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On 12th March 2010, the MHRA granted AstraZeneca UK Ltd a licence for the medicinal product Seroquel XL 150mg Prolonged-Release Tablets (PL 17901/0259). This is a prescription-only medicine (POM) to help with the effects of certain types of mental illness, such as:

- Hallucinations (like hearing unexplained voices), strange and frightening thoughts, changes in how you act and feeling alone and confused. This is also known as schizophrenia.
- Effects on your mood and feeling very 'high' or excited. You may find that you need to sleep less than usual. You may be more talkative and have racing thoughts or ideas. You may also feel more irritable than usual. This is also known as bipolar mania.
- Effects on your mood whereby you feel sad all the time. You may find that you feel depressed, feel guilty, lack energy, lose your appetite and/or can’t sleep. This is also known as bipolar depression.

Seroquel XL contains a medicine called quetiapine. This belongs to a group of medicines called antipsychotics.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Seroquel XL 150mg Prolonged-Release Tablets outweigh the risks, hence a Marketing Authorisation has been granted.
SEROQUEL XL 150MG PROLONGED-RELEASE TABLETS
PL 17901/0259

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted AstraZeneca UK Ltd a marketing authorisation for the medicinal product Seroquel XL 150mg Prolonged-Release Tablets (PL 17901/0259) on 12th March 2010. Seroquel XL is indicated for the treatment of:
- Schizophrenia, including preventing relapse in stable schizophrenic patients who have been maintained on Seroquel XL.

Bipolar disorder, including:
- manic episodes associated with bipolar disorder
- major depressive episodes in bipolar disorder
- preventing recurrence in bipolar disorder in patients whose manic, mixed or depressive episode has responded to quetiapine treatment.

The application was submitted under Article 8.3 of Directive 2001/83/EC, as amended, as a line extension to the existing products Seroquel XL 50, 200, 300 and 400mg Tablets (PL 17901/0249-52), which were granted licences in September 2008.

Seroquel XL 50mg, 200mg, 300mg and 400mg Prolonged-Release Tablets contain the active ingredient quetiapine, as quetiapine fumarate. Quetiapine fumarate is a dibenzothiazepine atypical antipsychotic drug. It is reported to have affinity for serotonin (5-HT2), histamine (H1), and adrenergic (α1 and α2) receptors, as well as dopamine D2 receptors. It is this combination of receptor antagonism with a higher selectivity for 5HT2 relative to D2 receptors, which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effect (EPS) liability of Seroquel compared to typical antipsychotics. Seroquel XL Tablets are indicated in the treatment of schizophrenia and bipolar disorder including manic episodes, major depressive episodes and preventing recurrence in bipolar disorder.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

INN: Quetiapine fumarate
Chemical Name: \[2\text{–}(2\text{–}[4\text{–}(\text{dibenzo}[b,f][1,4]\text{–} \text{thiazepin –11–yl})\text{piperazin–1–yl}] \text{ethoxy}) \text{ethanol}\]fumarate (2:1) (salt)

Molecular Formula: C_{21}H_{25}N_{3}O_{2}S,C_{4}H_{4}O_{4}

Structure:

Molecular Weight: 883.1
Appearance: White to off-white powder, slightly soluble in water, sparingly soluble in pH 3 buffer. Soluble in 0.1 N HCl. Slightly soluble in the organic solvents, methanol, ethanol and acetone.

The active substance, quetiapine fumarate, is not the subject of a European Pharmacopeia (EP) monograph.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin, and therefore comply with the TSE requirements.

An appropriate specification has been provided for the active substance, which is based on the specification for the reference products. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for reference standards used by the active substance manufacturer during validation studies.

The active substance is stored in appropriate packaging. Specifications and Certificates of Analysis have been provided for the packaging materials used. The primary packaging in direct contact with the active substance satisfies Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Appropriate stability data have been generated for active substance stored in a container closure system similar to the proposed packaging. These data demonstrate the stability of the active substance and supports a suitable retest period.
DRUG PRODUCT

Other ingredients
Other ingredients consist of microcrystalline cellulose, sodium citrate, lactose monohydrate, magnesium stearate, hypromellose, macrogol 400 and titanium dioxide (E171). All excipients comply with their respective European Pharmacopoeia monographs. Suitable certificates of analysis have been provided for all excipients, showing compliance with the proposed specifications.

With the exception of lactose monohydrate, none of the excipients is derived from materials of animal or human origin. The supplier of lactose monohydrate has stated that it is sourced from healthy animals under the same conditions as milk for human consumption. No genetically modified materials are used in the manufacture of any of the excipients.

Container-closure system
The tablets are packaged in polyvinylchloride/polychlorotrifluoroethylene/aluminium blisters, which are contained in cardboard outer cartons in pack sizes of 10, 30, 50, 60 and 100 tablets. The marketing authorisation holder has stated that not all pack sizes may be marketed, but has committed to providing for approval mock-ups of any pack sizes it intends to market.

Suitable specifications and certificates of analysis have been provided for the finished packaging. All packaging components comply with relevant guidelines concerning contact with foodstuff.

Product development
A suitable product development section has been provided. Percentage composition of the different strengths are similar. The dissolution profile of the 150mg strength is similar to the dissolution profiles of the other licensed strengths (50mg, 200mg, 300mg & 400mg), for which a Level A IVIVC has been established and used to set dissolution acceptance limits. The dissolution of all strengths are controlled by the same acceptance limits.

Manufacture
A satisfactory batch formula has been provided for the manufacture of the product along with an appropriate account of the manufacturing process.

In-process controls are appropriate considering the nature of the product and the method of manufacture.

The manufacturing process has been validated and has shown satisfactory results.

Finished product specification
The finished product specifications proposed for both release and shelf life are acceptable, and provide an assurance of the quality and consistency of the finished products. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any reference standards used.
Stability of the product
Stability data has been provided for batches of the finished product stored in-line with ICH guidelines. All batches were manufactured by the finished product manufacturer, according to the proposed manufacturing method and stored in the packaging proposed for marketing.

Based on these stability studies, a shelf-life of 3 years has been proposed with storage conditions of “Do not store above 30°C. Store in the original package.” These are acceptable.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL) and Labelling
The SPC, PIL and labels are pharmaceutically acceptable.

The applicant has submitted results of PIL user testing. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA Form
The MAA form is pharmaceutically satisfactory.

Pharmaceutical expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

CONCLUSION
It is recommended that a Marketing Authorisation is granted for this application.
PRECLINICAL ASSESSMENT

This application is a line-extension to the existing products Seroquel XL 50, 200, 300 and 400mg Tablets (PL 17901/0249-52), which were granted licences in September 2008.

No new preclinical data have been supplied with this application and none are required for an application of this type. A preclinical expert report has been written by an appropriately qualified person. It is a suitable summary of the preclinical aspects of the dossier.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY, EFFICACY AND SAFETY

This application is a line-extension to the existing products Seroquel XL 50, 200, 300 and 400mg Tablets (PL 17901/0249-52), which were granted licences in September 2008.

