SEROQUEL XL 50MG PROLONGED-RELEASE TABLETS
PL 17901/0249

SEROQUEL XL 200MG PROLONGED-RELEASE TABLETS
PL 17901/0250

SEROQUEL XL 300MG PROLONGED-RELEASE TABLETS
PL 17901/0251

SEROQUEL XL 400MG PROLONGED-RELEASE TABLETS
PL 17901/0252

(QUETIAPINE FUMARATE)

UKPAR

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SEROQUEL XL 50MG, 200MG, 300MG & 400MG PROLONGED-RELEASE TABLETS  
(QUETIAPINE FUMARATE)  
PL 17901/0249-0252

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted AstraZeneca UK Ltd. Marketing Authorisations (licences) for the medicinal products Seroquel XL 50mg, 200mg, 300mg and 400mg prolonged-release Tablets (PL 17901/0249-0252) on 10th September 2008. These are prescription-only medicines (POM) used to help with the effects of certain types of mental illness, such as:

- Hallucinations, 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 disorder.

The active ingredient, quetiapine fumarate, is one of a group of medicines known as antipsychotics. In adults, for the treatment of both schizophrenia and episodes associated with bipolar disorder, the daily dose at the start of therapy is 300mg on Day 1 and 600mg on Day 2. The dose is then adjusted within the dose range of 400mg to 800mg per day, to suit the individual patient.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Seroquel XL 50mg, 200mg, 300mg and 400mg prolonged-release Tablets outweigh the risks; hence Marketing Authorisations (MAs) have been granted.

The terms XL, XR and SR are used interchangeably in the report and refer to the sustained (prolonged) release formulation of the product. The term IR refers to the immediate release formulation.
SEROQUEL XL 50MG, 200MG, 300MG & 400MG PROLONGED-RELEASE TABLETS
(QUETIAPINE FUMARATE)
PL 17901/0249-0252

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 Marketing Authorisations for the medicinal products Seroquel XL 50mg, 200mg, 300mg and 400mg prolonged-release Tablets (PL 17901/0249-0252) on 10th September 2008. The products are prescription-only medicines (POM).

These are national complex full applications for Seroquel XL 50mg, 200mg, 300mg and 400mg prolonged-release Tablets, four strengths of quetiapine, submitted under Article 8.3 of Directive 2001/83/EC, as amended. The applications were submitted as Extension Applications in accordance with Annex II of EC/1084/2003, cross referring to Seroquel 25mg, 100mg, 200mg and 150mg film coated tablets (PL 17901/0038-0041 respectively - AstraZeneca UK Ltd); the reference products contain the same active substance, quetiapine fumarate; the extension applications are prolonged release pharmaceutical forms of the immediate release reference product.

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. Seroquel XL Tablets are indicated in the treatment of schizophrenia and manic episodes of bipolar disorder.

In adults, for the treatment of schizophrenia, the daily dose at the start of therapy is 300mg on Day 1 and 600mg on Day 2. Doses greater than 600 mg per day should be initiated by a specialist. The dose is then adjusted within the effective dose range of 400mg to 800mg per day, depending on the clinical response and tolerability of the patient.

In adults, for the treatment of manic episodes associated with bipolar disorder, the daily dose at the start of therapy is 300mg on Day 1, 600mg on Day 2 and up to 800mg after Day 2. Again, the dose is then adjusted within the effective dose range of 400mg to 800mg per day, depending on the clinical response and tolerability of the patient.

The applications were referred to the Commission on Human Medicines (CHM) who met in December 2007 for consideration whether the safety, quality and efficacy of the product was demonstrated. At that time, the Commission advised that Marketing Authorisations should not be approved. Following consideration of the applicant’s responses and further data that were submitted, the approval of the Marketing Authorisations was recommended.

These applications for Seroquel XL 50mg, 200mg, 300mg and 400mg prolonged-release Tablets were submitted at the same time and depend on the various pre-clinical and clinical studies presented. Consequently, all sections of the Scientific Discussion refer to all four products. The terms XL, XR and SR are used interchangeably in the report and refer to the sustained (prolonged) release formulation of the product. The term IR refers to the immediate release formulation.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

Quetiapine fumarate

Nomenclature:

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

Structure:

![Structure diagram]

Molecular formula: \(C_{21}H_{25}N_3O_2S, C_4H_4O_4\)
Molecular weight: 883.1
CAS No: 111974–69–7 (base); 111974–72–2 (fumarate salt)
Physical form: White to off-white powder
Solubility: 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 retest period of 3 years when stored at a temperature below 30°C.

**DRUG PRODUCT**

**Description and Composition**

Seroquel XL 50mg, 200mg, 300mg and 400mg prolonged-release Tablets are all bi-convex and capsule shaped. The 50mg strength tablets are peach coloured and marked with ‘XR50’ on one side. The 200mg strength tablets are yellow and marked with ‘XR200’ on one side. The 300mg strength tablets are pale yellow and marked with ‘XR300’ on one side. The 400mg strength tablets are white and marked with ‘XR400’ on one side.

Other ingredients consist of pharmaceutical excipients, namely sodium citrate, microcrystalline cellulose, lactose monohydrate, hypromellose and magnesium stearate making up the tablet cores; and hypromellose, macrogol 400, and titanium dioxide (E171) making up the tablet coatings. Additionally, the tablet coatings for the 200mg and 300mg strength tablets contain ferric oxide, yellow (E172); and the tablet coating for the 50mg strength tablets contain ferric oxide, yellow (E172) and ferric oxide, red (E172). Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis (CofAs) have been provided for all excipients.

The magnesium stearate is of vegetable origin. The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption.

There were no novel excipients used and no overages.

**Dissolution profiles**

A satisfactory dissolution profile was provided.

**Pharmaceutical development**

Details of the pharmaceutical development of the drug products have been supplied and are satisfactory.

**Manufacture**

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are satisfactory.
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.

Container Closure System

The tablets are marketed in PVC (polyvinylchloride) / PCTFE (Polychlorotrifluoroethylene) blister strips, bonded to aluminium foil, which are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons. The finished products are packaged in carton pack sizes of 10, 30, 50, 60 and 100 tablets. The MA Holder has stated that not all pack sizes may be marketed.

Specifications and Certificates of Analysis for all packaging components used have been provided. These are satisfactory. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 3 years has been set, which is satisfactory. Storage conditions are ‘Do not store above 30°C’ and ‘Store in the original package’.

Bioequivalence Study

Several bioequivalence studies were presented, comparing the bioavailability of the test product formulation (prolonged release) to the reference product formulation (immediate release).

An evaluation of the bioequivalence studies, and of the other pharmacokinetic, pharmacodynamic, clinical efficacy, and safety studies is found in the Clinical Assessment section.

Expert Report

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

Product Information

The approved SmPCs, leaflet, and labelling are satisfactory. Colour mock-ups of the labelling have been provided. The labelling is satisfactory and fulfils the statutory requirements for Braille.

Conclusion

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. It was recommended that Marketing Authorisations be granted.
PRECLINICAL ASSESSMENT

These are full national applications for Seroquel XL 50mg, 200mg, 300mg and 400mg prolonged-release Tablets, submitted under Article 8.3 of Directive 2001/83/EC, as amended. The applications were submitted as Extension Applications, cross referring to Seroquel 25mg, 100mg, 150mg and 200mg film coated tablets, AstraZeneca UK Ltd (PL 17901/0038, 0039, 0041 and 0040 respectively) The reference products contain the same active substance, quetiapine fumarate; the extension applications are prolonged release pharmaceutical forms of the immediate release reference product.

No new preclinical data have been supplied with these applications and none are required for applications of this type. A preclinical overview has been written by a suitably qualified person and is satisfactory.
**CLINICAL ASSESSMENT**

1  INTRODUCTION

1.1  TYPE OF APPLICATION AND REGULATORY BACKGROUND

These national applications are for prolonged release tablets containing 50, 200, 300 and 400mg of quetiapine, as quetiapine fumarate. The applicant is AstraZeneca UK Limited. This application is submitted under Article 8.3(i) of Directive 2001/83/EC, as amended. The dossier is submitted as an Extension Application in accordance with Annex II of EC/1084/2003, cross referring to Seroquel film coated tablets (PL 17901/0038-0041).

