

## **NEW ZEALAND DATA SHEET**

### **NAME OF MEDICINE**

SEROQUEL XR™

Quetiapine fumarate 50 mg, 150 mg, 200 mg, 300 mg, 400 mg

### **PRESENTATION**

SEROQUEL XR 50 mg is presented as a peach coloured, biconvex capsule shaped, modified release tablet containing quetiapine fumarate delivering a dose of 50 mg of quetiapine free base. The tablets are 16.24 mm x 6.52 mm. XR and the strength are impressed on one side and the tablet is plain on the other.

SEROQUEL XR 150 mg is presented as a white coloured, biconvex capsule shaped, modified release tablet containing quetiapine fumarate delivering a dose of 150 mg of quetiapine free base. The tablets are 17.22 mm x 6.65 mm. XR and the strength are impressed on one side and the tablet is plain on the other.

SEROQUEL XR 200 mg is presented as a yellow coloured, biconvex capsule shaped, modified release tablet containing quetiapine fumarate delivering a dose of 200 mg of quetiapine free base. The tablets are 17.22 mm x 6.65 mm. XR and the strength are impressed on one side and the tablet is plain on the other.

SEROQUEL XR 300 mg is presented as a pale-yellow coloured, biconvex capsule shaped, modified release tablet containing quetiapine fumarate delivering a dose of 300 mg of quetiapine free base. The tablets are 19 mm x 7.62 mm. XR and the strength are impressed on one side and the tablet is plain on the other.

SEROQUEL XR 400 mg is presented as a white coloured, biconvex capsule shaped, modified release tablet containing quetiapine fumarate delivering a dose of 400 mg of quetiapine free base. The tablets are 19 mm x 7.62 mm. XR and the strength are impressed on one side and the tablet is plain on the other.

### **USES**

#### **ACTIONS**

##### **Mechanism of action**

Quetiapine is an atypical antipsychotic agent. Quetiapine and the active human plasma metabolite, norquetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and norquetiapine exhibit affinity for brain serotonin (5HT<sub>2</sub>) and dopamine D<sub>1</sub> and D<sub>2</sub> receptors. It is this combination of receptor antagonism with a higher selectivity for 5HT<sub>2</sub> relative to dopamine D<sub>2</sub> receptors which 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 for the noradrenaline transporter (NET). Quetiapine and norquetiapine also have high affinity at histaminergic and adrenergic  $\alpha_1$  receptors, with a lower affinity at adrenergic  $\alpha_2$  and serotonin 5HT<sub>1A</sub> receptors. Quetiapine has no appreciable affinity at cholinergic muscarinic or benzodiazepine receptors.

### **Pharmacodynamic effects**

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 dopamine D<sub>2</sub> receptor blockade.

In pre-clinical tests predictive of EPS, quetiapine is unlike typical antipsychotics and has an atypical profile. Quetiapine does not produce dopamine D<sub>2</sub> receptor supersensitivity after chronic administration. Quetiapine produces only weak catalepsy at effective dopamine D<sub>2</sub> receptor blocking doses. Quetiapine demonstrates selectivity for the limbic system by producing depolarisation blockade of the A10 mesolimbic but not the A9 nigrostriatal dopamine-containing neurones following chronic administration. Quetiapine exhibits minimal dystonic liability in haloperidol-sensitised or drug-naïve Cebus monkeys after acute and chronic administration.

### **Clinical efficacy**

#### Schizophrenia

The efficacy of SEROQUEL XR in the treatment of schizophrenia was demonstrated in one 6-week placebo-controlled trial in patients who met DSM-IV criteria for schizophrenia, and one active-controlled SEROQUEL<sup>®</sup> immediate release (SEROQUEL IR)-to-SEROQUEL XR switching study in clinically stable outpatients with schizophrenia.

The primary outcome variable in the placebo-controlled trial was change from baseline to final assessment in the Positive and Negative Syndrome Scale (PANSS) total score. 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 were greater than that of the 400 mg dose.

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 randomisation to any visit. In patients stabilised on SEROQUEL IR 400 mg to 800 mg, efficacy was maintained when patients were switched to an equivalent daily dose of SEROQUEL XR given once daily.

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%) 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.

### Bipolar Mania

In a clinical trial, SEROQUEL XR has been shown to be effective as monotherapy in reducing manic symptoms in patients with bipolar mania at doses between 400 and 800 mg/day. The effect of SEROQUEL XR was significant at Day 4 and was maintained through the end of the trial (Week 3).

In clinical trials, quetiapine (SEROQUEL) has been shown to be effective as monotherapy or as adjunct therapy in reducing manic symptoms in patients with bipolar mania. The mean last week median dose of quetiapine in responders, was approximately 600 mg and approximately 85% of the responders were in the dose range of 400 to 800 mg/day.

### Bipolar Depression

In a clinical trial, which included patients who are bipolar I, bipolar II and patients with and without rapid cycling courses, SEROQUEL XR has been shown to be effective in patients with bipolar depression at doses of 300 mg/day. SEROQUEL XR was superior to placebo in reduction of MADRS total score. The antidepressant effect of SEROQUEL XR was significant at Day 8 (Week 1) and was maintained through the end of the trial (Week 8).