No new clinical data have been supplied with this application and none are required for an application of this type.

No bioequivalence study has been submitted. Considering the criteria specified in the *Note for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98) and the data collected on the Level A IVIVC (see Product Development section), this is acceptable.

CLINICAL EXPERT REPORT

The clinical expert report has been written by an appropriately qualified physician. It is an appropriate summary of the clinical aspects of the dossier.

PRODUCT LITERATURE

Summary of Product Characteristics (SPC)

The SPC is satisfactory and consistent with those for Seroquel XL 50, 200, 300 and 400mg Tablets (PL 17901/0249-52).

Patient Information Leaflet (PIL)

The PIL is satisfactory and consistent with that for Seroquel XL 50, 200, 300 and 400mg Tablets (PL 17901/0249-52).

Labels

The labels are appropriate for a product of this type and consistent with those for Seroquel XL 50, 200, 300 and 400mg Tablets (PL 17901/0249-52).

CONCLUSIONS

The safety and efficacy of quetiapine fumarate have been well-established. The clinical data has already been approved for Seroquel XL 50, 200, 300 and 400mg Tablets (PL 17901/0249-52). No new clinical data have been submitted with this application.

The grant of a Marketing Authorisation is recommended.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Seroquel XL 150mg Prolonged-Release Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for an application of this type.

EFFICACY
The efficacy has previously been demonstrated in previous applications for Seroquel XL 50, 200, 300 and 400mg Tablets (PL 17901/0249-52). No new data have been submitted or are required for this application.

No bioequivalence study has been submitted. Considering the criteria specified in the "Note for Guidance on the Investigation of Bioavailability and Bioequivalence" (CPMP/EWP/QWP/1401/98) and the data collected on the Level A IVIVC (see Product Development section), this is acceptable.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with those for Seroquel XL 50, 200, 300 and 400mg Tablets (PL 17901/0249-52).

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with quetiapine fumarate is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
**SEROQUEL XL 150MG PROLONGED-RELEASE TABLETS**
**PL 17901/0259**

**STEPS TAKEN FOR ASSESSMENT**

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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 9\textsuperscript{th} October 2008.</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 14\textsuperscript{th} October 2008.</td>
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<tr>
<td>3</td>
<td>Following assessment of the application, the MHRA requested further information relating to the quality dossiers on 20\textsuperscript{th} May 2009 and 20\textsuperscript{th} October 2009. No requests for further information were made for the clinical dossiers.</td>
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<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information for the quality dossier on 10\textsuperscript{th} July 2009 and 21\textsuperscript{st} December 2009.</td>
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<td>5</td>
<td>The application was determined on 12\textsuperscript{th} March 2010.</td>
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SEROQUEL XL 150MG PROLONGED-RELEASE TABLETS
PL 17901/0259

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

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<th>Application type</th>
<th>Scope</th>
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Seroquel XL 150 mg prolonged-release tablets ▼

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 150 mg quetiapine (as quetiapine fumarate)
Excipient: 74.65 mg lactose (anhydrous) per tablet.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Prolonged-release tablet

White, bi-convex, capsule shaped tablets, marked with XR150.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Seroquel XL is indicated for the treatment of:
- Schizophrenia including: preventing relapse in stable schizophrenic patients who have been
  maintained on Seroquel XL (see section 5.1 Pharmacodynamic properties).

Bipolar disorder including:
- manic episodes associated with bipolar disorder
- major depressive episodes in bipolar disorder
- preventing recurrence in bipolar disorder in patients whose manic, mixed or depressive
  episode has responded to quetiapine treatment.

4.2 Posology and method of administration
Seroquel XL should be administered once daily, without food (at least one hour before a
meal). 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 and 600 mg on Day 2. The
recommended daily dose is 600 mg. Enhanced efficacy at doses higher than 600 mg has not
been demonstrated, although individual patients may benefit from a dose up to 800 mg daily.
Doses greater than 600 mg should be initiated by a specialist. 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 XL should be administered once daily at bedtime. 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).
The recommended daily dose is 300 mg. In clinical trials, no additional benefit was seen in the
600 mg group compared to the 300 mg group. Individual patients may benefit from a 600 mg
dose. In individual patients, in the event of tolerance concerns, clinical trials have indicated
that dose reduction to a minimum of 200 mg could be considered. When treating depressive
episodes in bipolar disorder, treatment should be initiated by physicians experienced in
treating bipolar disorder.

For preventing recurrence in bipolar disorder
For prevention of recurrence of manic, depressive or mixed episodes in bipolar disorder, patients who have responded to Seroquel XL for acute treatment of bipolar disorder should continue on Seroquel XL at the same dose administered at bedtime. The dose may be adjusted depending on clinical response and tolerability of the individual patient within the dose range of 300 mg to 800 mg/day. It is important that the lowest effective dose is used for maintenance therapy.

Switching from Seroquel immediate-release tablets:
For more convenient dosing, patients who are currently being treated with divided doses of immediate-release Seroquel tablets (Seroquel IR, tradename Seroquel®) may be switched to Seroquel XL at the equivalent total daily dose taken once daily. To ensure the maintenance of clinical response, a period of dose titration may be required.

Elderly:
As with other antipsychotics, Seroquel XL should be used with caution in the elderly, especially during the initial dosing period. The rate of dose titration of Seroquel XL 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 patients when compared to 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.

Efficacy and safety have not been evaluated in patients over 65 years with depressive episodes in the framework of bipolar disorder.

Children and Adolescents:
Seroquel XL is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. The available evidence from placebo-controlled clinical trials with Seroquel is presented in sections 4.4, 4.8, 5.1 and 5.2.

Renal impairment:
Dosage adjustment is not necessary in patients with renal impairment.

Hepatic impairment:
Quetiapine is extensively metabolised by the liver. Therefore, Seroquel XL should be used with caution in patients with known hepatic impairment, especially during the initial dosing period. Patients with known hepatic impairment should be started with 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.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients of this product.

Concomitant administration of cytochrome P450 3A4 inhibitors, such as HIV-protease inhibitors, azole-antifungal agents, erythromycin, clarithromycin and nefazodone, is contraindicated. (See also section 4.5 Interaction with other medicinal products and other forms of interaction).

4.4 Special warnings and precautions for use
Children and adolescents (10 to 17 years of age)
Seroquel XL is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. Clinical trials with Seroquel have shown that in addition to the known safety profile identified in adults (see section 4.8 Undesirable effects), certain adverse events occurred at a higher frequency in children and adolescents compared to adults (increased appetite, elevations in serum prolactin and extrapyramidal symptoms) and one was identified that has not been previously seen in adult studies (increases in blood pressure). Changes in thyroid function tests have also been observed in children and adolescents.
Furthermore, the long-term safety implications of treatment with Seroquel on growth and maturation have not been studied beyond 26 weeks. Long-term implications for cognitive and behavioural development are not known.