1.2  CLINICAL BACKGROUND

Quetiapine is an atypical antipsychotic agent. Quetiapine and the active human plasma metabolite, N-desalkyl quetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and N-desalkyl quetiapine exhibit affinity for brain serotonin (5HT₂) and dopamine D₁ and D₂ receptors. Quetiapine exhibits a higher affinity for serotonin (5HT₂) receptors in the brain than it does for dopamine D₁ and D₂ receptors in the brain. Additionally, N-desalkyl quetiapine has high affinity at serotonin 5HT₁ receptors. Quetiapine and N-desalkyl quetiapine 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.

The currently available immediate release (IR) formulation of quetiapine is marketed as Seroquel. In addition to its established efficacy in the treatment of schizophrenia, Seroquel IR is also indicated for the treatment of manic episodes associated with bipolar disorder. Seroquel IR tablets for the treatment of schizophrenia are administered twice a day, with a recommended 4 day treatment initiation period to reach a dose of 300mg/day. The usual effective dose is 300-450mg/day, though the maximum recommended dose is currently 750mg/day.

AstraZeneca has developed a sustained release formulation of quetiapine (Seroquel XL) to allow once daily administration instead of twice daily as required with the IR preparation. The maximum proposed dose for Seroquel XL is increased to 800mg/day, compared with the 750mg/day for the IR formulation. The applicant proposes to accelerate the dose titration of the XL preparation, starting with a 300mg dose on Day 1 of treatment, with dose increases to 600mg on Day 2 and up to 800mg after Day 2. AstraZeneca UK Ltd. has conducted additional pharmacological and pharmacokinetic studies and efficacy studies. No new non-clinical studies have been conducted.

1.3  INDICATIONS

Seroquel XL prolonged-release tablets are indicated in the treatment of schizophrenia, and manic episodes associated with bipolar disorder. The indications are satisfactory.

1.4  DOSE AND DOSE REGIMEN

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. Full dosing information is provided in the SPC.
1.5 GCP ASPECTS
The applicant makes the statement that the clinical study programme was carried out in accordance with Good Clinical Practice guidelines. Appropriate regulatory and ethics approval of the clinical studies was obtained in accordance with local requirements.

1.6 ORPHAN MEDICINAL PRODUCTS
These indications have not been designated as orphan conditions, therefore information on market exclusivity or similarity is not applicable.

2 CLINICAL PHARMACOLOGY

2.1 PHARMACOKINETICS

2.1.1 Introduction and overview
The CPMP notes for guidance on the investigation of modified release oral and transdermal dosage forms (CPMP/EWP/280/96) state that in the investigation of bioavailability of such products, the following are to be addressed:

- the rate and extent of absorption
- fluctuations in drug concentrations
- variability in pharmacokinetics arising from the drug formulation
- dose proportionality
- factors influencing the performance of the modified drug formulation
- the risk of unexpected release characteristics (eg dose dumping)

In addressing these requirements, the clinical pharmacology programme was designed to characterise those aspects of quetiapine pharmacokinetics or pharmacodynamics pertinent to the sustained release formulation. The first three studies in the programme focused on characterising the pharmacokinetics of pilot scale formulation variants at various dose strengths. These data aided in the selection of a suitable formulation to develop into commercial scale tablets, which were then investigated further in the subsequent studies.

From the published literature concerning the immediate release preparation, quetiapine is found to be well absorbed and the bioavailability is not significantly affected by administration with food. It circulates approximately 83% bound to plasma proteins.

Quetiapine is extensively metabolised by the liver so that <5% of an oral dose is found excreted unchanged in the urine. In vitro studies suggest that the CYP3A4 enzyme is the enzyme principally responsible for drug metabolism. The major, active, metabolite is N-desalkyl quetiapine, which is also eliminated via CYP3A4. CYP2D6 and CYP2C9 are also involved in quetiapine metabolism. Other known metabolites include 7-hydroxy quetiapine and quetiapine sulfoxide.

Both quetiapine and its metabolites are found to be weak inhibitors of Cytochrome P450 3A4, 2C19, 2D6, 1A2 and 2C9 in vitro. This inhibition is only seen at concentrations 5-50 fold higher than those observed at a dose range of 300 to 800mg/day in humans. Therefore, it is deemed unlikely that co-administration of
quetiapine with other P450 metabolised drugs will result in their altered metabolism. From animal studies, it appears that quetiapine can induce cytochrome p450 enzymes. No increase in activity was found in a specific interaction study performed in psychotic patients during the investigation of the IR preparation, however.

In total, the biopharmaceutical program was comprised of 7 pharmacokinetic studies:

<table>
<thead>
<tr>
<th>Study identifiers</th>
<th>Study design and objective</th>
<th>Study population*</th>
</tr>
</thead>
<tbody>
<tr>
<td>5077L/0036; 036</td>
<td>Open-label, crossover study to compare the bioavailability of quetiapine from the IR formulation (150 mg twice daily) and each of three 300-mg SR formulations (SR-A, SR-B, SR-C) with different in vitro drug-release rates and the effect of food on the bioavailability of the SR formulations</td>
<td>Patients with schizophrenia, schizoaffective disorder, or bipolar disorder</td>
</tr>
<tr>
<td>5077L/0037; 037</td>
<td>Open-label, pseudo-single-dose study to compare the bioavailability of quetiapine from the IR formulation and each of two 300-mg SR formulations (SR-C, SR-D) and to assess dose-unit proportionality of the 50-mg, 200-mg, and 300-mg formulations with the target dissolution profile (SR-C)</td>
<td>Patients with schizophrenia, schizoaffective disorder, or bipolar disorder</td>
</tr>
<tr>
<td>5077L/0086; 086</td>
<td>Open-label, steady-state study to evaluate dose proportionality of quetiapine SR over the proposed dose range (100 mg, 200 mg, 300 mg, 600 mg, and 800 mg) and to assess the effect of food on the 200-mg and 300-mg SR tablets</td>
<td>Patients with schizophrenia</td>
</tr>
<tr>
<td>5077L/0097; 097</td>
<td>Open-label, steady-state, randomized, crossover study to compare the bioavailability of quetiapine SR 300 mg once daily to quetiapine IR 150 mg twice daily</td>
<td>Patients with schizophrenia, schizoaffective disorder, or bipolar disorder</td>
</tr>
<tr>
<td>5077L/0118; 118</td>
<td>Open-label, steady-state study to evaluate the dose-unit dose-proportionality of 4 commercial-scale quetiapine SR tablets (50 mg, 200 mg, 300 mg, and 400 mg) and to evaluate the effect of food on the bioavailability of 50-mg and 300-mg SR tablets</td>
<td>Patients with schizophrenia or schizoaffective disorder</td>
</tr>
<tr>
<td>D1444C00001; 001</td>
<td>Open-label, randomized crossover study to compare the bioavailability of quetiapine and its metabolites from the IR formulations (400 mg), three 400-mg SR formulations (SR-F, SR-T, SR-S), and a 50-mg SR-T tablet</td>
<td>Patients with schizophrenia or schizoaffective disorder</td>
</tr>
<tr>
<td>D1444C00003; 002</td>
<td>Open-label, 2-cohort, randomized, crossover, steady-state study to evaluate the effect of food on the bioavailability of quetiapine and its metabolites for the 50-mg and 300-mg SR tablets</td>
<td>Patients with schizophrenia, schizoaffective disorder or bipolar disorder and healthy volunteers</td>
</tr>
</tbody>
</table>

* Enrolled population.

b After each of the 4 randomized treatments, patients were given quetiapine IR 150 mg every 12 hours, beginning at 1900 hours on the day following the randomized treatment and ending at 1900 hours on the day preceding the next randomized treatment (a total of 3 doses).

c Study treatments were separated by 2 days of quetiapine IR 200 mg administered twice daily, with the 50-mg dose administered 48 hours after the last 400-mg treatment.

IR Immediate release. SR Sustained release

All 7 studies enrolled patients with schizophrenia or other selected psychotic disorders, except for study D1444C00003 which also involved healthy volunteers. This was because orthostatic hypotension and somnolence had been noted to occur during initiation of therapy in healthy volunteers when the IR preparation was being studied. The studies all involved a multiple dosing design in an effort to maintain clinical stability in the patient population and avoid potential relapse of their symptomatology.
2.2 STUDIES IN PILOT SCALE PREPARATIONS

2.2.1 Study 5077IL/0036

The objective of this study was to compare the bioavailability of the immediate release formulation and three pilot-scale 300mg sustained release formulations of Seroquel, and to determine the effect of a meal on the bioavailability of each formulation. As a secondary objective, the steady state plasma quetiapine concentration-time profiles of the 150mg IR formulation were compared.