In two clinical trials, which included patients who are bipolar I, bipolar II and patients with and without rapid cycling courses, SEROQUEL has been shown to be effective in patients with bipolar depression at doses of 300 and 600 mg/day, however, no additional benefit was seen with the 600 mg dose during short-term treatment.

In both studies, SEROQUEL was superior to placebo in reduction of MADRS total score. The antidepressant effect of SEROQUEL was significant at Day 8 (Week 1) and was maintained through the end of the studies (Week 8). Treatment with either SEROQUEL 300 or 600 mg at bedtime reduced depressive symptoms and anxiety symptoms in patients with bipolar depression. There were fewer episodes of treatment emergent mania with either dose of SEROQUEL than with placebo. For the 300 mg dose group, statistically significant improvements over placebo were seen in reductions in suicidal thinking as measured by MADRS item 10 and overall quality of life and satisfaction related to various areas of functioning, as measured using the Q-LES-Q (SF).

In two bipolar depression clinical trials with SEROQUEL, maintenance of antidepressant efficacy was established. These trials included an 8-week placebo-controlled acute phase, followed by a placebo-controlled continuation phase of at least 26 weeks but up to 52-weeks in duration. Patients were required to be stable at the end of the acute phase in order to be randomized into continuation phase. In both trials, SEROQUEL was superior to placebo in increasing the time to recurrence of any mood event (depressed, mixed or manic). The risk reduction from the pooled trials was 49%. 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.

### Preventing Recurrence in Maintenance Treatment of Bipolar Disorder

The efficacy of SEROQUEL in the monotherapy treatment for recurrence prevention was established in 1 placebo-controlled trial in 1226 patients who met DSM-IV criteria for Bipolar I Disorder. The trial included patients whose most recent mood episode was manic, mixed, or depressive, with or without psychotic features. In the open-label phase, patients were required to be stabilized on SEROQUEL for a minimum of 4 weeks in order to be randomized. In the randomization phase, patients either continued treatment with SEROQUEL (300 to 800 mg per day: average dose 546 mg per day ) or were to receive lithium or placebo for up to 104 weeks. SEROQUEL was superior to placebo in increasing the time to recurrence of any

mood event (manic, mixed, or depressive), the primary endpoint. The risk reductions were 74%, 73%, and 75% for mood, manic and depressive events, respectively.

The efficacy of SEROQUEL in the combination treatment for recurrence prevention was established in 2 placebo-controlled trials in 1326 patients who met DSM-IV criteria for Bipolar I Disorder. The trials included patients whose most recent mood episode was manic, mixed, or depressive, with or without psychotic features. In the open-label phase, patients were required to be stabilised on SEROQUEL in combination with mood stabilizer (lithium or valproate) for a minimum of 12 weeks in order to be randomized. In the randomisation phase, patients either continued treatment with SEROQUEL (400 to 800 mg per day average dose 507 mg per day) in combination with mood stabiliser or received placebo in combination with mood stabiliser for up to 104 weeks. SEROQUEL was superior to placebo in increasing the time to recurrence of any mood event (manic, mixed or depressive), the primary endpoint. The risk reductions were 70%, 67%, and 74% for mood, manic and depressive events, respectively.

### Generalised Anxiety Disorder

In clinical trials, SEROQUEL XR has been shown to be effective as monotherapy for the treatment of patients who met DSM-IV criteria for generalised anxiety disorder.

Three short-term (8 week) monotherapy trials, randomised 2678 patients who had a mean Hamilton Rating Scale for Anxiety (HAM-A) total score of 26 at enrolment. SEROQUEL XR at doses of 50 mg, 150 mg, and 300 mg demonstrated superiority over placebo in reducing anxiety symptoms as measured by improvement in the HAM-A total score at week 8. SEROQUEL XR was superior to placebo in reducing psychic symptoms at all doses and somatic symptoms at the 150 mg dose. Statistically significant improvements of symptoms of generalised anxiety disorder as measured by change in HAM-A total score was observed by day 4. SEROQUEL XR also demonstrated improvement in depressive symptoms as measured by the MADRS total score (mean total score at enrolment was  $\leq 16$ ). Statistically significant improvements in the 150 mg dose group were also seen in quality of life and satisfaction related to various areas of functioning, as measured using the Q-LES-Q (SF). Superior improvements at all doses were seen in sleep symptoms, as measured with the PSQI global score. The majority of the patients were dosed once daily with SEROQUEL XR 150 mg.

In a relapse prevention study, patients (n=433 randomised patients) responding to at least 12 weeks of acute open-label treatment with SEROQUEL XR were randomised to either SEROQUEL XR once daily or placebo for up to 52 weeks. SEROQUEL XR was more effective than placebo in preventing relapse. The risk of relapse was 10.2% for quetiapine XR-treated patients and 38.9% for placebo-treated patients. The mean dose was 163 mg/day.