In placebo-controlled clinical trials with children and adolescent patients treated with Seroquel, quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for schizophrenia and bipolar mania (see section 4.8 Undesirable effects).

**Suicide/suicidal thoughts or clinical worsening:**
Depression in bipolar disorder 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.

In clinical studies of patients with major depressive episodes in bipolar disorder an increased risk of suicide-related events was observed in young adult patients less than 25 years of age who were treated with quetiapine as compared to those treated with placebo (3.0% vs. 0%, respectively).

**Somnolence:**
Quetiapine treatment has been associated with somnolence and related symptoms, such as sedation (see section 4.8 Undesirable effects). In clinical trials for treatment of patients with bipolar depression, onset was usually within the first 3 days of treatment and was predominantly of mild to moderate intensity. Bipolar depression patients experiencing somnolence of severe intensity may require more frequent contact for a minimum of 2 weeks from onset of somnolence, or until symptoms improve and treatment discontinuation may need to be considered.

**Cardiovascular:**
Seroquel XL 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 and therefore dose reduction or more gradual titration should be considered if this occurs.

**Seizures:**
In controlled clinical trials there was no difference in the incidence of seizures in patients treated with quetiapine or placebo. As with other antipsychotics, caution is recommended when treating patients with a history of seizures (see section 4.8 Undesirable effects).

**Extrapyramidal symptoms:**
In placebo controlled clinical trials of adult patients quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for major depressive episodes in bipolar disorder (see section 4.8 Undesirable effects).

**Tardive Dyskinesia:**
Tardive dyskinesia is a syndrome of potentially irreversible, involuntary, dyskinetic movements that may develop in patients treated with antipsychotic drugs including quetiapine. If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of Seroquel XL should be considered. The symptoms of tardive dyskinesia can worsen or even arise after discontinuation of treatment (see section 4.8 Undesirable effects).

**Neuroleptic Malignant Syndrome:**
Neuroleptic malignant syndrome has been associated with antipsychotic treatment, including quetiapine (see section 4.8 Undesirable effects). Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatinine phosphokinase. In such an event, Seroquel XL should be discontinued and appropriate medical treatment given.
**Severe neutropenia:**
Severe neutropenia (neutrophil count <0.5 x 10^9/L) has been uncommonly reported in quetiapine clinical trials. Most cases of severe neutropenia have occurred within a couple of months of starting therapy with quetiapine. There is no apparent dose relationship. During post-marketing experience, resolution of leucopenia and/or neutropenia has followed cessation of therapy with quetiapine. 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. Patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed 1.5 x 10^9/L). (See section 5.1 Pharmacodynamic properties).

**Interactions:**
See also section 4.5 Interaction with other medicinal products and other forms of interaction.

Concomitant use of quetiapine with a strong hepatic enzyme inducer such as carbamazepine or phenytoin substantially decreases quetiapine plasma concentrations, which could affect the efficacy of quetiapine therapy. In patients receiving a hepatic enzyme inducer, initiation of Seroquel XL treatment should only occur if the physician considers that the benefits of Seroquel XL outweigh the risks of removing the hepatic enzyme inducer. It is important that any change in the inducer is gradual, and if required, replaced with a non-inducer (e.g. sodium valproate).

**Hyperglycaemia:**
Hyperglycaemia or exacerbation of pre-existing diabetes has been reported during treatment with quetiapine. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus (see section 4.8 Undesirable effects).

**Lipids:**
Increases in triglycerides, LDL and total cholesterol, and decreases in HDL cholesterol have been observed in clinical trials with quetiapine (see section 4.8 Undesirable effects). Lipid changes should be managed as clinically appropriate.

**QT Prolongation:**
In clinical trials and use in accordance with the SPC, quetiapine was not associated with a persistent increase in absolute QT intervals. However, with overdose (see section 4.9 Overdose) QT prolongation was observed. 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 with medicines known to increase QTc interval, and concomitant neuroleptics, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia (see section 4.5 Interaction with other medicinal products and other forms of interaction).

**Withdrawal:**
Acute withdrawal symptoms such as nausea, vomiting, insomnia, headache, diarrhoea, dizziness and irritability have been described after abrupt cessation of high doses of quetiapine. Gradual withdrawal over a period of at least one to two weeks is advisable (see section 4.8 Undesirable effects).

**Elderly patients with dementia-related psychosis:**
Seroquel XL is not approved for the treatment of dementia-related psychosis.

An approximately 3-fold increased risk of cerebrovascular adverse events has been seen in randomised placebo controlled 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. Seroquel XL should be used with caution in patients with risk factors for stroke.
In a meta-analysis of atypical antipsychotic drugs, it has been reported that elderly patients with dementia-related psychosis are at an increased risk of death compared to placebo. However in two 10-week placebo controlled quetiapine studies in the same patient population (n=710; mean age: 83 years; range: 56-99 years) the incidence of mortality in quetiapine treated patients was 5.5% versus 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.

**Hepatic effects:**
If jaundice develops, Seroquel XL should be discontinued.

**Concomitant Illness:**
Dysphagia (see section 4.8 Undesirable effects) and aspiration have been reported with Seroquel XL. Although a causal relationship with aspiration pneumonia has not been established, Seroquel XL should be used with caution in patients at risk for aspiration pneumonia.

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

**Lactose:**
Seroquel XL tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

**Additional information:**
Quetiapine data in combination with divalproex or lithium in moderate to severe manic episodes is limited; however, combination therapy was well tolerated (see section 4.8 Undesirable effects and 5.1 Pharmacodynamic properties). The data showed an additive effect at week 3. A second study did not demonstrate an additive effect at week 6. There are no combination data available beyond week 6.

### 4.5 Interaction with other medicinal products and other forms of interaction

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

Cytochrome P450 CYP3A4 is the enzyme that is primarily responsible for the cytochrome P450 mediated metabolism of quetiapine. In an interaction study in healthy volunteers, concomitant administration of quetiapine (dosage of 25 mg) with ketoconazole, a CYP3A4 inhibitor, caused a 5- to 8-fold increase in the AUC of quetiapine. On the basis of this, concomitant use of quetiapine with CYP3A4 inhibitors is contraindicated. It is also not recommended to take quetiapine together with grapefruit juice.

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, which could affect the efficacy of Seroquel XL therapy.

Co-administration of quetiapine and phenytoin (another microsomal enzyme inducer) caused a greatly increased clearance of quetiapine by approx. 450%. In patients receiving a hepatic enzyme inducer, initiation of Seroquel XL treatment should only occur if the physician considers that the benefits of Seroquel XL outweigh the risks of removing the hepatic enzyme inducer. It is important that any change in the inducer is gradual, and if required, replaced with
a non-inducer (e.g. sodium valproate) (see section 4.4 Special warnings and precautions for use).

The pharmacokinetics of quetiapine were not significantly altered by co-administration of the antidepressants imipramine (a known CYP2D6 inhibitor) or fluoxetine (a known CYP3A4 and CYP2D6 inhibitor).