Statistical evaluation was performed for AUC\(_{(0-24h)}\), C\(_{\text{max}}\) and C\(_{\text{min}}\) with ANOVA and the 90% confidence intervals for the ratio of test formulation over the reference formulation were calculated. There were no statistically significant differences in pre-dose plasma concentrations of quetiapine from the IR formulation, indicating that the PK parameters were calculated under steady state conditions.

The 90% confidence intervals for AUC\(_{0-24h}\) were within 80-125%, indicating that the bioavailabilities of the three SR formulations were comparable to that of the IR formulation. Both the C\(_{\text{max}}\) and the C\(_{\text{min}}\) of the SR formulations were lower than that of the IR formulation, except for the C\(_{\text{min}}\) of SR formulation C, which was found to have the most sustained plasma concentration-time profile.

No statistical analyses were performed on the data comparing the effect of food on the bioavailability of the SR formulations, though the effects of food on the bioavailability of the SR-C formulation were numerically smaller than those on the other two formulations.

2.2.2 Study 5077IL/0037

Formulation C, as investigated above, was found to have the slowest drug release characteristics, but the most sustainable plasma concentration-time profile. The decision was taken to test a further SR formulation - Formulation SR-D. In addition, a film coated version of the previously tested formulation C was included for comparison. The objective here was to compare the single dose bioavailability of quetiapine from each of 3 SR tablet dose strengths (50mg, 200mg and 300mg) and to assess the relative bioavailability of quetiapine 300mg tablets of the different SR formulations (C and D) using a 200mg IR formulation tablet as a reference (200mg being the highest IR dose strength available). In addition, the dose proportionality of the 50, 200 and 300mg SR tablets was investigated.

Statistical evaluation was performed for AUC\(_{(0-24h)}\), AUC\(_{(0-t)}\), C\(_{\text{max}}\) and T\(_{\text{max}}\). For the analysis of dose proportionality, AUC was the primary measurement and C\(_{\text{max}}\) the secondary, thereafter linear regression of the log transformed data was performed.

The results indicated that SR formulation D appeared to be even more bioavailable than the IR formulation. The estimate of the AUC slope calculated by linear regression was close to unity, suggesting that AUC is proportional to dose, or AUC = \(\alpha \times \text{dose}\), \(\alpha\) being the intercept.
2.2.3 Study 5077IL/0086 – Food Effect

This was a multiple dose pharmacokinetic and food effect study using pilot scale Quetiapine SR. This study was also designed to demonstrate dose proportionality of the SR dosages based on the SR-C film coated formulation used in Study 37, above, up to a total daily dose of 800mg.

The log transformed values for AUC0-$\tau$, Cmax, Tmax and Cmin were analysed using an ANOVA model. The relative bioavailability of the SR and IR formulations at steady state were evaluated by constructing a 90% confidence interval for the SR/IR ratio for AUC0-$\tau$. For the analysis of dose proportionality, AUC was the primary measurement and Cmax the secondary, thereafter linear regression of the log transformed data was performed. The results showed that both AUC0-$\tau$ and Cmax increase in proportion to the dose.

From the linear regression estimation of dose proportionality, it was seen that the estimate of the slope for AUC is close to unity (0.9), suggesting dose linearity between the 100, 200, 300, 600, and 800mg tablet strengths in the fasted state.

The results comparing absorption in the fed and fasted state at 200mg and 300mg show that food has reduced the mean values for AUC0-$\tau$ (ie absorption) by approximately 1% and 5% in the fed state compared with the fasted state for the 200mg and 300mg dose strengths respectively.

Assessor’s comment
The estimation of both food effect and dose linearity involved two different formulations of the test drug in combination.

2.3 STUDIES PERFORMED IN COMMERCIAL SCALE PREPARATIONS

2.3.1 Study 5077IL/0097

Twenty-eight subjects with a known history of psychotic disorders were randomised into this single centre, open label, 2 period crossover bioavailability trial. The study was designed to compare the steady state pharmacokinetics of commercial scale production SR quetiapine versus the IR formulation.

The log transformed values for AUC0-24, Cmax, Tmax and Cmin were analysed using an ANOVA model. The relative bioavailability of the SR and IR formulations at steady state were evaluated by constructing a 90% confidence interval for the SR/IR ratio for AUC0-24. The results for the trough concentrations were analysed. ANOVA of the Cmin data indicated that quetiapine concentrations reached steady state within each treatment sequence and trial period.

The SR/IR ratio for AUC0-24 was 1.04, with 90% confidence intervals within 80-125%. The Cmax of the SR formulation was approximately 13% lower than that of the IR formulation, as expected, while the Cmin was essentially similar. The median degree of fluctuation, a measure of how Cmax and Cmin fluctuate around the time averaged plasma concentration (AUC0-24/24), was similar for both the IR and SR formulations at 171.8 and 155.7% respectively. The percentage peak-to-trough variation for the SR formulation was 80.7%. That for the IR formulation was 83.0%.
2.3.2 Study 5077IL/0118 – Food Effect

The purpose of this study was to evaluate the steady state pharmacokinetics of commercial scale 50, 200, 300 and 400mg Quetiapine SR tablets and to evaluate the effect of food on the bioavailability of the 50 and 300mg tablet strengths, as these tablets differ in their composition. The composition of the 200mg and 400mg tablets strengths was claimed to be sufficiently similar as to preclude any significant differences in food effect.

The log transformed values for AUC0-τ, Cmax, Tmax and Cmin were analysed using an ANOVA model. The relative bioavailability of the SR and IR formulations at steady state were evaluated by constructing a 90% confidence interval for the SR/IR ratio for AUC0-τ. For the analysis of dose proportionality, AUC was the primary measurement and Cmax the secondary, thereafter linear regression of the log transformed data was performed.

The results from the ten evaluable subjects showed that, in the fasted state, the drug exposure increases in an approximately dose proportional fashion. This is confirmed using linear regression, where the slope of both Cmax and AUC0-τ is close to unity.

The results from the food effect seem to indicate an increase in bioavailability for both the 50mg and the 300mg strength following a high fat meal. The AUC0-24 was increased for both strengths by around 20% following a high fat meal. It was noted that there were no undue adverse events recorded in relation to these dose strengths, despite the increased bioavailability.

2.3.3 Study D1444C00001

The objective of this trial was to compare the multiple dose pharmacokinetics of four sustained release preparations versus immediate release quetiapine in patients known to tolerate antipsychotic medication.

Log transformed Cmax, AUC 0-24 and AUC 0-t were separately analysed by ANOVA, with 90% confidence intervals constructed for the ratio of SR/IR. The data from 14 patients were included in the PK analysis.

It was seen that all 3 of the SR formulations had lower Cmax concentrations than the IR drug, though the AUC0-24 for all three were comparable to the IR formulations. The half life of quetiapine and the exposure to its metabolites appears to be independent of the formulation administered.

2.3.4 Study D1444C00003

Study 5077IL/0118 established statistically significant increases in Cmax and AUC following a high fat meal. This study was a steady state, food effect study that examined the effect of a light meal on the PK profile of commercial scale 50mg and 300mg SR quetiapine.

Log transformed Cmax, Cmin, AUC 0-24 and AUC 0-t were separately analysed by ANOVA, with 90% confidence intervals constructed for the ratio of fed/fasted. The results demonstrated that a ‘light’ meal did not result in any effect on the bioavailability of the SR formulations.
Assessor’s comment
Regarding food intake, in the note for guidance on the bioavailability and bioequivalence guideline (EMEA/CHMP/40326/2006), it states that ‘…for modified release products, a high fat meal is required.’ This study has shown that a light meal produced no effect on the bioavailability of the SR formulation. Study 5077IL/0118 established statistically significant increases in Cmax and AUC following a high fat meal. These data would seem to suggest that there is indeed a food effect, although the ‘light meal’ probably most closely resembles reality in the clinical setting.

2.3.5 Assessor’s overall conclusions on pharmacokinetics

The pharmacokinetic profile of quetiapine is well known. The applicant has provided data outlining the major features of the sustained release formulation. From these data, it can be seen that the bioavailability, in terms of AUC, is similar following administration of equivalent total daily doses of either the SR or IR formulation. Under fasting conditions, peak plasma quetiapine concentrations are achieved approximately 6 hours after administration of Quetiapine SR. The Tmax of the IR formulation is around 1 hour. The SR formulation can be seen to exhibit unit dose proportionality and linear pharmacokinetics.

