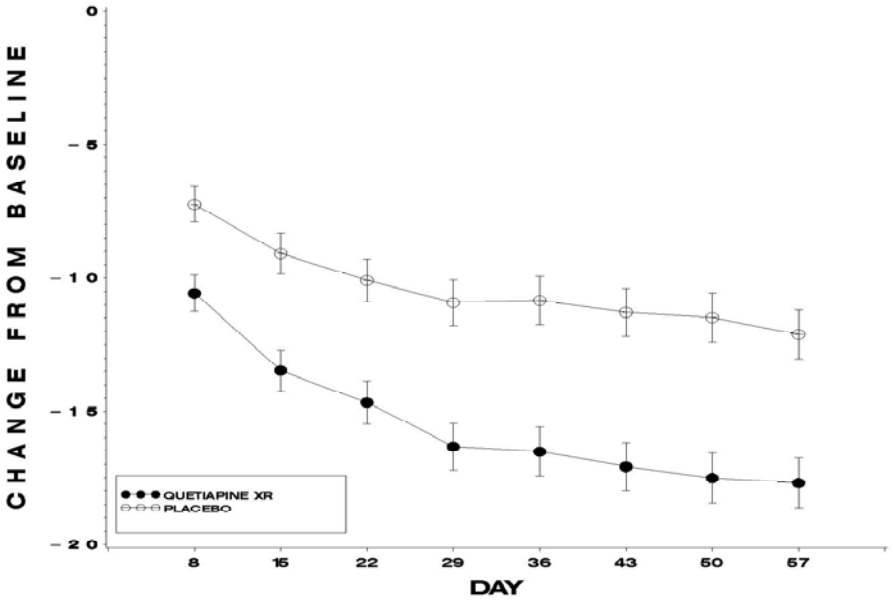
ITT Intent-to-treat. PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group.

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)

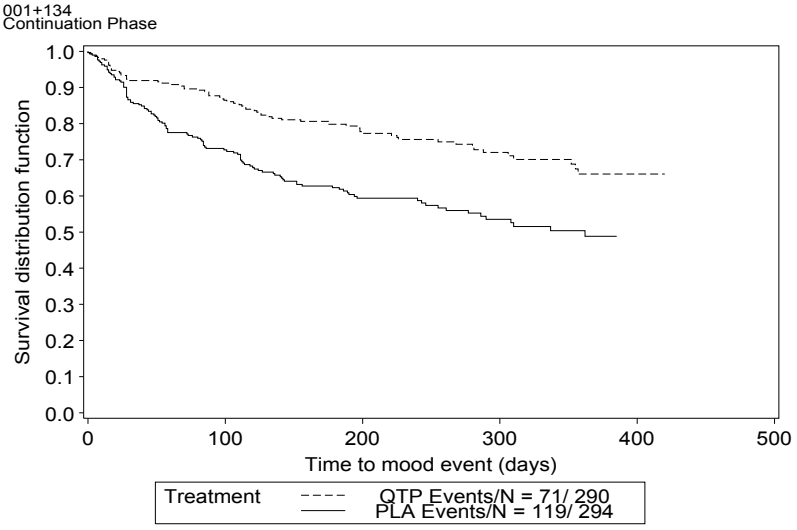


CI Confidence interval; LOCF Last observation carried forward; LS Least square; MITT Modified Intention to Treat; XR Extended-release; MADRS Montgomery-Asberg Depression Rating Scale.

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 depressed event at weeks 26 and 52 compared to patients on placebo. The analysis of time to a depressed event mirrored the overall mood event results with patients on quetiapine having a 57% less risk of experiencing a depressed event compared with patients treated with placebo (HR 0.43, 95% CI 0.30, 0.62, p<0.001). The risk of a depressed 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 depressed 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 (ie I or II), gender or age.