The pharmacokinetics of quetiapine were not significantly altered by co-administration of the antipsychotics risperidone or haloperidol. Concomitant use of quetiapine and thioridazine caused an increased clearance of quetiapine of approx. 70%.

The pharmacokinetics of quetiapine were not altered following co-administration with cimetidine.

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

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

Formal interaction studies with commonly used cardiovascular drugs have not been performed.

Caution should be exercised when quetiapine is used concomitantly with drugs known to cause electrolyte imbalance or to increase QTc interval.

4.6 Pregnancy and lactation
The safety and efficacy of quetiapine during human pregnancy have not yet been established. Up to now there are no indications for harmfulness in animal tests, possible effects on the foetal eye have not been examined, though. Therefore, Seroquel XL should only be used during pregnancy if the benefits justify the potential risks. Following pregnancies in which quetiapine was used, neonatal withdrawal symptoms were observed.

The degree to which quetiapine is excreted into human milk is unknown. Women who are breast-feeding should therefore be advised to avoid breast-feeding while taking Seroquel XL.

4.7 Effects 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 to this is known.

4.8 Undesirable 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 Organizations of Medical Sciences (CIOMS III Working Group 1995).

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common:</td>
</tr>
<tr>
<td>Leucopenia 1</td>
</tr>
<tr>
<td>Uncommon:</td>
</tr>
<tr>
<td>Eosinophilia, Thrombocytopenia</td>
</tr>
<tr>
<td>Unknown:</td>
</tr>
<tr>
<td>Neutropenia 1</td>
</tr>
</tbody>
</table>

**Immune system disorders**
### Side Effects

#### Uncommon:
- Hypersensitivity

#### Very rare:
- Anaphylactic reaction

### Endocrine disorders

**Common:**
- Hyperprolactinaemia

### Metabolism and nutritional disorders

**Common:**
- Increased appetite

### Psychiatric disorders

**Very rare:**
- Diabets Mellitus

### Nervous system disorders

**Common:**
- Abnormal dreams and nightmares
- Dizziness
- Syncope
- Seizure

### Cardiac disorders

**Common:**
- Tachycardia

### Eye disorders

**Common:**
- Vision blurred

### Vascular disorders

**Common:**
- Orthostatic hypotension

### Respiratory, thoracic and mediastinal disorders

**Common:**
- Rhinitis

### Gastrointestinal disorders

**Very Common:**
- Dry mouth
- Constipation, dyspepsia

**Common:**
- Dysphagia

### Hepato-biliary disorders

**Rare:**
- Jaundice

**Very rare:**
- Hepatitis

### Skin and subcutaneous tissue disorders

**Very rare:**
- Angioedema, Stevens-Johnson syndrome

### Reproductive system and breast disorders

**Rare:**
- Priapism, Galactorrhoea

### General disorders and administration site conditions

**Very common:**
- Withdrawal (discontinuation) symptoms
- Mild asthenia, peripheral oedema, irritability

**Rare:**
- Neuroleptic malignant syndrome

### Investigations

**Very common:**
- Elevation in serum triglyceride levels
- Elevation in total cholesterol (predominantly LDL cholesterol)
- Decreases in HDL cholesterol
- Weight gain

**Common:**
- Elevation in serum transaminases (ALT, AST)
- Decreased neutrophil count
- Blood glucose increased to hyperglycaemic levels

**Uncommon:**
- Elevations in gamma-GT levels
- Platelet count decreased

**Rare:**
- Elevations in blood creatine phosphokinase
- Venous thromboembolism

---

1. See section 4.4 Special warnings and precautions for use.
2. Somnolence may occur, usually during the first two weeks of treatment and generally resolves with the continued administration of quetiapine.
3. Asymptomatic elevations in serum transaminase (ALT, AST) or gamma-GT-levels have been observed in some patients administered quetiapine.
4. As with other antipsychotics with alpha1 adrenergic blocking activity, quetiapine may commonly induce orthostatic hypotension, associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period. (See section 4.4 Special warnings and precautions for use).
5. Exacerbation of pre-existing diabetes has been reported in very rare cases.
6. Elevated blood glucose ≥ 7.0 mmol/L or a non-fasting blood glucose ≥ 11.1 mmol/L on at least one occasion.
7. An increase in the rate of dysphagia with quetiapine vs. placebo was only observed in the clinical trials in bipolar depression.
8. Based on >7% increase in body weight from baseline. Occurs predominantly during the early weeks of treatment in adults.
9. The following withdrawal symptoms have been observed most frequently in acute placebo-controlled, monotherapy clinical trials, which evaluated discontinuation symptoms: insomnia, nausea, headache, diarhoea, vomiting, dizziness, and irritability. The incidence of these reactions had decreased significantly after 1 week post-discontinuation.
(11) Triglycerides $\geq 200$ mg/dL ($\geq 2.258$ mmol/L) (patients $\geq$ 18 years of age) or $\geq 150$ mg/dL ($\geq 1.694$ mmol/L) (patients $<$ 18 years of age) on at least one occasion.

(12) Cholesterol $\geq 240$ mg/dL ($\geq 6.2064$ mmol/L) (patients $\geq$ 18 years of age) or $\geq 200$ mg/dL ($\geq 5.172$ mmol/L) (patients $<$ 18 years of age) on at least one occasion. An increase in LDL cholesterol of $\geq 30$ mg/dL ($0.769$ mmol/L) has been very commonly observed. Mean change among patients who had this increase was 41.7 mg/dL ($1.07$ mmol/L).

(13) See text below.

(14) Platelets $\leq 100$ x 10⁹/L on at least one occasion.

(15) Based on clinical trial adverse event reports of blood creatine phosphokinase increase not associated with neuroleptic malignant syndrome.

(16) Prolactin levels (patients $>$ 18 years of age): $>20$ μg/L ($>869.56$ pmol/L) males; $>30$ μg/L ($>1304.34$ pmol/L) females at any time.

(17) May lead to falls.

(18) HDL cholesterol: $<$ 40 mg/dL ($1.025$ mmol/L) males; $<$ 50 mg/dL ($1.282$ mmol/L) females at any time.

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.

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 were generally low and did not exceed 4% in any treatment group. 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).

Quetiapine treatment was associated with small dose-related decreases in thyroid hormone levels, particularly total T₄ and free T₄. The reduction in total and free T₄ was maximal within the first two to four 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 T₄, irrespective of the duration of treatment. Smaller decreases in total T₃ and reverse T₃ were seen only at higher doses. Levels of TBG were unchanged and in general, reciprocal increases in TSH were not observed, with no indication that quetiapine causes clinically relevant hypothyroidism.

Children and adolescents (10 to 17 years of age)
The same ADRs 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 adolescents patients (10-17 years of age) than in the adult population or ADRs that have not been identified in the adult population.