Study 5077IL/0118 established statistically significant increases in Cmax and AUC following a high fat meal. Study D1444C00003 demonstrated no significant changes in absorption following a light meal (approx. 300 calories). In modified release products, the investigation of the effect of food on bioavailability should be performed with a high fat meal. In the absence of a high fat study that included the IR formulation for direct comparison, where the posology is not altered in regard to food, it remains difficult to interpret the clinical significance of the food effect, and it should not be concluded that the tablets can be taken without regard to food. In view of this, the approved SmPCs state that the medicine should be administered ‘once daily, without food (at least one hour before a meal)’.
2.4 PHARMACODYNAMICS

2.4.1 Introduction

The clinical pharmacology program commenced with two pharmacodynamic studies performed entirely in healthy volunteers: Study D1448C00008, and Study D1448C00013. Thereafter a further 4 pharmacodynamic studies, in which a total of 160 patients with schizophrenia, schizoaffective disorder, or bipolar disorder were given quetiapine SR, were performed. These studies were designed to investigate a starting dose of quetiapine SR considered appropriate for use in subsequent safety and efficacy studies. The studies also considered a suitable dose escalation scheme for subsequent safety and efficacy studies. The following studies were performed in patients:

<table>
<thead>
<tr>
<th>Study identifiers</th>
<th>Study design and objectives</th>
<th>Study population</th>
</tr>
</thead>
<tbody>
<tr>
<td>5077IL/0087; 087</td>
<td>Multi-center, double-blind, double-dummy, randomized, parallel group study with 4 treatment groups designed to establish a starting dose of quetiapine SR.</td>
<td>Patients with schizophrenia, schizoaffective disorder, or bipolar disorder.</td>
</tr>
<tr>
<td>5077IL/0098; 098</td>
<td>Single center, double-blind, double-dummy, randomized, parallel, 3 treatment group study designed to determine the highest tolerable starting dose of quetiapine SR.</td>
<td>Patients with schizophrenia, schizoaffective disorder, or bipolar disorder.</td>
</tr>
<tr>
<td>5077IL/0109; 109</td>
<td>Multicenter, double-blind, randomized, safety and tolerability 2-treatment-group study designed to compare a dose-escalation scheme for quetiapine SR with a fixed daily 300-mg dose of quetiapine SR.</td>
<td>Patients with schizophrenia, schizoaffective disorder, or disorganized schizophrenia.</td>
</tr>
<tr>
<td>5077IL/0145; 145</td>
<td>Multicenter, randomized, double-blind, parallel group, 3-treatment-group, inpatient, safety and tolerability study designed to compare 2 dose-escalation schedules of quetiapine SR to reach a daily dose of 800 mg with a fixed daily 300-mg dose of quetiapine SR.</td>
<td>Patients with schizophrenia or schizoaffective disorder.</td>
</tr>
</tbody>
</table>

SR: Sustained release.

2.4.2 PD Studies in Healthy Volunteers

Study D1448C00008

The purpose of this study was to assess the pharmacodynamic effects and tolerability of Quetiapine SR at a dose of 150mg in subjects who had not previously received atypical antipsychotic treatment. 63 healthy volunteers were randomised to receive either placebo or a dose of 150mg quetiapine SR in a treatment regimen of satisfactory design.

Nine subjects discontinued the study: 6 subjects withdrew consent; and 3 because of adverse effects. Two additional subjects completed at least two doses of each type of treatment and at least one post treatment measurement in each period, and so a total of 56 subjects were included for the purposes of tolerability analysis.

The overall intolerability of Quetiapine 150mg SR was more than 10% greater than compared with placebo. There was one serious adverse event recorded: a case of angioedema which occurred in a placebo subject and resolved within 40 minutes.
Quetiapine SR at 150mg was clinically intolerable compared to placebo in these normal, healthy volunteers. Additionally, the number of syncope and syncope-like events exceeded the limits defined in this study. Intolerability was primarily due to transient orthostasis and syncope events that occurred on the first day of exposure to quetiapine SR and attenuated within a day of continued treatment.

**Study 1448C00013**

This study, similarly to the previous, was performed in healthy volunteers and was designed to assess if there was a greater than 10% difference in intolerability between the escalated dosing of SR quetiapine and placebo.

68 healthy subjects were randomised to receive either placebo or an escalating dose of quetiapine SR in a treatment regimen of satisfactory design.

In all, 63 subjects completed the trial. Five subjects were withdrawn from the study, one due to adverse events. Two additional subjects, one in each arm, completed at least two doses of each type of treatment and at least one post-treatment measure in each period, which made their data eligible for the tolerability analysis. Thus, the tolerability analysis for each treatment contains data from 64 subjects in each period.

The number of subjects who had at least one intolerable event was higher for those subjects on quetiapine SR compared to those on placebo. There were no cases of syncope during this study. However, the number of subjects with syncope-like events exceeded the predefined study criteria for absolute intolerability. There was no apparent dose effect attributable to Quetiapine SR treatment for intolerability, the number of intolerable events increasing corresponding to the dose escalation days in the treatment group, as opposed to being proportional to the dose given.

The applicant concluded by stating that the lack of syncope with quetiapine SR allowed this dose escalation schedule to be considered for use in future clinical trials.

**Assessor’s comment**

Quetiapine SR was found to be clinically intolerable to healthy volunteers, that is to say subjects with no prior exposure to antipsychotic medications. It is acknowledged that there are known side effects associated with quetiapine, and that those experienced in these studies did not deviate from what would be expected. It is also of note that the side effects occurred at a similar frequency irrespective of dose strength administered.

The most concerning of the side effects experienced were the syncopal episodes, which occurred in 19.6% of the volunteers in the first trial. Appropriate warnings and information have been included in the SPC.

### 2.4.3 PD Studies in Patients

**Study 50771L/0087**

This trial was a multicentre, double-blind, double dummy, randomised, safety and tolerability trial designed to determine the highest tolerable starting dose of SR quetiapine in patients with prior exposure to antipsychotic medication.
87 patients were randomised to one of a number of treatment groups, each group receiving a different dose of quetiapine, either as the SR or IR formulation. The groups were balanced for demographic characteristics:

Of the 87 subjects enrolled, 81 completed the trial. Six subjects were withdrawn with satisfactory reasons for withdrawal. Safety assessments included adverse event recording, clinical laboratory tests, vital sign measurement, ECGs, physical examinations and interviews for subjective symptomatology. An adverse event was defined as the development of a new medical condition or the deterioration of a pre-existing one.

Overall, the most frequently reported adverse events during treatment with quetiapine were insomnia, somnolence and headache:

Among subjects treated with the SR formulation of quetiapine, no dose related pattern was apparent in the occurrence of these side effects. Average heart rates increased during treatment with quetiapine, but did so across all treatment groups with no apparent dose or formulation differences. There were no electrocardiographic alterations other than an increase in ventricular rate. There were no alterations of note in the clinical laboratory tests or physical examination findings.

There was one serious adverse event whereby a patient developed transient cerebral ischaemia. This resolved without treatment and was found to be unrelated to the study medications.

Assessor’s comment
No real safety signals of note were observed in the treatment groups. However, in addition to assessing the safety of the trial drugs, the study was also intended to assess tolerability. However, no conclusions regarding tolerability can be concluded from the presented data. Tolerability is discussed in section 5.

Study 50771L/0098

The objective of this trial was to determine the tolerable starting dose (400, 600, or 800mg/day) of sustained release quetiapine by comparing the safety and tolerability of escalating dose regimens of both the SR and IR formulations. Patients with prior exposure to antipsychotics were included as before.

The study was discontinued after the first 21 patients had been treated in the first dose group (400mg SR, 50mg titrated up to 300mg IR). Some subjects treated with the 400mg SR formulation developed tachycardia, with pulse rates of around 160 bpm. Three of the 16 SR treated subjects had multiple recorded standing pulse rates of more than 140bpm and 9 had multiple recorded supine pulse rates of more than 100bpm. None of the subjects treated with the IR formulation had similar patterns of rapid pulse rates. The trial was discontinued. No subjects received the 600 or 800mg doses. There were no adverse events reported in relation to the tachycardias.