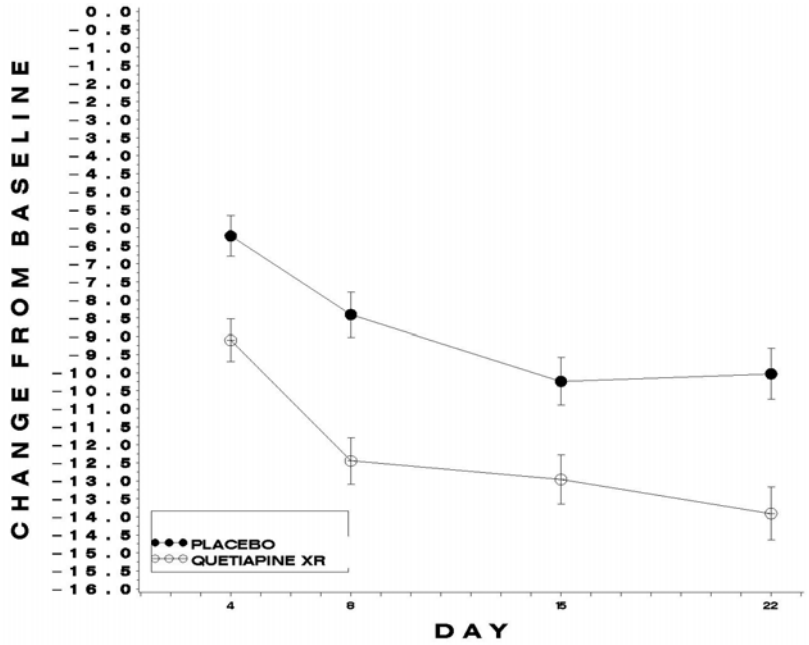
There was no increased risk of suicidal behaviour or ideation associated with quetiapine treatment for bipolar depression in either the acute or continuation phase.

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	-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	-13.6	[-15.2; -12.0]	0.067
	Quetiapine XR 300	-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	-15.3	[-16.7; -13.9]	0.003
	Quetiapine XR 300	-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	-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

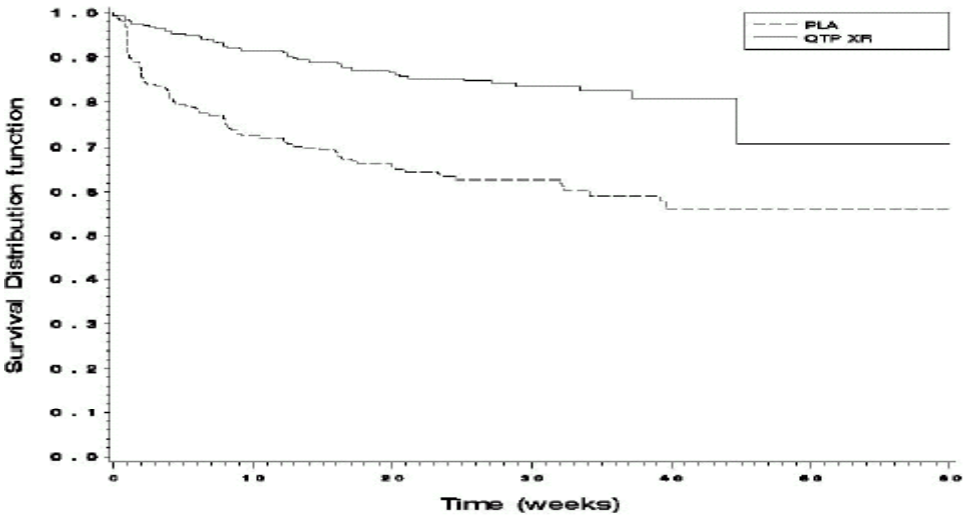
The safety and efficacy of SEROQUEL XR was evaluated in an 11-week, double-blind, randomised, placebo-controlled study in non-demented elderly patients (aged 66-89 years) with MDD. The mean dose of SEROQUEL XR was 160 mg/day. SEROQUEL XR flexibly dosed in the range of 50 to 300 mg per day demonstrated 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 depressed 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 depressed 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 depressed 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 depressed 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.