<table>
<thead>
<tr>
<th>Metabolism and nutritional disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very common:</strong></td>
</tr>
<tr>
<td>Increased appetite</td>
</tr>
</tbody>
</table>

**Investigations**

| Elevation in prolactin 1, increases in blood pressure 2 |

**Nervous system disorders**

| Extrapyramidal symptoms 3 |

**General disorders and administration site conditions**

| Irritability 4 |

(1) Prolactin levels (patients $<$ 18 years of age): $>20$ μg/L ($>869.56$ pmol/L) males; $>26$ μg/L ($>1130.428$ pmol/L) females at any time. Less than 1% of patients had an increase to a prolactin level $>100$ ug/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) See section 5.1 Pharmacodynamic properties.

(4) Note: The frequency is consistent to that observed in adults, but irritability might be associated with different clinical implications in children and adolescents as compared to adults.
4.9 Overdose

Fatal outcome has been reported in clinical trials following an acute overdose at 13.6 grams, and in post-marketing doses as low as 6 grams of Seroquel alone. However, survival has also been reported following acute overdoses of up to 30 grams. In post marketing experience, there have been very rare reports of overdose of quetiapine alone resulting in death or coma or QT-prolongation.

Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose. (See section 4.4 Special warnings and precautions for use: Cardiovascular).

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

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, gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipsychotics
ATC code: N05A H04

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 (5HT2) and dopamine D1- and D2-receptors. It is this combination of receptor antagonism with a higher selectivity for 5HT2 relative to D2-receptors, which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effect (EPS) liability of Seroquel compared to typical antipsychotics. Additionally, norquetiapine has high affinity at serotonin 5HT1 receptors. Quetiapine and norquetiapine also have high affinity at histaminergic and adrenergic α1-receptors, with a lower affinity at adrenergic α2-receptors. Quetiapine has no appreciable affinity at cholinergic muscarinic or benzodiazepine receptors.

Quetiapine is active in tests for antipsychotic activity, such as conditioned avoidance. It also blocks the action of dopamine agonists, measured either behaviourally or electrophysiologically, and elevates dopamine metabolite concentrations, a neurochemical index of D2-receptor blockade. The extent to which the norquetiapine metabolite contributes to the pharmacological activity of Seroquel in humans is not known.

Pharmacodynamic effects:
In pre-clinical tests predictive of EPS, quetiapine is unlike typical antipsychotics and has an atypical profile. Quetiapine does not produce dopamine D2-receptor supersensitivity after chronic administration. Quetiapine produces only weak catalepsy at effective dopamine D2-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.

Clinical efficacy:
The efficacy of Seroquel XL 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 IR-to-Seroquel XL 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 PANSS total score. Seroquel XL 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 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 XL given once daily.

In a long-term study in stable schizophrenic patients who had been maintained on Seroquel XL for 16 weeks, Seroquel XL was more effective than placebo in preventing relapse. The estimated risks of relapse after 6 months treatments was 14.3% for the Seroquel XL treatment group compared to 68.2% for placebo. The average dose was 669 mg. There were no additional safety findings associated with treatment with Seroquel XL for up to 9 months (median 7 months). In particular, reports of adverse events related to EPS and weight gain did not increase with longer-term treatment with Seroquel XL.

In the treatment of moderate to severe manic episodes, quetiapine demonstrated superior efficacy to placebo in reduction of manic symptoms at 3 and 12 weeks, in two monotherapy trials. There are no data from long-term studies to demonstrate quetiapine’s effectiveness in preventing subsequent manic or depressive episodes. Quetiapine data in combination with divalproex or lithium in moderate to severe manic episodes at 3 and 6 weeks is limited; however, combination therapy was well tolerated. The data showed an additive effect at week 3. A second study did not demonstrate an additive effect at week 6. There are no combination data available beyond week 6. The mean last week median dose of quetiapine in responders was approximately 600 mg/day and approximately 85% of the responders were in the dose range of 400 to 800 mg/day.

In a clinical trial, in patients with depressive episodes in bipolar I or bipolar II disorder, 300 mg/day Seroquel XL showed superior efficacy to placebo in reduction of MADRS total score. The antidepressant effect of Seroquel XL was significant at Day 8 (week 1) and was maintained through the end of the trial (week 8).

In 4 additional clinical trials in patients with depressive episodes in bipolar I or bipolar II disorder, with and without rapid cycling courses, 51% of quetiapine treated patients had at least a 50% improvement in MADRS total score at week 8 compared to 37% of the placebo treated patients. The antidepressant effect was significant at Day 8 (week 1). There were fewer episodes of treatment-emergent mania with Seroquel than with placebo. In continuation treatment the anti-depressant effect was maintained for patients on Seroquel (mean duration of treatment 30 weeks). Seroquel reduced the risk of a recurrent mood (manic and depressed) event by 49%. Seroquel was superior to placebo in treating the anxiety symptoms associated with bipolar depression as assessed by mean change from baseline to week 8 in HAM-A total score.

In one long-term study (up to 2 years treatment, mean quetiapine exposure 191 days) evaluating recurrence prevention in patients with manic, depressed or mixed mood episodes quetiapine was superior to placebo in increasing the time to recurrence of any mood event (manic, mixed or depressed), in patients with bipolar I disorder. The number of patients with a mood event was 91 (22.5%) in the quetiapine group, 208 (51.5%) in the placebo group and 95 (26.1%) in the lithium treatment groups respectively. In patients who responded to quetiapine, when comparing continued treatment with quetiapine to switching to lithium, the
results indicated that a switch to lithium treatment does not appear to be associated with an increased time to recurrence of a mood event.

In two recurrence prevention studies evaluating quetiapine in combination with mood stabilizers, in patients with manic, depressed or mixed mood episodes, the combination with quetiapine was superior to mood stabilizers monotherapy in increasing the time to recurrence of any mood event (manic, mixed or depressed). The risk of a recurrent event was reduced by 70%. Quetiapine was administered twice-daily totalling 400 mg to 800 mg a day as combination therapy to lithium or valproate.

In placebo-controlled monotherapy trials in 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 all clinical trials (placebo-controlled, open-label, active comparator; patients with a baseline neutrophil count \( \geq 1.5 \times 10^9/L \)), the incidence of at least one occurrence of neutrophil count \( < 0.5 \times 10^9/L \) was 0.21% in patients treated with quetiapine and 0% in placebo treated patients and the incidence \( \geq 0.5 - < 1.0 \times 10^9/L \) was 0.75% in patients treated with quetiapine and 0.11% in placebo-treated patients.

In placebo-controlled studies in elderly patients with dementia-related psychosis, the incidence of cerebrovascular adverse events per 100 patient years was not higher in quetiapine-treated patients than in placebo-treated patients.

**Children and adolescents (10 to 17 years of age)**

The efficacy and safety of Seroquel was studied in a 3-week placebo controlled study for the treatment of mania (n= 284 patients from the US, aged 10-17). About 45% of the patient population had an additional diagnosis of ADHD. In addition, a 6-week placebo controlled study for the treatment of schizophrenia (n = 222 patients, aged 13-17) was performed. In both studies, patients with known lack of response to Seroquel were excluded. Treatment with Seroquel was initiated at 50 mg/day and on day 2 increased to 100 mg/day; subsequently the dose was titrated to a target dose (mania 400-600 mg/day; schizophrenia 400-800 mg/day) using increments of 100 mg/day given two or three times daily.