In non-demented elderly patients (aged 66 to 86 years) SEROQUEL XR dosed flexibly in the range of 50 mg to 300 mg per day demonstrated superiority over placebo in reducing anxiety symptoms as measured by improvement in HAM-A total score. In this study patients randomised to SEROQUEL XR received 50 mg/day on Days 1-3, the dose could be increased to 100 mg/day on Day 4, 150 mg/day on Day 8 and up to 300 mg/day depending on clinical response and tolerability. The tolerability of SEROQUEL XR once daily in elderly patients was comparable to that seen in adults (aged 18-65 years). The proportion of randomised patients over 75 years of age was 13%. The mean dose of SEROQUEL XR was 168 mg/day.

### Suicide/suicidal thoughts or clinical worsening

In short-term placebo-controlled clinical trials across all indications and ages, the incidence of suicide-related events was 0.8% for both quetiapine (75/9238) and for placebo (37/4745).

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  $\geq$  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 (5/463) in patients  $\geq$  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  $\geq$  25 years of age. There have been no trials conducted in patients <18 years of age with bipolar depression.

#### Cataracts / lens opacities

In a clinical trial to evaluate the cataractogenic potential of SEROQUEL versus risperidone in the long-term treatment of patients with schizophrenia of schizoaffective disorder, SEROQUEL at doses of 200-800 mg/day was non-inferior for the 2-year event rate of increase in LOCS II (Lens Opacities Classification System II) lens opacity grade (Nuclear opalescence, Cortical, and Posterior subcapsular standards for LOCS II) to risperidone at doses of 2 to 8 mg/day for patients with at least 21 months of exposure (see FURTHER INFORMATION).

## **PHARMACOKINETICS**

### **General:**

Quetiapine is well absorbed and extensively metabolised following oral administration. 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 dosing range. The kinetics of quetiapine does not differ between men and women.

SEROQUEL XR achieves peak plasma concentrations at approximately 6 hours after administration ( $T_{max}$ ). SEROQUEL XR displays dose-proportional pharmacokinetics for doses 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 (SEROQUEL) administered twice daily. When SEROQUEL XR administered once daily is compared to the same total daily dose of immediate-release quetiapine fumarate (SEROQUEL) administered twice daily, the area under the quetiapine plasma concentration-time curve (AUC) is equivalent, but the maximum plasma concentration ( $C_{max}$ ) is 13% lower. When SEROQUEL XR administered once daily is compared to the same total daily dose of the immediate release formulation of quetiapine (SEROQUEL) administered once daily, the quetiapine XR AUC is equivalent; and  $C_{max}$  is 59% lower. The AUC and ( $C_{max}$ ) for the metabolite norquetiapine are 18% and 37% lower than for SEROQUEL, respectively.

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

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

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.

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<sup>2</sup>) but the individual clearance values are within the range for normal subjects. The average molar dose fraction of free quetiapine and the active human plasma metabolite norquetiapine is <5% excreted in the urine.

### **Metabolism:**

Quetiapine is extensively metabolised by the liver with parent compound accounting for less than 5% of unchanged drug-related material in the urine or faeces, following the administration of radiolabelled quetiapine. Approximately 73% of the radioactivity is excreted in the urine and 21% in the faeces. The mean plasma clearance of quetiapine is reduced by approximately 25% in subjects with hepatic impairment (stable alcoholic cirrhosis). 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).

*In vitro* investigations established that CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. Norquetiapine is primarily formed and eliminated via CYP3A4.

Quetiapine and several of its metabolites (including norquetiapine) were found to be weak inhibitors of human cytochrome P450 1A2, 2C9, 2C19, 2D6 and 3A4 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 SEROQUEL XR with other medicines will result in clinically significant drug inhibition of cytochrome P450 mediated metabolism of the other medicine.

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<sub>max</sub> and AUC of 44% to 52% and 20% to 22%, respectively, for the 50 mg and 300 mg tablets. In comparison, a light meal had no significant effect on the C<sub>max</sub> or AUC of quetiapine. This increase in exposure is not clinically significant, and therefore SEROQUEL XR can be taken with or without food.

### **INDICATIONS**

SEROQUEL XR is indicated for the treatment of:

- Schizophrenia.
- Preventing relapse in stable patients with schizophrenia who have been maintained on SEROQUEL XR.
  
- Bipolar Disorder including:
  - manic episodes associated with bipolar disorder
  - depressive episodes associated with bipolar disorder
  - preventing recurrence in maintenance treatment of bipolar disorder (manic, mixed or depressive episode) as monotherapy or in combination with mood

stabilizers

- Generalised Anxiety Disorder
- Preventing relapse in stable patients with generalised anxiety disorder who have been maintained on SEROQUEL XR

### **DOSAGE AND ADMINISTRATION**

SEROQUEL XR should be administered once daily, with or without food. The tablets should be swallowed whole and not split, chewed or crushed.

### **ADULTS**

#### **For the treatment of 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 effective dose range of 400 mg to 800 mg per day, depending on the clinical response and tolerability of the patient. For maintenance therapy in schizophrenia no dosage adjustment is necessary.

#### **For the treatment of manic episodes associated with bipolar disorder**

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 effective dose range of 400 mg to 800 mg per day, depending on the clinical response and tolerability of the patient.

#### **For the treatment of depressive episodes associated with bipolar disorder:**

SEROQUEL XR should be administered once daily in the evening.

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.