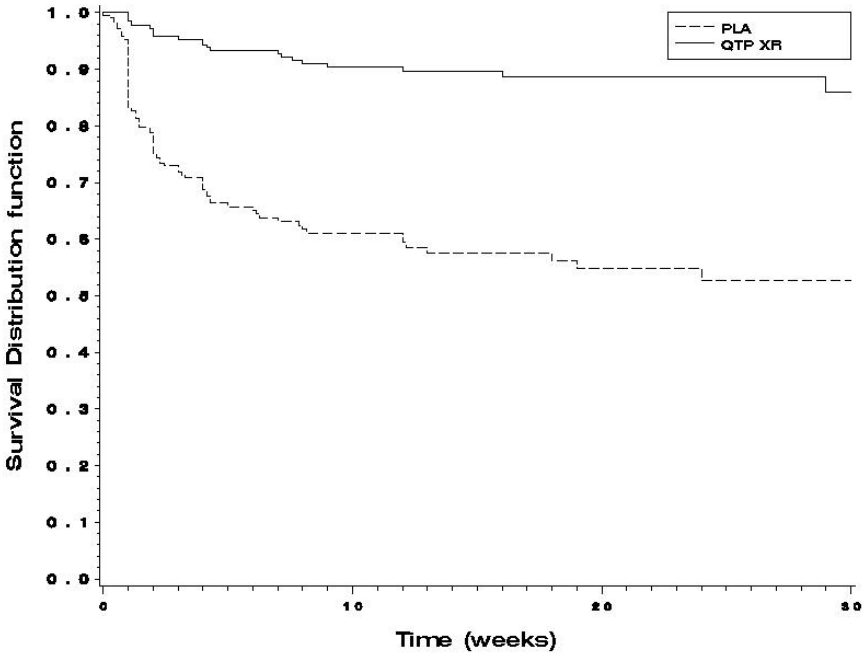
Maintenance treatment of anti-anxiety effects

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 (ie, 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 3 week trial in schizophrenia (patients aged 13-17 years) and a 6 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

SEROQUEL XR 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).

SEROQUEL XR 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 SEROQUEL XR, 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). 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. Also caution should be exercised when quetiapine is prescribed with medicines known to prolong the QTc interval, and concomitant neuroleptics, especially the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia (see Interactions with other medicines).

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

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 of adult patients with 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).

Tardive dyskinesia

SEROQUEL XR 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 SEROQUEL XR 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, SEROQUEL XR 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 SEROQUEL XR 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

Severe neutropenia (<0.5 x 10^9/L) has been uncommonly reported in quetiapine clinical trials. Most 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) and history of drug induced neutropenia. Quetiapine should be discontinued in patients with a neutrophil count <1.0 x 10^9/L. These patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed 1.5 x 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).

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.

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 SEROQUEL (quetiapine) immediate release. 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 (eg heart failure, sudden death) or infectious (eg pneumonia) in nature. SEROQUEL XR 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. SEROQUEL XR and other antipsychotic medicines should be used cautiously in patients at risk for aspiration pneumonia (eg elderly patients).

Lipids

Increases in triglycerides and 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 increases should be managed as clinically appropriate.

Lactose

SEROQUEL XR tablets contain lactose. 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.

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 pregnancy – Category B3

The safety and efficacy of quetiapine during human pregnancy have not been established. Therefore, SEROQUEL XR should only be used during pregnancy if the benefits justify the potential risks.

Use in lactation

The degree to which quetiapine is excreted into human milk is unknown, however 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 SEROQUEL XR.

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 SEROQUEL 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 SEROQUEL 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 SEROQUEL, are not available for children and adolescents (10 to 17 years of age).

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.

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).

Interactions with other medicines

Antipsychotic and other centrally acting medicines

Given the primary central nervous system effects of quetiapine, SEROQUEL XR 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, SEROQUEL XR 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 SEROQUEL XR 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 SEROQUEL XR 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 (e.g. 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 SEROQUEL XR may

be required to maintain control of psychotic symptoms in patients co-administered SEROQUEL XR 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 SEROQUEL XR 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 SEROQUEL XR, 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 SEROQUEL XR is used concomitantly with medicines known to cause electrolyte imbalance or to increase QTc interval (see Precautions – QT interval).

Because of it's potential for inducing hypotension, SEROQUEL XR 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.

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).

Triglycerides and cholesterol

Small elevations in non-fasting serum triglyceride levels and total cholesterol (predominantly LDL cholesterol) have been observed during treatment with quetiapine (see Adverse effects).

Thyroid hormone levels

Quetiapine treatment was associated with small dose-related decreases in thyroid hormone levels, particularly total T_4 and free T_4. The reduction in total and free T_4 was maximal within the first 2 to 4 weeks of quetiapine treatment, with no further reduction during long-term treatment. There was no evidence of clinically significant changes in thyrotropin (thyroid stimulating hormone, TSH) concentration over time. 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.

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.

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	
MedDRA 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
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 11 regardless of causality.