Assessor’s comment
The study conclusion is agreed that initiation of therapy with daily 400mg doses of SR quetiapine may not be generally well tolerated.
**Study 50771L/0109**

The objective of this trial was to determine the tolerability of the titration scheme proposed for use in the efficacy trials with the sustained release formulation using a fast titration scheme: 300mg on Day 1-4; 600mg on day 5-7; and 800mg on Days 8-12. If it was found that this regime was not tolerated, then a slower titration was to be investigated: 300mg on Days 1-3; 400mg on days 4-6; 600mg on Days 7-9 and 800mg on days 10-12. As a secondary objective, a correlation between any cardiovascular symptoms and plasma quetiapine concentration at Cmax was to be investigated.

One subject was withdrawn before the trial began as he tested positive for drugs of abuse. The other six withdrawals occurred because subjects failed to return for treatment.

Tachycardia and hypertension were the most common adverse events during treatment in each group. In the titrated SR group, 84% had at least one episode of tachycardia and 58% had at least one episode of hypertension. This is compared with 63% of subjects in the fixed dose developing a tachycardia or 63% hypertension:

There was no apparent correlation between plasma quetiapine concentration and changes in any of the measured vital signs and no additional exploratory analyses of these data were performed. Subjects who were treated according to the titrated dose regimen appeared to have few, if any, new side effects as their dose escalated. Despite the changes in vital sign measurements, there were few adverse events recorded in relation to these. The study concluded that a starting daily dose of 300mg was generally well tolerated with most subjects adapting to treatment with SR quetiapine during the first few days. The results of the safety assessments remained similar between treatment groups.

**Assessor’s comment**

It is considered that in addition to assessing the safety of the trial drugs, this trial was also intended to assess tolerability. The variables measured were not considered sufficient to address this area; therefore, no conclusions regarding tolerability can be concluded from the presented data. Tolerability is discussed in section 5.

While there may not have been any recorded ‘adverse events’ relating to changes in vital signs, it remains the case that there was a 21% increase in the frequency of tachycardia in the dose escalation group compared with the fixed dose group.

**Study 50771L/0145**

This study compared two different dose escalation regimens to a constant dose of SR quetiapine over a 7 day period. The following treatments were administered:

1. Fixed dose: 300mg quetiapine SR
2. Day 1: 200mg quetiapine SR  
Day 2: 400mg quetiapine SR  
Day 3: 600mg quetiapine SR  
Days 4-7: 800mg quetiapine SR
3. Day 1: 300mg quetiapine SR  
Day 2: 600mg quetiapine SR  
Day 3-7: 800mg quetiapine SR
A total of 52 patients were randomised, 16 to the fixed dose group, 19 to regime 2 and 17 to regime 3. All subjects had previously been exposed to antipsychotic medication, as before. 49 patients completed the trial: 14 in group 1, 19 in group 2 and 16 in group 3. The same safety variables were recorded as before.

Overall, the 10 most frequently reported adverse events during treatment were sedation, dizziness, somnolence, dry mouth, heart rate increased, reduction in systolic blood pressure, headache, agitation, anxiety, and nausea. Both dose escalation groups suffered a similar degree of adverse events to those in the fixed dose group. It was concluded that either titration scheme would be suitable for use in Phase III efficacy studies.

### 2.4.4 Assessor's overall conclusions on Pharmacodynamics

It is agreed that an acceptable level of safety was demonstrated in both of the rapid dose escalation regimes, when compared to a fixed dose patient group. To this end, Study 5077IL/0145 has provided a justification for a similar regime to be used in Phase III trials.

Tolerability has not been adequately demonstrated, particularly in subjects not previously exposed to atypical antipsychotics. The assessment of ‘tolerability’ in the healthy volunteers engaged a patient centred, subjective approach, supported by physiological variables. It was found that dose initiation at 150mg was clinically intolerable. Even the low initial dose escalation study was considered to fail to achieve tolerability, though it is agreed that any side effects were not considered to exhibit dose proportionality.

None of the pre-exposed patient studies assessed ‘tolerability’, as defined in the healthy volunteer studies. In assessing safety, the PK/PD studies performed in pre-exposed patients have confirmed possible signals – namely tachycardia and syncope/syncope-like events – upon treatment initiation. The main signal here was an unacceptably high frequency of heart rate increases in the 400mg SR treatment initiation group. This was the basis for selecting a lower treatment initiation dose. In the dose escalation initiated at 300mg when compared with a fixed dose, this group displayed a 21% greater frequency of tachycardias. Therefore the proposed product cannot be considered to be without risk. The approved SmPCs address this by stating that the dose should be adjusted ‘depending on the clinical response and tolerability of the patient.’ and by giving appropriate warnings.

The concerns are resolved by the general consideration that healthy volunteers are more sensitive to antipsychotic medications than patients with psychotic illness (Cutler 2001). Additionally, evidence from patients in the 3 large scale efficacy trials (Studies 132, 133 and 041) suggests that the safety and tolerability issues described in the healthy volunteer studies are not replicated in patients with psychotic illness. The two placebo-controlled, Phase III studies in patients with acute schizophrenia (Study 132 and 133) had similar design characteristics, including the 3-day dose-escalation scheme. These pooled studies had a large number of patients (n=679) exposed to quetiapine XL. During the first week of therapy the frequency of postural hypotension (orthostatic hypotension, orthostatic hypotension tachycardia syndrome and dizziness postural) was similar between the XL and IR regimens (0.6% and 0.8%). The observed incidence of syncope was also similar between treatment groups, 0.1% and
0.4% (XL and IR treatment groups respectively) during the first seven days. Overall there were no differences in the safety data between the 2 treatment groups, thereby confirming the tolerability of the proposed starting dose and titration regimen for quetiapine XL.

It is agreed that there were no particular safety signals raised in the Phase III trials provided by the applicant and there were no clinically significant differences seen between IR and SR formulations in the frequency of adverse events. This offers some reassurance. Overall it is assessed that no particular restriction in use need be applied.
3 CLINICAL EFFICACY

3.1 INTRODUCTION

The applicant has provided five phase III studies evaluating the efficacy and safety of quetiapine SR in patients with schizophrenia. Three studies address the treatment of acute schizophrenia, one study examines the prevention of relapse in clinically stable patients, and a further study investigates switching from the IR to the SR formulation in clinically stable patients:

<table>
<thead>
<tr>
<th>Study identifiers</th>
<th>Study design and objectives</th>
<th>Study population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo-controlled studies in acute schizophrenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D1444C00132 (132)</td>
<td>Multicentered, 6-week, placebo-controlled, double-blind, double-dummy, randomized, parallel-group study to demonstrate superior efficacy of quetiapine SR (400 mg/day, 600 mg/day, 800 mg/day) compared with placebo. Quetiapine IR (400 mg/day) was included to demonstrate assay sensitivity and provide guidance for SR-IR comparability.</td>
<td>Patients with acute exacerbation of schizophrenia</td>
</tr>
<tr>
<td>D1444C00133 (133)</td>
<td>Multicentered, 6-week, placebo-controlled, double-blind, double-dummy, randomized, parallel-group study to demonstrate superior efficacy of quetiapine SR (400 mg/day, 600 mg/day, 800 mg/day) compared with placebo. Quetiapine IR (400 mg/day) was included to demonstrate assay sensitivity and provide guidance for SR-IR comparability.</td>
<td>Patients with acute exacerbation of schizophrenia</td>
</tr>
<tr>
<td>5677E-0041 (041)</td>
<td>Multicentered, 6-week, placebo-controlled, double-blind, double-dummy, randomized, parallel-group study to demonstrate superior efficacy of quetiapine SR (300 mg/day, 600 mg/day, 800 mg/day) compared with placebo. Quetiapine IR (300 mg/day and 600 mg/day) was included to demonstrate assay sensitivity and provide guidance for SR-IR comparability.</td>
<td>Patients with acute exacerbation of schizophrenia</td>
</tr>
<tr>
<td>Placebo-controlled relapse-prevention study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D1444C00004 (004)</td>
<td>Multicentered, 1-year, randomized, double-blind, placebo-controlled, parallel-group study to evaluate prevention of relapse in patients who were treated with either quetiapine SR (flexible dosing in 200 mg increments [SR 400 mg/day, 600 mg/day, or 800 mg/day] or placebo. Patients were switched to quetiapine SR 400 mg/day to 800 mg/day and treated for 16 weeks during the stabilization period prior to randomization to blinded quetiapine SR or placebo and were then followed for a planned period of up to 3 years.*</td>
<td>Clinically stable outpatients with schizophrenia treated with antipsychotic medication at enrollment and who remained stable during a 15-week open-label quetiapine SR treatment.</td>
</tr>
<tr>
<td>Active-controlled study IR to SR switching study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D1444C00146 (146)</td>
<td>Multicentered, 6-week, double-blind, double-dummy, randomized, parallel-group study to demonstrate continued efficacy of quetiapine SR compared to quetiapine IR, 400 mg/day, 600 mg/day, or 800 mg/day, as an equivalent total daily dose of quetiapine SR or continued treatment with quetiapine IR, after a 4-week run-in period with quetiapine IR.</td>
<td>Clinically stable outpatients with schizophrenia stabilized on treatment with quetiapine IR at enrollment and who remained stable during a 4-week open-label quetiapine treatment.</td>
</tr>
</tbody>
</table>

DSMB Data Safety Monitoring Board. IR Immediate release. SR Sustained release.