Antidepressant efficacy was demonstrated with SEROQUEL at 300 mg and 600 mg however no additional benefit was seen in the 600 mg group during short term treatment. (See CLINICAL EFFICACY – BIPOLAR DEPRESSION and ADVERSE EFFECTS).

#### **For preventing recurrence in maintenance treatment of bipolar disorder**

Patients who have responded to SEROQUEL XR for acute treatment of bipolar disorder should continue on SEROQUEL XR therapy at the same dosing regimen. SEROQUEL XR dose can be re-adjusted depending on clinical response and tolerability of the individual patient within the dose range of 300 mg to 800 mg/day.

#### **For the treatment of generalised anxiety disorder:**

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. 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.

For maintenance therapy in generalised anxiety disorder 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 patient.

**Switching from SEROQUEL immediate-release (SEROQUEL IR) tablets:**

For more convenient dosing, patients who are currently being treated with divided doses of SEROQUEL IR (immediate release tablets) may be switched to SEROQUEL XR at the equivalent total daily dose taken once daily. 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 of SEROQUEL XR 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 major depressive disorder or generalised anxiety disorder 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 (see USES).

**CHILDREN AND ADOLESCENTS**

SEROQUEL XR is not indicated for use in children and adolescents below 18 years of age. Data from SEROQUEL placebo-controlled studies are detailed within the data sheet (see WARNINGS and PRECAUTIONS, ADVERSE EFFECTS).

**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.

**CONTRAINDICATIONS**

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

**WARNINGS AND PRECAUTIONS**

**SUICIDE/SUICIDAL THOUGHTS OR CLINICAL WORSENING**

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which quetiapine is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. An FDA meta-analysis of placebo-controlled clinical trials of antidepressant drugs in approximately 4,400 children and adolescents and 77,000 adult patients with psychiatric disorders showed an increased risk of suicidal behavior with antidepressants compared to placebo in children, adolescents, and young adult patients less than 25 years old. This meta-analysis did not include trials involving quetiapine. (see PHARMACODYNAMIC PROPERTIES).

### **CONCOMITANT ILLNESS**

SEROQUEL XR should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension. Quetiapine may induce orthostatic hypotension especially during the initial dose-titration period.

Dysphagia (see ADVERSE EFFECTS) and aspiration have been reported with SEROQUEL XR. Although a causal relationship with aspiration pneumonia has not been established, SEROQUEL XR should be used with caution in patients at risk for aspiration pneumonia.

### **SEIZURES**

In controlled clinical trials there was no difference in the incidence of seizures in patients treated with SEROQUEL XR or placebo. As with other antipsychotics, caution is recommended when treating patients with a history of seizures (see ADVERSE EFFECTS).

### **TARDIVE DYSKINESIA AND EXTRAPYRAMIDAL SYMPTOMS (EPS)**

Tardive dyskinesia is a syndrome of potentially irreversible, involuntary, dyskinetic movements that may develop in patients treated with antipsychotic medicines including quetiapine. 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).

In placebo-controlled clinical trials for schizophrenia and bipolar mania, the incidence of EPS was no different from that of placebo across the recommended therapeutic dose range. This predicts that quetiapine has less potential than typical antipsychotic agents to induce tardive dyskinesia in schizophrenia and bipolar mania patients. In short-term, placebo-controlled clinical trials for bipolar depression, major depressive disorder and generalised anxiety disorder 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).

### **NEUROLEPTIC MALIGNANT SYNDROME**

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

**QT PROLONGATION**

In clinical trials quetiapine was not associated with a persistent increase in absolute QT intervals. However, in post-marketing experience there were cases reported of QT prolongation with overdose (see OVERDOSAGE). As with other antipsychotics, caution should be exercised when quetiapine is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also caution should be exercised when quetiapine is prescribed either with medicines known to increase QT interval or with concomitant neuroleptics, especially for patients with increased risk of QT prolongation, i.e. the elderly, patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia, or hypomagnesaemia (see INTERACTIONS).

**NEUTROPENIA**

Severe neutropenia ( $<0.5 \times 10^9/L$ ) 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  $<1.0 \times 10^9/L$ . These patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed  $1.5 \times 10^9/L$ ). See ADVERSE EFFECTS.

**WITHDRAWAL**

Acute withdrawal symptoms such as insomnia, nausea and vomiting 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.

**HYPERGLYCAEMIA AND DIABETES MELLITUS**

Increases in blood glucose and hyperglycaemia, and occasional reports of diabetes, have been observed in clinical trials with quetiapine. Although a causal relationship with diabetes has not been established, patients who are at risk for developing diabetes are advised to have appropriate clinical monitoring. Similarly, patients with existing diabetes should be monitored for possible exacerbation (see ADVERSE EFFECTS).

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 (eg. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at baseline 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 antidiabetic treatment despite discontinuation of the suspect drug.

**LIPIDS**

Increases in triglycerides and cholesterol, and decreases in HDL have been observed in clinical trials with quetiapine (see ADVERSE EFFECTS). Lipid changes should be managed as clinically appropriate.

**METABOLIC FACTORS**

In some patients, a worsening of more than one of the metabolic factors of weight, blood glucose and lipids was observed in clinical studies. Changes in these parameters should be managed as clinically appropriate.