Table 11 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	
MedDRA 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 12 (pooled non-elderly short term trials) and 13 (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 12 **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				
MedDRA preferred term	**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

Table 13 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	
MedDRA preferred term[a]	**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 (eg, 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 placebo controlled monotherapy clinical trials in adults, among patients with a baseline neutrophil count $\geq 1.5 \times 10^9$/L, the incidence of at least one occurrence of neutrophil count $< 1.5 \times 10^9$/L was 1.72% in patients treated with quetiapine, compared to 0.73% in placebo-treated patients. In clinical trials conducted prior to a protocol amendment for discontinuation of patients with treatment-emergent neutrophil count $< 1.0 \times 10^9$/L, among patients with a baseline neutrophil count $\geq 1.5 \times 10^9$/L, the incidence of at least one occurrence of neutrophil count $< 0.5 \times 10^9$/L (severe neutropenia) was 0.21% (uncommon) in patients treated with quetiapine and 0% in placebo treated patients and the incidence ≥ 0.5 - $< 1.0 \times 10^9$/L (moderate neutropenia) was 0.75% (uncommon) in patients treated with quetiapine and 0.11% in placebo-treated patients (see Precautions).

Cholesterol and triglyceride elevations (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.

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 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 (eg 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 Precautions - Extrapyramidal symptoms.

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 reactionsIn 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 14

Frequency	System Organ Class	Reaction
Common	Eye disorders	Vision blurred
(≥1% to <10%)	Cardiac disorders	Tachycardia[2]
	General disorders and administration site conditions	Mild asthenia; Peripheral oedema; irritability
	Investigations	Elevations in serum transaminases (ALT, AST)[2]; Elevations in serum prolactin[3]
	Nervous system disorders	Syncope[2]; Dysarthria
	Metabolism & nutritional disorders	Increased appetite
	Respiratory, thoracic and mediastinal disorders	Rhinitis
	Psychiatric disorders	Abnormal dreams and nightmares
Uncommon (≥0.1% to <1%)	Blood and lymphatic system disorders	Eosinophilia
	Gastrointestinal disorders	Dysphagia
	Investigations	Elevations in γ-GT levels[2]; Platelet count decreased[1]
	Immune system disorders	Hypersensitivity
	Nervous system disorders	Seizure[2]; Restless legs syndrome; Tardive dyskinesia[2]
Rare (≥0.01% to <0.1%)	General disorders and administration site conditions	Neuroleptic malignant syndrome[2]
	Investigations	Elevations in blood creatine phosphokinase (not associated with neuroleptic malignant syndrome)
	Reproductive system and breast disorders	Priapism

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

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; administered as SEROQUEL immediate release tablets) than in the adult population, or adverse drug reactions that have not been identified in the adult population.

Table 15

Frequency	System Organ Class	Reaction
Very common (≥10%)	Metabolism & nutrition disorders	Increased appetite
	Investigations	Elevations in serum prolactin [1]; Increases in blood pressure [2]
	Nervous system disorders	Extrapyramidal symptoms [3]

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

3 Refer text below

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 SEROQUEL group and -0.4 kg in the placebo group. 21% of SEROQUEL-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 SEROQUEL group and 0.4 kg in the placebo group. 12% of SEROQUEL-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 SEROQUEL. 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).

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 SEROQUEL and 5.3% for placebo, though the incidence of the individual adverse events (eg, 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 SEROQUEL and 1.1% 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 0.9% for both quetiapine (61/6270) and placebo (27/3047).

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.

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% for quetiapine (0/178) and 1.0% for placebo (1/101) in patients 18-24 years of age and 0.6% for quetiapine (8/1391) and 0.2% for placebo (1/564) in patients ≥ 25 years of age. There have been no trials conducted in patients <18 years of age with GAD (see Precautions).

Post-marketing experience

Very rare post-marketing cases of anaphylactic reaction and rare post-marketing cases of galactorrhea have been received.

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.

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

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 (refer 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 have not been evaluated in patients under 18 years of age, 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, ie drowsiness and sedation, tachycardia and hypotension.

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.

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 for the 50 mg, 150 mg, 200 mg or 400 mg tablets.

150 mg strength only. Not supplied in Australia

not supplied in Australia for the 150 mg tablets

Storage conditions

Store below 30°C.

NAME AND ADDRESS OF SPONSOR

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POISONS SCHEDULE OF THE MEDICINE

S4 – Prescription Medicine

DATE OF APPROVAL

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