In the mania study, the difference in LS mean change from baseline in YMRS total score (active minus placebo) was –5.21 for Seroquel 400 mg/day and –6.56 for Seroquel 600 mg/day. Responder rates (YMRS improvement \( \geq 50\% \)) were 64% for Seroquel 400 mg/day, 58% for 600 mg/day and 37% in the placebo arm.

In the schizophrenia study, the difference in LS mean change from baseline in PANSS total score (active minus placebo) was –8.16 for Seroquel 400 mg/day and –9.29 for Seroquel 800 mg/day. Neither low dose (400 mg/day) nor high dose regimen (800 mg/day) quetiapine was superior to placebo with respect to the percentage of patients achieving response, defined as \( \geq 30\% \) reduction from baseline in PANSS total score. Both in mania and schizophrenia higher doses resulted in numerically lower response rates.

No data are available on maintenance of effect or recurrence prevention in this age group.

A 26-week open-label extension to the acute trials (n= 380 patients), with Seroquel flexibly dosed at 400-800 mg/day, provided additional safety data. Increases in blood pressure were reported in children and adolescents and increased appetite, extrapyramidal symptoms and elevations in serum prolactin were reported with higher frequency in children and adolescents than in adult patients (see section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects).

**Extrapyramidal Symptoms**

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

**Weight Gain**

In short-term clinical trials with Seroquel in paediatric patients (10-17 years of age), 17% of quetiapine treated patients and 2.5% of placebo treated patients gained ≥7% of their body weight. When adjusting for normal growth over longer term, an increase of at least 0.5 standard deviation from baseline in Body Mass Index (BMI) was used as a measure of a clinically significant change; 18.3% of patients who were treated with quetiapine for at least 26 weeks met this criterion.

**Suicide/Suicidal thoughts or Clinical worsening**

In short-term placebo-controlled clinical trials with Seroquel in paediatric patients with schizophrenia, the incidence of suicide related events was 1.4% (2/147) for quetiapine and 1.3% (1/75) for placebo in patients <18 years of age. In short-term placebo-controlled trials with Seroquel in paediatric patients with bipolar mania, the incidence of suicide related events was 1.0% (2/193) for quetiapine and 0% (0/90) for placebo in patients <18 years of age.

5.2 **Pharmacokinetic properties**

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 XL achieves peak plasma concentrations at approximately 6 hours after administration (Tmax). Seroquel XL displays dose-proportional pharmacokinetics for doses of up to 800 mg administered once daily. The maximum plasma concentration (Cmax) and the area under the plasma concentration-time curve (AUC) for Seroquel XL administered once daily are comparable to those achieved for the same total daily dose of immediate-release quetiapine fumarate (Seroquel IR) administered twice daily. 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/1.73m²), 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.

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 quetiapine plasma clearance decreases by approx. 25% in persons with known hepatic impairment (stable alcohol cirrhosis). As quetiapine is extensively metabolised by the liver, elevated plasma levels are expected in the population with hepatic impairment. Dose adjustments may be necessary in these patients (see section 4.2 Posology and method of 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 quetiapine with other drugs 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.

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 XL Cmax and AUC of 44% to 52% and 20% to 22%, respectively, for the 50 mg and 300 mg tablets. Seroquel XL should be taken at least one hour before a meal.

Children and adolescents (10 to 17 years of age)
Pharmacokinetic data were sampled in 9 children aged 10-12 years old and 12 adolescents, who were on steady-state treatment with 400 mg quetiapine (Seroquel) twice daily. At steady-state, the dose-normalised plasma levels of the parent compound, quetiapine, in children and adolescents (10-17 years of age) were in general similar to adults, though Cmax in children was at the higher end of the range observed in adults. The AUC and Cmax for the active metabolite, norquetiapine, were higher, approximately 62% and 49% in children (10-12 years), respectively and 28% and 14% in adolescents (13-17 years), respectively, compared to adults.

No information is available for Seroquel XL in children and adolescents.

5.3 Preclinical safety data
There was no evidence of genotoxicity in a series of in vitro and in vivo genotoxicity studies. In laboratory animals at a clinically relevant exposure level the following deviations were seen, which as yet have not been confirmed in long-term clinical research:

In rats, pigment deposition in the thyroid gland has been observed; in cynomolgus monkeys thyroid follicular cell hypertrophy, a lowering in plasma T3 levels, decreased haemoglobin concentration and a decrease of red and white blood cell count have been observed; and in dogs lens opacity and cataracts.

Taking these findings into consideration, the benefits of the treatment with quetiapine need to be balanced against the safety risks for the patient.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Core
- Microcrystalline cellulose
- Sodium citrate
- Lactose monohydrate
- Magnesium stearate
- Hypromellose

Coating
- Hypromellose
- Macrogol 400
- Titanium dioxide (E171)

6.2 Incompatibilities
Not applicable.
6.3 Shelf life
3 years

6.4 Special precautions for storage
Do not store above 30°C. Store in the original package.

6.5 Nature and contents of container
PVC+PCTFE/aluminium blisters

<table>
<thead>
<tr>
<th>Carton (pack) contents</th>
<th>Blisters</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 tablets</td>
<td>1 blister of 10 tablets</td>
</tr>
<tr>
<td>30 tablets</td>
<td>3 blisters of 10 tablets</td>
</tr>
<tr>
<td>50 tablets</td>
<td>10 blisters of 5 tablets</td>
</tr>
<tr>
<td>60 tablets</td>
<td>6 blisters of 10 tablets</td>
</tr>
<tr>
<td>100 tablets</td>
<td>10 blisters of 10 tablets</td>
</tr>
</tbody>
</table>

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
AstraZeneca UK Ltd
600 Capability Green
Luton
LU1 3LU
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 17901/0259

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
12/03/2010

10 DATE OF REVISION OF THE TEXT
12/03/2010
UKPAR Seroquel XL 150mg Prolonged-Release Tablets

PATIENT INFORMATION LEAFLET (PIL)

The PIL below is the PIL agreed at the end of procedure. The marketing authorisation holder has stated that it is not intending to market the product and, thus, no PIL mock-up has been submitted. The marketing authorisation holder has committed to submit the UK PIL and labelling mock-ups for review to the regulatory authority before marketing the product.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Seroquel XL 50 mg, 150 mg, 200 mg, 300 mg, 400 mg prolonged-release tablets:

quetiapine fumarate

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Seroquel XL is and what it is used for
2. Before you take Seroquel XL
3. How to take Seroquel XL
4. Possible side effects
5. How to store Seroquel XL
6. Further information

1. What Seroquel XL is and what it is used for

Seroquel XL contains a medicine called quetiapine. This belongs to a group of medicines called antipsychotics. These medicines help with the effects of certain types of mental illness, such as:

- Hallucinations (like hearing unexplained voices), strange and frightening thoughts, changes in how you act and feeling alone and confused. This is also known as schizophrenia.
- Effects on your mood and feeling very 'high' or excited. You may find that you need to sleep less than usual. You may be more talkative and have racing thoughts or ideas. You may also feel more irritable than usual. This is also known as bipolar mania.
- Effects on your mood whereby you feel sad all the time. You may find that you feel depressed, feel guilty, lack energy, lose your appetite and/or can't sleep. This is also known as bipolar depression.