**CHILDREN AND ADOLESCENTS (10 TO 17 YEARS OF AGE)**

SEROQUEL XR is not indicated for use in children and adolescents below 18 years of age. Although not all adverse reactions that have been identified in adult patients have been observed in clinical trials in children and adolescent patients, the same warnings and precautions for use that appear for adults should be considered for paediatrics. Additionally, changes in blood pressure and thyroid function tests and increases in weight and prolactin levels have been observed and should be managed as clinically appropriate (see ADVERSE EFFECTS).

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

**SAFETY EXPERIENCE IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS**

Seroquel XR is not approved for the treatment of dementia-related psychosis.

An approximately 3-fold increase of cerebrovascular adverse events has been seen in randomised placebo-controlled clinical trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Quetiapine should be used with caution in patients with risk factors for stroke.

In a meta-analysis of atypical antipsychotic medicines, it has been reported that elderly patients with dementia-related psychosis are at an increased risk of death compared to placebo.

In two 10-week placebo-controlled quetiapine studies in elderly patients (n=710; mean age: 83 years; range: 56-99 years) with dementia-related psychosis, the incidence of death in quetiapine-treated patients was 5.5% vs. 3.2 % in the placebo group. The patients in these trials died from a variety of causes that were consistent with expectations for this population. These data do not establish a causal relationship between quetiapine treatment and death in elderly patients with dementia.

**INTERACTIONS**

Also see INTERACTIONS section below.

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

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 XR 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.

### USE IN PREGNANCY

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

There have been published reports of quetiapine excretion into human breast milk, however the degree of excretion was not consistent. Women who are breast-feeding should therefore be advised to avoid breast-feeding while taking SEROQUEL XR.

### EFFECT ON ABILITY TO DRIVE AND USE MACHINES

Given its primary central nervous system effects, quetiapine may interfere with activities requiring mental alertness. Therefore, patients should be advised not to drive or operate machinery, until individual susceptibility is known.

### ADVERSE EFFECTS

The most commonly reported Adverse Drug Reactions (ADRs) with quetiapine are somnolence, dizziness, dry mouth, mild asthenia, constipation, tachycardia, orthostatic hypotension and dyspepsia.

As with other antipsychotics, weight gain, syncope, neuroleptic malignant syndrome, leucopenia, neutropenia and peripheral oedema, have been associated with quetiapine.

The incidences of ADRs associated with quetiapine therapy, are tabulated below according to the format recommended by the Council for International Organisations of Medical Sciences (CIOMS III Working Group; 1995).

Frequency	System Organ Class	Event
Very Common (≥10%)	Gastrointestinal disorders	Dry mouth
	General disorders and administration site conditions	Withdrawal (discontinuation) symptoms <sup>1, 10</sup>
	Investigations	Elevations in serum triglyceride levels <sup>1, 11</sup> Elevations in total cholesterol (predominantly LDL cholesterol) <sup>1, 12</sup> Decreases in HDL cholesterol <sup>1, 18</sup> Weight gain <sup>3</sup> Decreased haemoglobin <sup>19</sup>
	Nervous system disorders	Dizziness <sup>1, 5, 17</sup> Somnolence <sup>2, 17</sup>
Common (≥1% - <10%)	Blood and lymphatic system disorders	Leukopenia <sup>1, 24</sup>
	Cardiac disorders	Tachycardia <sup>1, 5</sup> Palpitations <sup>20</sup>

Frequency	System Organ Class	Event
	Eye Disorders	Vision blurred
	Gastrointestinal disorders	Constipation Dyspepsia Vomiting <sup>22</sup>
	General disorders and administration site conditions	Mild asthenia Peripheral oedema Irritability Pyrexia
	Investigations	Elevations in serum alanine aminotransferase (ALT) <sup>4</sup> Elevations in gamma-GT levels <sup>4</sup> Neutrophil count decreased <sup>1,7</sup> Eosinophils increased <sup>23</sup> Blood glucose increased to hyperglycaemic level <sup>1,8</sup> Elevations in serum prolactin <sup>15</sup> Decreases in Total T <sub>4</sub> <sup>21</sup> Decreases in Free T <sub>4</sub> <sup>21</sup> Decreases in Total T <sub>3</sub> <sup>21</sup> Increases in TSH <sup>21</sup>
	Nervous system disorders	Extrapyramidal symptoms <sup>1,16</sup> Dysarthria
	Metabolism and nutrition disorders	Increased appetite
	Respiratory, thoracic, and mediastinal disorders	Dyspnoea <sup>20</sup>
	Vascular disorders	Orthostatic hypotension <sup>1, 5, 17</sup>
	Psychiatric disorders	Abnormal dreams and nightmares
Uncommon (≥0.1% - <1%)	Gastrointestinal disorders	Dysphagia <sup>1,9</sup>
	Immune system disorders	Hypersensitivity
	Investigations	Elevations in serum aspartate aminotransferase (AST) <sup>4</sup> Platelet count decreased <sup>14</sup> Decreases in Free T <sub>3</sub> <sup>21</sup>
	Nervous system disorders	Seizure <sup>1</sup> Restless legs syndrome Tardive dyskinesia <sup>1</sup> Syncope <sup>1, 5, 17</sup>
	Respiratory, thoracic, and mediastinal	Rhinitis