* The protocol-specified interim analysis in Study 004 performed by the independent DSMB after 45 reported relapses showed that quetiapine SR significantly prolonged time to relapse compared with placebo. Based on these results and the recommendation of the DSMB, the study was terminated. Patients were followed for up to 9 months.

The 3 placebo controlled Phase III studies in the quetiapine SR program, Studies 132, 133 and 041, were designed to compare the superior efficacy and safety of the quetiapine SR formulation with placebo. Quetiapine IR was included in each study to support evaluation of the relative efficacy and safety of the two formulations across the proposed dose range.
3.2 STUDIES IN ACUTE SCHIZOPHRENIA

3.2.1 Study 5077IL/0041

This was a multicentre, randomised, double blind, placebo controlled, parallel group comparison of the efficacy and safety of the SR quetiapine formulation with placebo in the treatment of patients with schizophrenia.

After screening, patients were to be assigned to one of six treatments: quetiapine SR at 300, 600 or 800mg daily, quetiapine IR at 300 or 600mg daily (in two divided doses), or placebo. Any other oral antipsychotic medications were to be discontinued at least 48 hours before baseline assessment was performed, while depot preparations were to have been discontinued 1 dosing interval earlier.

The randomised study population comprised 532 patients enrolled from 49 centres, 45 in the USA and 4 in Canada. 402 (75.6%) were men and 130 (24.4%) were women. 49.2% were white, 37.2% were black, 11.1% were Hispanic, and 2.4% were Asian or other races. The mean age of the patients was 39 years (18-64). In order to be eligible for participation, patients had to fulfil the following criteria:

- Diagnosis according to DSM-IV Criteria of schizophrenia of one of the following subtypes: catatonic; disorganised; paranoid or undifferentiated.
- Positive and negative syndrome scale (PANSS) score of at least 60
- PANSS individual item score of at least 4 on one or more of the following items:
  - P1: Delusions
  - P2: Conceptual disorganisation
  - P3: Hallucinatory behaviour
  - P6: Suspiciousness / persecution
- Clinical Global Impression (CGI) Severity of Illness score of at least 4

The PANSS is a 30 item rating instrument that assesses the positive and negative symptoms of schizophrenia as well as symptoms of general psychopathology. PANSS items are grouped into 3 subscales: positive (p) scale; negative (n) scale; and general (g) psychopathology scales. Individual items are rated on a 7 point scale, where 1 = absent and 7 = extreme. The CGI scale ranges from 1 = normal to 7 = extremely ill.

Those patients assigned to receive quetiapine SR all began with an initial dose of 300mg once daily, for four days. On days 5-7, for those assigned to higher dosages, the dose increased to 600mg once daily, and on Day 8 escalated to 800mg where randomised. Those patients receiving Quetiapine IR all started with an initial total daily dose of 50mg. On day 2 this increased to 100mg; 200mg on day 3; 300mg on day 4; and for those randomised to receive 600mg, a further increase occurred to 400mg on day 5 and 600mg on day 6. The study treatment duration was 42 days. Patients treated with the SR medication took active tablets in the morning, and a matching placebo in the evening, those receiving the IR took active tablets morning and night in order to maintain the blind. Treatments were administered with or without food.
84 patients were randomised to placebo; 91 to 300mg SR; 92 to 600mg SR; 89 to 800mg SR; 90 to 300mg IR; and 86 to 600mg IR.

The primary objective was to demonstrate superior efficacy of the SR tablets compared with placebo in patients with schizophrenia. The efficacy assessment was based on PANSS total score compared with a baseline score on Days 4, 8, 15, 28 and 42. Secondary efficacy assessments were based on the clinical global impression scores, which were assessed along with the PANSS scores.

There were a large number of early withdrawals from the study: 66% in the placebo group; 62% 300mg SR; 57% 600mg SR; 51% 800mg SR; 54% 300mg IR; and 62% 600mg IR. These early withdrawals were most commonly due to lack of efficacy or withdrawal of consent. Overall, 222 patients completed treatment. Of note, patients treated with SR had a better completion rate (43.8%) than those on placebo (34.5%) and a completion rate similar to that seen with the IR formulation (42.0%).

For each treatment group, the mean PANSS total score decreased from baseline to Day 42 (or final visit). The greatest mean change (-13.7) was seen with quetiapine SR 600mg and this was the only treatment to meet with statistical significance (P=0.033):

<table>
<thead>
<tr>
<th>Summary statistic</th>
<th>Placebo (n=78)</th>
<th>QTP SR 300 mg (n=53)</th>
<th>QTP SR 600 mg (n=87)</th>
<th>QTP SR 800 mg (n=55)</th>
<th>QTP IR 300 mg (n=85)</th>
<th>QTP IR 600 mg (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Within treatment group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, mean (SD)</td>
<td>91.1 (16.3)</td>
<td>91.5 (19.2)</td>
<td>92.4 (17.2)</td>
<td>89.0 (14.9)</td>
<td>89.5 (15.7)</td>
<td>88.6 (17.3)</td>
</tr>
<tr>
<td>Day 42, mean (SD)</td>
<td>85.5 (23.4)</td>
<td>86.1 (25.0)</td>
<td>78.7 (23.8)</td>
<td>77.8 (22.1)</td>
<td>80.1 (23.3)</td>
<td>81.7 (25.3)</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-5.6 (18.6)</td>
<td>-5.5 (19.1)</td>
<td>-13.7 (22.1)</td>
<td>-11.1 (19.0)</td>
<td>-9.4 (22.8)</td>
<td>-6.9 (19.2)</td>
</tr>
<tr>
<td>Least-squares mean (SE)</td>
<td>-5.19 (2.34)</td>
<td>-5.01 (2.28)</td>
<td>-13.01 (2.23)</td>
<td>-11.17 (2.25)</td>
<td>-9.42 (2.24)</td>
<td>-6.97 (2.32)</td>
</tr>
<tr>
<td>95% CI</td>
<td>-9.78, -0.60</td>
<td>-9.49, -0.52</td>
<td>-17.39, -8.83</td>
<td>-15.60, -8.75</td>
<td>-13.83, -5.01</td>
<td>-11.54, -2.41</td>
</tr>
</tbody>
</table>

| Difference from placebo*          |                |                      |                      |                      |                      |                      |
| Estimated mean (SE)               | N/A            | 0.19 (3.09)          | -7.82 (3.06)         | -5.98 (3.08)         | -4.23 (3.07)         | -1.78 (3.12)         |
| 95% CI                            | N/A            | -5.88, 6.26          | -13.83, -1.81        | -12.03, 0.06         | -10.37, 1.81         | -7.92, 4.36          |
| p-value (unadjusted)              | N/A            | 0.952                | 0.011                | 0.052                | 0.169                | 0.569                |
| p-value (adjusted)*               | N/A            | 0.952                | 0.033                | 0.105                | N/D                  | N/D                  |

*a* From analysis of covariance.

*b* Interpretation of analysis after adjustment for multiplicity (Hochberg method).

CI: Confidence interval. LOCF: Last observation carried forward. MITT: Modified intent-to-treat population.


Data derived from Tables 11.2.1.1.1, 11.2.1.2.1, 11.2.1.2.7, and 11.2.2.1.5, Section 11.2.

Decreases from baseline in mean CGI scores at Day 42 were not met with statistical significance.