Your doctor may continue to give you Seroquel XL when you are feeling better to prevent your symptoms from returning.

You may find it helpful to tell a friend or relative that you are suffering from these symptoms, and ask them to read this leaflet. You might ask them to tell you if they think your symptoms are getting worse, or if they are worried about any other changes in your behaviour.

2. Before you take Seroquel XL

Do not take Seroquel XL if:

- you are allergic (hypersensitive) to quetiapine or any of the other ingredients of Seroquel XL (see section 6. Further information)
- you are taking any of the following medicines:
  - protease inhibitors, such as nelfinavir (for HIV infection)
  - azole medicines (for fungal infections)
  - medicines for an infection (like erythromycin or clarithromycin)
  - nefazodone (for depression).

Do not take Seroquel XL if the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking Seroquel XL.
Take special care with Seroquel XL

Seroquel XL should not be taken by elderly people with dementia (loss of brain function). This is because the group of medicines that Seroquel XL belongs to may increase the risk of stroke, or in some cases the risk of death, in elderly people with dementia.

Before you take your medicine, tell your doctor if:
- You have any health problems (like heart problems or low blood pressure) or you have had a stroke.
- You have problems with your liver.
- You have ever had a fit (seizure).
- You know that you have had low levels of white blood cells in the past (which may or may not have been caused by other medicines).
- You have diabetes or have a risk of getting diabetes. If you do, your doctor may check your blood sugar levels while you are taking Seroquel XL.
- You or someone else in your family has a history of blood clots, as medicines like these have been associated with formation of blood clots.

Thoughts of suicide and worsening of your depression
If you are depressed you may sometimes have thoughts of harming or killing yourself. These may be increased when first starting treatment, since these medicines take time to work, usually about two weeks but sometimes longer. You may be more likely to think like this if you are a young adult. Information from clinical trials has shown an increased risk of suicidal thoughts and/or suicidal behaviour in young adults aged less than 25 years with depression.

If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away. You may find it helpful to tell a relative or close friend that you are depressed, and ask them to read this leaflet. You might ask them to tell you if they think your depression is getting worse, or if they are worried about changes in your behaviour.

Taking other medicines
Please tell your doctor if you are taking or have recently taken any other medicines. This includes medicines obtained without a prescription and herbal medicines.

In particular, tell your doctor or pharmacist if you are taking:
- Medicines for anxiety or depression.
- Epilepsy medicines (like phenytoin or carbamazepine).
- High blood pressure medicines.
- Rifampicin (for tuberculosis).
- Barbiturates (for difficulty sleeping).
- Thioridazine (another anti-psychotic medicine).

Before you stop taking any of your medicines, please talk to your doctor or pharmacist first.

Taking Seroquel XL with food and drink
- Seroquel XL should be taken without food, at least one hour before a meal.
- Be careful how much alcohol you drink. This is because the combined effect of Seroquel XL and alcohol can make you sleepy.
- Do not drink grapefruit juice while you are taking Seroquel XL. It can affect the way the medicine works.

Pregnancy and breast-feeding
If you are pregnant, trying to get pregnant, or breast-feeding, talk to your doctor or pharmacist before taking Seroquel XL.
Driving and using machines:
Your tablets may make you feel sleepy. Do not drive or use any tools or machines until you know how the tablets affect you.

Hospital - If you go into hospital, tell the medical staff that you are taking Seroquel XL.

Important information about some of the ingredients of Seroquel XL:
Seroquel XL contains lactose which is a type of sugar. If you have been told by your doctor or pharmacist that you cannot tolerate or digest some sugars, talk to your doctor before taking this medicine.

If you have been on other medication for this condition, and that medication has stopped your periods, changing to Seroquel XL may allow them to return.

3. How to take Seroquel XL
Always take Seroquel XL exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. Your doctor will decide on your starting dose and may gradually increase it. After this the dose will usually be between 200 mg and 800 mg each day. It depends on your illness and needs.
- You will take your tablets once a day.
- Swallow your tablets whole with a drink of water.
- Do not split, chew, or crush the tablets.
- Do not stop taking your tablets even if you feel better, unless your doctor tells you.

Seroquel XL tablets are available in 3 different strengths and each strength is a different colour.
- Even though the dose might stay the same, it might be supplied as different strength tablets. For example one 400 mg tablet (white) or two 200 mg tablets (yellow).
- So don’t be surprised if the colour of your tablets changes from time to time.

Liver problems:
If you have liver problems your doctor may give you a lower dose.

Elderly people:
If you are elderly your doctor may give you a lower dose.

Children and adolescents under 18 years:
Seroquel XL should not be used by children and adolescents aged under 18 years.

If you take more Seroquel XL than you should:
If you take more Seroquel XL than prescribed by your doctor, go to your doctor or nearest hospital straight away. Take the Seroquel XL tablets with you.

If you forget to take a dose of Seroquel XL:
If you forget to take a dose, take it as soon as you remember. If it is almost time to take the next dose, wait until then. Do not take a double dose to make up for a forgotten tablet.

If you stop taking Seroquel XL:
If you suddenly stop taking Seroquel XL, you may feel nauseous or vomit, or be unable to sleep or have jerky movements, or your original illness might come back. Your doctor may suggest you reduce the dose gradually before stopping treatment.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects:
Like all medicines, Seroquel XL can cause side effects, although not everybody gets them.
If any of the following happen, stop taking Seroquel XL and contact a doctor or go to the nearest hospital straight away, as you may need urgent medical attention:

**Uncommon** (affects less than 1 in 100 people):
- Fits or seizures
- Allergic reactions that may include raised lumps (wells), swelling of the skin and swelling around the mouth
- Uncontrollable movements, mainly of your face or tongue (Tardive dyskinesia).

**Rare** (affects less than 1 in 1,000 people):
- A high temperature (fever), long lasting sore throat or mouth ulcers, faster breathing, sweating, stiff muscles, feeling very drowsy or faint, large increase in blood pressure or heartbeat.
- Jaundice (yellowing of the skin and eyes).
- Priapism (a long-lasting and painful erection).
- Blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing.

**Very rare** (affects less than 1 in 10,000 people):
- Severe allergic reaction that may include difficulty in breathing, dizziness and collapse.
- Hepatitis (inflammation of the liver).
- Rapid swelling of the skin, usually around the eyes, lips and throat.