Frequency	System Organ Class	Event
	disorders	
Rare (0.01% - <0.1%)	General disorders and administration site conditions  Investigations  Psychiatric disorders  Reproductive system and breast disorders	Neuroleptic malignant syndrome <sup>1</sup> Hypothermia  Elevations in blood creatine phosphokinase <sup>13</sup>  Somnambulism and other related events  Priapism Galactorrhoea
Very Rare (<0.01%)	Immune system disorders	Anaphylactic reaction <sup>6</sup>

- (1) See WARNINGS AND PRECAUTIONS
- (2) Somnolence may occur, usually during the first two weeks of treatment and generally resolves with the continued administration of quetiapine.
- (3) Based on  $\geq 7\%$  increase in body weight from baseline. Occurs predominantly during the early weeks of treatment in adults.
- (4) Asymptomatic elevations (shift from normal to  $> 3 \times \text{ULN}$  at any time) in serum transaminase (ALT, AST) or gamma-GT levels have been observed in some patients administered quetiapine. These elevations were usually reversible on continued quetiapine treatment.
- (5) As with other antipsychotics with  $\alpha_1$  adrenergic blocking activity, quetiapine may induce orthostatic hypotension, associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period.
- (6) The inclusion of anaphylactic reaction is based on post marketing reports.
- (7) In all short-term placebo-controlled monotherapy trials among patients with a baseline neutrophil count  $\geq 1.5 \times 10^9/\text{L}$ , the incidence of at least one occurrence of neutrophil count  $< 1.5 \times 10^9/\text{L}$ , was 1.9% in patients treated with quetiapine, compared to 1.3% in placebo-treated patients. The incidence  $\geq 0.5 - < 1.0 \times 10^9/\text{L}$  was 0.2% in patients treated with quetiapine and 0.2% in placebo-treated patients. In clinical trials conducted prior to a protocol amendment for discontinuation of patients with treatment-emergent neutrophil count  $< 1.0 \times 10^9/\text{L}$ , among patients with a baseline neutrophil count  $\geq 1.5 \times 10^9/\text{L}$ , the incidence of at least one occurrence of neutrophil count  $< 0.5 \times 10^9/\text{L}$  was 0.21% in patients treated with quetiapine and 0% in placebo treated patients.
- (8) Fasting blood glucose  $\geq 126 \text{ mg/dL}$  or a non fasting blood glucose  $\geq 200 \text{ mg/dL}$  on at least one occasion.
- (9) An increase in the rate of dysphagia with quetiapine vs. placebo was only observed in the clinical trials in bipolar depression.
- (10) In acute placebo-controlled, monotherapy clinical trials, which evaluated discontinuation symptoms, the aggregated incidence of discontinuation symptoms after abrupt cessation was 12.1% for quetiapine and 6.7% for placebo. The aggregated incidence of the individual adverse events (eg, insomnia, nausea, headache, diarrhoea, vomiting, dizziness and irritability) did not exceed 5.3% in any treatment group and usually resolved after 1 week post-discontinuation.
- (11) Triglycerides  $\geq 200 \text{ mg/dL}$  (patients  $\geq 18$  years of age) or  $\geq 150 \text{ mg/dL}$  (patients  $< 18$  years of age) on at least one occasion.
- (12) Cholesterol  $\geq 240 \text{ mg/dL}$  (patients  $\geq 18$  years of age) or  $\geq 200 \text{ mg/dL}$  (patients  $< 18$  years of age) on at least one occasion.

- (13) Based on clinical trial adverse event reports of blood creatine phosphokinase increase not associated with neuroleptic malignant syndrome.
- (14) Platelets  $\leq 100 \times 10^9/L$  on at least one occasion.
- (15) Prolactin levels (patients  $\geq 18$  years of age):  $> 20$  mcg/L males;  $> 30$  mcg/L females at any time
- (16) See text below
- (17) May lead to falls
- (18) HDL cholesterol:  $< 40$  mg/dL males;  $< 50$  mg/dL females at any time
- (19) Decreased haemoglobin to  $\leq 13$  g/dL males,  $\leq 12$  g/dL 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  $\leq 13$  g/dL males,  $\leq 12$  g/dL females on at least one occasion occurred in 8.3% of quetiapine patients compared to 6.2% of placebo patients.
- (20) These reports often occurred in the setting of tachycardia, dizziness, orthostatic hypotension, and/or underlying cardiac/respiratory disease.
- (21) Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in total  $T_4$ , free  $T_4$ , total  $T_3$  and free  $T_3$  are defined as  $< 0.8 \times LLN$  (pmol/L) and shift in TSH is  $> 5$  mIU/L at any time.
- (22) Based on the increased rate of vomiting in elderly patients ( $\geq 65$  years of age).
- (23) Based on shifts from normal baseline to potentially clinically important value at any time post-baseline in all trials. Shifts in eosinophils are defined as  $> 1 \times 10^9$  cells/L at any time.
- (24) Based on shifts from normal baseline to potentially clinically important value at any time post-baseline in all trials. Shifts in WBCs are defined as  $< 3 \times 10^9$  cells/L at any time.