Incidences of commonly reported ARs were similar between quetiapine SR and quetiapine IR treatment groups. Minor exceptions were seen for dry mouth (SR, 15.8%; IR, 9.7%) and tachycardia (SR 7.7%; IR 13.1%). Except for headache, all adverse events were more common in patients treated with quetiapine SR than in patients on placebo, as expected.
Assessor’s comment
The study met its primary endpoint in only one of the strengths of the SR formulation tested, 600mg. Of note, neither of the already marketed IR formulations met with statistically significant efficacy greater than placebo either. The 300mg SR preparation actually performed numerically worse than placebo, and certainly worse than the equivalent dose of the IR preparation.

From the PK data provided, one would expect a similar degree of efficacy for both the IR and the SR formulation at equivalent dose strength. Yet there would appear to be marked differences. These data would support the argument that the sensitivity of this study was poor. This may be related in some way to the high number of early withdrawals from the study.

3.2.2 Study D1444C00132

This was a 6 week, multicentre, double blind, double dummy, randomised, placebo controlled study comparing the efficacy and safety of quetiapine SR 400mg/day, 600mg/day and 800mg/day and quetiapine IR 400mg/day with that of placebo in the treatment of adults with schizophrenia.

The randomised study population comprised 588 patients enrolled from 39 centres. Inclusion criteria were as before, with an increase in the pre-trial PANSS score to 70. All prior antipsychotic medications were to be discontinued, as before. Patients were randomised to one of five treatment arms and dose escalation commenced on day 1, as per the following regime:

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6-42</th>
</tr>
</thead>
<tbody>
<tr>
<td>SR 400 mg</td>
<td>300 mg</td>
<td>400 mg</td>
<td>400 mg</td>
<td>400 mg</td>
<td>400 mg</td>
<td>400 mg</td>
</tr>
<tr>
<td>SR 600 mg</td>
<td>300 mg</td>
<td>600 mg</td>
<td>600 mg</td>
<td>600 mg</td>
<td>600 mg</td>
<td>600 mg</td>
</tr>
<tr>
<td>SR 800 mg</td>
<td>300 mg</td>
<td>600 mg</td>
<td>800 mg</td>
<td>800 mg</td>
<td>800 mg</td>
<td>800 mg</td>
</tr>
<tr>
<td>IR 400 mg</td>
<td>50 mg</td>
<td>100 mg</td>
<td>200 mg</td>
<td>300 mg</td>
<td>400 mg</td>
<td>400 mg</td>
</tr>
<tr>
<td>Placebo</td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>P</td>
</tr>
</tbody>
</table>

SR, Quetiapine sustained-release; IR, Quetiapine immediate-release; P, placebo.

The primary objective was to demonstrate superior efficacy of quetiapine SR for the 3 doses, 400mg/day, 600mg/day and 800mg/day, compared with placebo in the treatment of patients with schizophrenia. The primary efficacy assessment was based on PANSS total score compared with a baseline score on Days 4, 8, 15, 28 and 42. Secondary efficacy assessments were based on the clinical global impression scores, which were assessed along with the PANSS scores.

Approximately 76% of patients completed the study; with higher rates of completion across all quetiapine SR treated groups compared to placebo.
The results were as follows:

<table>
<thead>
<tr>
<th></th>
<th>PLA N=115</th>
<th>QTP SR 400 mg N=111</th>
<th>QTP SR 600 mg N=111</th>
<th>QTP SR 800 mg N=117</th>
<th>QTP IR 400 mg N=119</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>115</td>
<td>111</td>
<td>111</td>
<td>117</td>
<td>119</td>
</tr>
<tr>
<td>Baseline mean (SD)</td>
<td>96.2 (13.3)</td>
<td>95.8 (13.9)</td>
<td>96.8 (14.1)</td>
<td>97.3 (14.7)</td>
<td>96.5 (16.0)</td>
</tr>
<tr>
<td>Day 42 mean (SD)</td>
<td>78.2 (25.4)</td>
<td>71.6 (24.1)</td>
<td>66.9 (20.4)</td>
<td>66.0 (24.0)</td>
<td>70.2 (25.3)</td>
</tr>
<tr>
<td>Change from baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS mean (SE)</td>
<td>-18.3 (2.5)</td>
<td>-24.8 (2.5)</td>
<td>-30.9 (2.5)</td>
<td>-31.3 (2.5)</td>
<td>-26.6 (2.4)</td>
</tr>
<tr>
<td>95% CI</td>
<td>-23.6, -13.9</td>
<td>-29.8, -19.9</td>
<td>-35.8, -26.0</td>
<td>-36.1, -26.4</td>
<td>-31.4, -21.7</td>
</tr>
</tbody>
</table>

Difference between active therapy and placebo

<table>
<thead>
<tr>
<th></th>
<th>PLA N=115</th>
<th>QTP SR 400 mg N=111</th>
<th>QTP SR 600 mg N=111</th>
<th>QTP SR 800 mg N=117</th>
<th>QTP IR 400 mg N=119</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-value (adjusted)*</td>
<td>0.030</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.004</td>
<td></td>
</tr>
</tbody>
</table>

* The assessment made at randomization was considered baseline.

Overall, the study treatments were well tolerated and there were no significant differences between the IR and SR formulations in terms of frequency or intensity of adverse events.

Assessor’s comments:
These results are reassuring and confirm superiority to placebo.
3.2.2.1 Study D1444C00133

This was a six week duration, multicentre, double blind, double dummy, randomised comparison study designed to demonstrate the superior efficacy of quetiapine SR for the three doses: 400mg/day; 600mg/day and 800mg/day, compared with placebo in the treatment of patients with schizophrenia. The study population consisted of 565 patients, across 35 treatment centres in the USA, divided into 5 treatment groups. Treatments were administered as per the following regime:

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7-42</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTSP 400 mg</td>
<td>300 mg</td>
<td>400 mg</td>
<td>400 mg</td>
<td>400 mg</td>
<td>400 mg</td>
<td>400 mg</td>
<td>400 mg</td>
</tr>
<tr>
<td>QTSP 600 mg</td>
<td>300 mg</td>
<td>600 mg</td>
<td>600 mg</td>
<td>600 mg</td>
<td>600 mg</td>
<td>600 mg</td>
<td>600 mg</td>
</tr>
<tr>
<td>QTSP 800 mg</td>
<td>300 mg</td>
<td>600 mg</td>
<td>800 mg</td>
<td>800 mg</td>
<td>800 mg</td>
<td>800 mg</td>
<td>800 mg</td>
</tr>
<tr>
<td>QTSP IR 800 mg</td>
<td>50 mg</td>
<td>100 mg</td>
<td>200 mg</td>
<td>300 mg</td>
<td>400 mg</td>
<td>600 mg</td>
<td>800 mg</td>
</tr>
<tr>
<td>Placebo</td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>P</td>
</tr>
</tbody>
</table>

IR: immediate-release, QTSP: quetiapine, SR: sustained-release

Inclusion criteria were as before, with a pre-trial PANSS score of 70. All prior antipsychotic medications were to be discontinued, as before.

The primary outcome variable was the change from baseline of the PANSS total score at the end of treatment at Day 42. Secondary efficacy objectives were:

- To demonstrate a higher response rate to treatment for the three doses of quetiapine SR tablets compared to placebo by evaluating:
- PANSS response rate, defined as a reduction of at least 30% from baseline PANSS total score at the end of treatment.
- CGI improvement rating < 3 at the end of treatment.
- To demonstrate superior efficacy in patients’ overall clinical status for the three doses of quetiapine SR compared to placebo by evaluating the change in CGI severity of illness score from baseline to end of treatment.
- To document efficacy on psychotic symptoms for all doses of quetiapine tablets, SR and IR, by evaluating clinical symptoms assessed by:
  i) The change from baseline PANSS total score at all subsequent visits.
  ii) The change in PANSS positive, negative and general subscales from baseline at all subsequent visits.
  iii) The change in PANSS aggression, depression and hostility clusters from baseline at all subsequent visits.