**Other possible side effects:**

**Very common** (affects more than 1 in 10 people):
- Dizziness (may lead to falls), headache, dry mouth.
- Feeling sleepy (this may go away with time, as you keep taking Seroquel XL) (may lead to falls).
- Discontinuation symptoms (symptoms which occur when you stop taking Seroquel) include not being able to sleep (insomnia), feeling sick (nausea), headache, dizziness, being sick (vomiting), dizziness and irritability. They usually go away after 1 week from your last dose.
- Putting on weight.

**Common** (affects less than 1 in 10 people):
- Rapid heartbeat.
- Stuffy nose.
- Constipation, upset stomach (indigestion).
- Feeling weak, fainting (may lead to falls).
- Swelling of arms or legs.
- Low blood pressure when standing up. This may make you feel dizzy or faint (may lead to falls).
- High blood sugar.
- Blurred vision.
- Abnormal muscle movements. These include difficulty starting muscle movements, shaking, feeling restless or muscle stiffness without pain.
- Abnormal dreams and nightmares.
- Feeling more hungry.
- Feeling iritated
- Disturbance in speech or language.

Uncommon (affects less than 1 in 100 people):
- Restless legs.
- Difficulty swallowing.

Rare (affects less than 1 in 1,000 people):
- Swelling of breasts and unexpected production of breast milk (galactorrhoea).

Very rare (affects less than 1 in 10,000 people):
- Worsening of pre-existing diabetes.
- A severe rash, blisters or red patches on the skin.

Some side effects are only seen when a blood test is taken. These include changes in the amount of certain fats (triglycerides and total cholesterol) or sugar in the blood, decreases in the number of certain types of blood cells and increases in the amount of the hormone prolactin in the blood. Increases in the hormone prolactin could in rare cases lead to the following:
- Men and women to have swelling of breasts and unexpectedly produce breast milk.
- Women to have no monthly period or irregular periods.

Your doctor may ask you to have blood tests from time to time.

If any of the side effects get serious, or if you notice side effects not listed in this leaflet, please tell your doctor or pharmacist.

Children and adolescents:
The same side effects that may occur in adults may also occur in children and adolescents.

The following side effect has been seen only in children and adolescents:

Very Common (affects more than 1 in 10 people):
- Increase in blood pressure.

The following side effects have been seen more often in children and adolescents:

Very Common (affects more than 1 in 10 people):
- Increase in the amount of a hormone called prolactin in the blood. Increases in the hormone prolactin could in rare cases lead to the following:
  - boys and girls to have swelling of breasts and unexpectedly produce breast milk
  - girls to have no monthly period or irregular periods.
- Increased appetite.
- Abdominal muscle movements. These include difficulty starting muscle movement, shaking, feeling restless or muscle stiffness without pain.

5. How to store Seroquel XL:
- Do not store above 30°C. Store in the original package.
- Keep your Seroquel XL tablets in a safe place, where children cannot see or reach them.
- Do not use Seroquel XL after the expiry date which is stated on the container. The expiry date refers to the last day of that month.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.
6. Further information

What Seroquel XL contains:

- Each tablet contains either 50 mg, 150 mg, 200 mg, 300 mg or 400 mg of quetiapine (as quetiapine fumarate).
- The other ingredients are microcrystalline cellulose, sodium citrate, lactose monohydrate, magnesium stearate, hypromellose, macrogol 6000, titanium dioxide (E171). The 50 mg, 200 mg and 300 mg tablets also contain ferric oxide (E172).

What Seroquel XL looks like and contains: of the pack:

All tablet strengths are capsule shaped and marked with XR and the strength. 50 mg tablets are peach coloured; 150 mg tablets are white coloured; 200 mg tablets are yellow coloured; 300 mg tablets are pale yellow coloured; 400 mg tablets are white coloured.

Pack sizes of 10, 30, 50, 60 and 100 tablets are registered for all strengths. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer:

- The marketing authorisations for Seroquel XL are held by AstraZeneca UK Ltd, 600 Capability Green, Luton, LU1 3LU, United Kingdom.
- The tablets are made by AstraZeneca UK Ltd, Silk Road Business Park, Macclesfield, Cheshire, SK10 2NA, United Kingdom.

This leaflet was last updated in February 2010

Seroquel XL is a trade mark of the AstraZeneca group of companies.

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You can also get information on mental health from the following national organisations:

- MIND (National Association for Mental Health): Mindline: 0845 7660163
- REHAB (formerly the National Schizophrenia Fellowship) Advice Service: 0208 9746814
- National Schizophrenia Fellowship (Scotland): 0131 662 4359
- SANELINE Helpline: 0845 7678000

To listen to, or request a copy of this leaflet in Braille, large print or audio please call, free of charge: 0800 198 5000 (UK only). Please be ready to give the following information:

**Product name** | **Reference number**
--- | ---
Seroquel XL, prolonged release tablets 50 mg | PL 17901/0249
Seroquel XL, prolonged release tablets 150 mg | PL 17901/0259
Seroquel XL, prolonged release tablets 200 mg | PL 17901/0259
Seroquel XL, prolonged release tablets 300 mg | PL 17901/0251
Seroquel XL, prolonged release tablets 400 mg | PL 17901/0252

This is a service provided by the Royal National Institute of Blind People.

CNS 10 0034
PACKAGING
The labelling below is the label agreed at the end of procedure. The marketing authorisation holder has stated that it is not intending to market the product and, thus, no labelling mock-ups have been submitted. The marketing authorisation holder has committed to submit the UK PIL and labelling mock-ups for review to the regulatory authority before marketing the product.

Carton Text Seroquel XL 150 mg Tablets

Front panel 60 tablets:
150 mg

[Seroquel XL Brand logo]
150 mg prolonged release tablets
quetiapine (as fumarate)

[Information in Braille: Seroquel XL 150 mg]
[AstraZeneca logo and blue strips]

Side panel 1 Each tablet contains 150 mg quetiapine (as fumarate). Contains lactose monohydrate. See leaflet for further details. Do not split, chew or crush the tablets. Read the package leaflet before use. Oral use. Use as directed by your physician. Keep out of the reach and sight of children. Do not store above 30°C. Store in the original package.

[Seroquel XL Brand logo]
150 mg prolonged release tablets
quetiapine (as fumarate)

Side panel 2 AstraZeneca UK Ltd, 600 Capability Green, Luton, LU1 3LU, United Kingdom
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[Blue box for local requirements]
[Bar code area]
PL 17901/0259

Back panel 60 tablets:
150 mg

[Seroquel XL Brand logo]
150 mg prolonged release tablets
quetiapine (as fumarate)

[POM]

[AstraZeneca Logo]

End panel 1  
EXP  [Variable data to be overprinted during production]
LOT

End panel 2  
150 mg

[Seroquel XL Brand logo]
150 mg prolonged release tablets
quetiapine (as fumarate)
Blister Text Seroquel XL 150 mg Tablets

[Seroquel XL Brand logo] 150 mg quetiapine (as fumarate)

AstraZeneca

EXP [Variable data to be overprinted during production]
LOT