## EXTRAPYRAMIDAL SYMPTOMS

The following clinical trials (monotherapy and combination therapy) included treatment with SEROQUEL and SEROQUEL XR.

In short-term, placebo-controlled clinical trials in schizophrenia and bipolar mania the aggregated incidence of extrapyramidal symptoms was similar to placebo (schizophrenia: 7.8% for quetiapine and 8.0% for placebo; bipolar mania: 11.2% for quetiapine and 11.4% for placebo. In short-term, placebo-controlled clinical trials in bipolar depression the aggregated incidence of extrapyramidal symptoms 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 major depressive disorder 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 major depressive disorder, the aggregated incidence of extrapyramidal symptoms was 9.0% for SEROQUEL XR and 2.3% for placebo. In short-term, placebo-controlled monotherapy clinical trials in generalised anxiety disorder, the aggregated incidence of extrapyramidal symptoms was 4.9% for SEROQUEL XR and 3.2% for placebo. In a short-term placebo controlled monotherapy trial in elderly patients with generalized anxiety disorder, the aggregated incidence of extrapyramidal symptoms was 5.4% for SEROQUEL XR and 2.2% for placebo

In long-term studies of schizophrenia, bipolar disorder, major depressive disorder and generalised anxiety disorder the aggregated exposure adjusted incidence of treatment-emergent extrapyramidal symptoms was similar between quetiapine and placebo.

### DIABETES MELLITUS

Exacerbation of pre-existing diabetes mellitus, and diabetic ketoacidosis, have occurred very rarely with quetiapine therapy. The causal association with quetiapine has not been established (see WARNINGS AND PRECAUTIONS).

### THYROID LEVEL

Quetiapine treatment was associated with dose-related decreases in thyroid hormone levels. In short term placebo-controlled clinical trials, the incidence of potentially clinically significant shifts in thyroid hormone levels were: total T<sub>4</sub>: 3.4% for quetiapine versus 0.6% for placebo; free T<sub>4</sub>: 0.7% for quetiapine versus 0.1% for placebo; were total T<sub>3</sub>: 0.54% for quetiapine versus 0.0% for placebo and free T<sub>3</sub>: 0.2% for quetiapine versus 0.0% for placebo. The incidence shifts in TSH was 3.2% for quetiapine versus 2.7% for placebo. In short term placebo-controlled monotherapy trials, the incidence of reciprocal, potentially clinically significant shifts in T<sub>3</sub> and TSH was 0.0% for both quetiapine and placebo and 0.1% for quetiapine versus 0.0% for placebo for shifts in T<sub>4</sub> and TSH. These changes in thyroid hormone levels are generally not associated with clinically symptomatic hypothyroidism. The reduction in total and free T<sub>4</sub> was maximal within the first six 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<sub>4</sub>, irrespective of the duration of treatment. In eight patients, where TBG was measured, levels of TBG were unchanged.

### QT PROLONGATION

Cases of QT prolongation, ventricular arrhythmia, sudden unexplained death, cardiac arrest and torsades de pointes have been reported very rarely with the use of neuroleptics and are considered class effects.

### CHILDREN AND ADOLESCENTS (10 TO 17 YEARS OF AGE)

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

Frequency	System Organ Class	Event
Very Common (≥10%)	Metabolism and nutrition disorders	Increased appetite
	Investigations	Elevations in prolactin <sup>1</sup> Increases in blood pressure <sup>2</sup> Weight gain <sup>3</sup>
	Nervous system disorders	Extrapyramidal symptoms <sup>3</sup>

1. Prolactin levels (patients < 18 years of age): >20 mcg/L (>869.56 pmol/L) males; >26 mcg/L (>1130.428 pmol/L) females at any time. Less than 1% of patients had an increase to a prolactin level >100 mcg/L

2. Based on shifts above clinically significant thresholds (adapted from the National Institutes of Health criteria) or increases >20mmHg 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. See text below

### **Weight Gain in Children and Adolescents (10 to 17 years of age)**

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. Twenty one percent of SEROQUEL-treated patients and 7% of placebo-treated patients gained  $\geq 7\%$  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. Twelve percent of SEROQUEL-treated patients and 0% of placebo-treated patients gained  $\geq 7\%$  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 increase in body weight was 4.4 kg. Forty five percent of patients gained  $\geq 7\%$  of their body weight, not adjusted for normal growth. In order to adjust for normal growth over 26 weeks an increase of at least 0.5 standard deviation from baseline in BMI was used as a measure of a clinically significant change; 18.3% of patients on SEROQUEL met this criterion after 26 weeks of treatment.

### **Extrapyramidal Symptoms in Children and Adolescent Population (10 to 17 years of age)**

In a short-term placebo-controlled monotherapy trial in adolescent patients (13-17 years of age) with schizophrenia, the aggregated incidence of extrapyramidal symptoms 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 extrapyramidal symptoms was 3.6% for SEROQUEL IR and 1.1% for placebo.

### **INTERACTIONS**

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.

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

The pharmacokinetics of lithium were not altered when co-administered with SEROQUEL.

The pharmacokinetics of sodium valproate and quetiapine were not altered to a clinically relevant extent when co-administered.

The pharmacokinetics of quetiapine were not significantly altered following co-administration with the antipsychotics risperidone or haloperidol. However, co-administration of quetiapine and thioridazine caused increases in the clearance of quetiapine.

Quetiapine did not induce the hepatic enzyme systems involved in the metabolism of antipyrine. However, 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. The safety of doses above 800 mg/day has not been established in 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. Co-administration of SEROQUEL with another microsomal enzyme inducer, phenytoin, also caused increases in the clearance of quetiapine. Increased doses of SEROQUEL XR may be required to maintain control of psychotic symptoms in patients co-administered SEROQUEL XR and phenytoin, and other hepatic enzyme inducers (e.g. barbiturates, rifampicin etc.). The dose of SEROQUEL XR may need to be reduced if phenytoin or carbamazepine or other hepatic enzyme inducers are withdrawn and replaced with a non-inducer (e.g. sodium valproate).

CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. The pharmacokinetics of quetiapine were not altered following co-administration with cimetidine, a known P450 enzyme inhibitor. The pharmacokinetics of quetiapine were not significantly altered following co-administration with the antidepressants imipramine (a known CYP2D6 inhibitor) or fluoxetine (a known CYP3A4 and CYP2D6 inhibitor). 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 resulted in an increase in mean  $C_{max}$  and AUC of quetiapine of 235% 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. Due to the potential for an interaction of a similar magnitude in a clinical setting, the dosage of SEROQUEL XR should be reduced during concomitant use of quetiapine and potent CYP3A4 inhibitors (such as azole antifungals, macrolide antibiotics and protease inhibitors).

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.

## **OVERDOSAGE**

In clinical trials, 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 WARNINGS AND PRECAUTIONS: Concomitant illness).

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

### **MANAGEMENT OF OVERDOSE**

There is no specific antidote to quetiapine. In cases of severe intoxication, 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.

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

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

### **PHARMACEUTICAL PRECAUTIONS**

#### **SHELF-LIFE**

3 years

#### **STORAGE CONDITIONS**

Store below 30°C.

#### **LIST OF EXCIPIENTS**

##### **Core**

- Microcrystalline cellulose (Ph. Eur)
- Sodium citrate (Ph. Eur)
- Lactose monohydrate (Ph. Eur)
- Magnesium stearate (Ph. Eur)
- Hypromellose (Ph. Eur)

##### **Coating**

- Hypromellose (Ph. Eur)
- Macrogol (Ph. Eur)
- Titanium dioxide (Ph. Eur, E171)
- Iron oxide, red (E172) (50 mg tablets)
- Iron oxide, yellow (E172) (50, 200 and 300 mg tablets)

### **MEDICINE CLASSIFICATION**

Prescription Medicine.

**PACKAGE QUANTITIES**

SEROQUEL XR 50 mg tablets are presented in a PVC+PCTFE/aluminium foil blister pack containing 10 (1 x 10) tablets, 60 (6 x 10) tablets or 100 (10 x 10) tablets.

SEROQUEL XR 150 mg tablets are presented in a PVC+PCTFE/aluminium foil blister pack containing 60 (6 x 10) tablets.

SEROQUEL XR 200 mg tablets are presented in a PVC+PCTFE/aluminium foil blister pack containing 10 (1 x 10) tablets, 60 (6 x 10) tablets or 100 (10 x 10) tablets.

SEROQUEL XR 300 mg tablets are presented in a PVC+PCTFE/aluminium foil blister pack containing 10 (1 x 10) tablets, 60 (6 x 10) tablets or 100 (10 x 10) tablets.

SEROQUEL XR 400 mg tablets are presented in a PVC+PCTFE/aluminium foil blister pack containing 10 (1 x 10) tablets, 60 (6 x 10) tablets or 100 (10 x 10) tablets.

**FURTHER INFORMATION****ACUTE TOXICITY STUDIES**

Quetiapine has low acute toxicity. Findings in mice and rats after oral (500 mg/kg) or intraperitoneal (100 mg/kg) dosing were typical of an effective neuroleptic agent and included decreased motor activity, ptosis, loss of righting reflex, 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 (e.g. sedation at lower doses and tremor, convulsions or prostration at higher exposures).

Hyperprolactinaemia, induced through the dopamine D<sub>2</sub> 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 and concomitant changes in plasma thyroid hormone levels occurred in rat and monkey.

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

Transient increases in heart rate, unaccompanied by an effect on blood pressure, occurred 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, nor in rodents. Monitoring in clinical studies did not reveal drug-related corneal opacities in man (See PHARMACODYNAMICS).

No evidence of neutrophil reduction or agranulocytosis was seen in any of the toxicity studies.

### **CARCINOGENICITY STUDIES**

In the rat study (doses 0, 20, 75 and 250 mg/kg/day) the incidence of mammary adenocarcinomas was increased at all doses in female rats, consequential to prolonged hyperprolactinaemia.

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.

### **REPRODUCTION STUDIES**

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.

Quetiapine had no teratogenic effects.

### **MUTAGENICITY STUDIES**

Genetic toxicity studies with quetiapine show that it is not a mutagen or clastogen.

### **NAME AND ADDRESS**

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