Approximately 60% of patients completed the study, with similar rates of completion across all quetiapine SR groups.
The results were as follows:

Primary efficacy outcome:

<table>
<thead>
<tr>
<th></th>
<th>PLA N=111</th>
<th>QTP SR 400 mg N=113</th>
<th>QTP SR 600 mg N=101</th>
<th>QTP SR 800 mg N=110</th>
<th>QTP IR 800 mg N=109</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline: mean (SD)¹</td>
<td>90.5 (11.9)</td>
<td>91.1 (13.4)</td>
<td>93.1 (14.0)</td>
<td>92.6 (13.2)</td>
<td>93.0 (13.5)</td>
</tr>
<tr>
<td>Day 42: mean (SD)</td>
<td>79.0 (21.1)</td>
<td>78.6 (18.7)</td>
<td>77.0 (18.6)</td>
<td>78.5 (20.4)</td>
<td>78.5 (19.6)</td>
</tr>
</tbody>
</table>

Change from baseline

<table>
<thead>
<tr>
<th>LS mean (SE)</th>
<th>PLA N=111</th>
<th>QTP SR 400 mg N=113</th>
<th>QTP SR 600 mg N=101</th>
<th>QTP SR 800 mg N=110</th>
<th>QTP IR 800 mg N=109</th>
</tr>
</thead>
<tbody>
<tr>
<td>-12.1 (1.9)</td>
<td>-13.8 (1.9)</td>
<td>-16.8 (2.0)</td>
<td>-14.8 (1.9)</td>
<td>-15.0 (1.9)</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>-15.8, -8.4</td>
<td>-17.5, -10.1</td>
<td>-20.7, -13.0</td>
<td>-18.5, -11.1</td>
<td>-18.8, -11.3</td>
</tr>
</tbody>
</table>

Difference between active therapy and placebo

<table>
<thead>
<tr>
<th>Estimated difference (SE)</th>
<th>PLA N=111</th>
<th>QTP SR 400 mg N=113</th>
<th>QTP SR 600 mg N=101</th>
<th>QTP SR 800 mg N=110</th>
<th>QTP IR 800 mg N=109</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1.7 (2.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-4.7 (2.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-2.7 (2.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-3.0 (2.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>-5.9, 2.5</td>
<td>-9.1, -0.4</td>
<td>-7.0, 1.6</td>
<td>-7.3, 1.3</td>
<td></td>
</tr>
<tr>
<td>p-value (unadjusted)</td>
<td>0.434</td>
<td>0.033</td>
<td>0.214</td>
<td>0.172</td>
<td></td>
</tr>
<tr>
<td>p-value (adjusted)</td>
<td>0.434</td>
<td>0.099</td>
<td>0.429</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹ The assessment made at randomization was considered baseline.
² 95% CI of difference corresponds to the unadjusted p-value.
³ p-values adjusted using Holm's procedure for multiplicity.


Note: Analysis using analysis of covariance (ANCOVA) with the baseline score as covariate, treatment as fixed effect and center as random effect. Only patients with assessment at baseline and Day 42 (or final assessment) are included.


There was a failure to reach statistical significance greater than placebo in any of the dose strengths tested.

Secondary outcome measures:

PANSS response rate at Day 42:

<table>
<thead>
<tr>
<th>PL A N=111</th>
<th>QTP SR 400 mg N=113</th>
<th>QTP SR 600 mg N=101</th>
<th>QTP SR 800 mg N=110</th>
<th>QTP IR 800 mg N=109</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients responding at Day 42: n (%)</td>
<td>23 (20.7)</td>
<td>22 (19.5)</td>
<td>27 (26.7)</td>
<td>26 (23.6)</td>
</tr>
<tr>
<td>Difference between active therapy and placebo</td>
<td>0.9</td>
<td>1.4</td>
<td>1.2</td>
<td>1.1</td>
</tr>
<tr>
<td>Estimated odds ratio</td>
<td>0.5, 1.8</td>
<td>0.7, 2.6</td>
<td>0.6, 2.2</td>
<td>0.6, 2.2</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.8, 16</td>
<td>0.3, 041</td>
<td>0.6, 031</td>
<td>0.6, 09</td>
</tr>
<tr>
<td>p-value</td>
<td>0.816</td>
<td>0.304</td>
<td>0.603</td>
<td>0.691</td>
</tr>
</tbody>
</table>

¹ Response was defined as ≥30% improvement from baseline (randomization) in PANSS total score.


Note: Cochran-Mantel-Haenszel analysis including only patients with assessment at baseline and Day 42 (or final assessment).

CGI Severity of Illness Score:

<table>
<thead>
<tr>
<th></th>
<th>PLA N=111</th>
<th>QTP SR 400 mg N=113</th>
<th>QTP SR 600 mg N=201</th>
<th>QTP SR 500 mg N=110</th>
<th>QTP IR 500 mg N=109</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>111</td>
<td>113</td>
<td>101</td>
<td>110</td>
<td>109</td>
</tr>
<tr>
<td>Baseline mean (SD)*</td>
<td>4.5 (0.6)</td>
<td>4.4 (0.5)</td>
<td>4.5 (0.5)</td>
<td>4.5 (0.6)</td>
<td>4.5 (0.6)</td>
</tr>
<tr>
<td>Day 42 mean (SD)</td>
<td>4.0 (1.0)</td>
<td>3.9 (0.8)</td>
<td>4.0 (0.9)</td>
<td>3.9 (0.9)</td>
<td>3.9 (1.0)</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-0.5 (0.1)</td>
<td>-0.6 (0.1)</td>
<td>-0.6 (0.1)</td>
<td>-0.6 (0.1)</td>
<td>-0.6 (0.1)</td>
</tr>
<tr>
<td>95% CI</td>
<td>-0.6, -0.3</td>
<td>-0.8, -0.4</td>
<td>-0.8, -0.4</td>
<td>-0.8, -0.4</td>
<td>-0.8, -0.4</td>
</tr>
</tbody>
</table>

* The assessment made at randomization was considered baseline.

CGI Clinical Global Improvement. CI Confidnece interval. IR Immediate-release. LOCF Last observation carried forward. n Number of patients. MITT Modified intention-to-treat. N Number of patients in treatment group. QTP Quetiapine. SE Standard error. SR Sustained-release.

Note: Analysis using analysis of covariance (ANCOVA) with the baseline score as covariate, treatment as fixed effect and center as random effect. Only patients with assessment at baseline and Day 42 (or final assessment) are included.


CGI Global Improvement Score:

<table>
<thead>
<tr>
<th></th>
<th>PLA N=111</th>
<th>QTP SR 400 mg N=113</th>
<th>QTP SR 600 mg N=201</th>
<th>QTP SR 500 mg N=110</th>
<th>QTP IR 500 mg N=109</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients showing improvement* at Day 42: n (%)</td>
<td>63 (56.8)</td>
<td>74 (65.5)</td>
<td>68 (67.3)</td>
<td>59 (52.7)</td>
<td>67 (61.5)</td>
</tr>
<tr>
<td>Difference between active therapy and placebo</td>
<td>1.4</td>
<td>1.6</td>
<td>1.3</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Estimated odds ratio</td>
<td>0.6</td>
<td>2.5</td>
<td>0.0</td>
<td>2.7</td>
<td>0.7</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.1</td>
<td>0.15</td>
<td>0.0</td>
<td>0.27</td>
<td>0.7</td>
</tr>
<tr>
<td>p-value</td>
<td>0.181</td>
<td>0.115</td>
<td>0.367</td>
<td>0.478</td>
<td></td>
</tr>
</tbody>
</table>

* Improvement was defined as a rating of much improved, improved or minimally improved on the CGI Global Improvement scale.

CGI Clinical Global Improvement. CI Confidence interval. IR Immediate-release. LOCF Last observation carried forward. MITT Modified intention-to-treat. N Number of patients in treatment group. QTP Quetiapine. SE Standard error. SR Sustained-release.

Note: Cochran-Mantel-Haenszel analysis including only patients with assessment at baseline and Day 42 (or final assessment).


The other secondary efficacy variable outcomes were not presented with p values and so cannot be used for interpretation. There were no safety signals raised.

Assessor’s comment

Of three Phase III trials examining efficacy in comparison to placebo, two (Study 041 and study 132) demonstrated a greater effect with statistical significance at the 600mg strength. Study number 0132 showed statistical significance at 800mg also, though the actual clinical improvement seen was no better than that at 600mg.

In those trials where the IR formulation failed to demonstrate significant efficacy also, it could be considered that the assay sensitivity of these trials was poor. If those studies were disregarded then there could be argued to lend support to a single pivotal trial’ style approach toward Study number 0132. In this case, the 600mg strength could be said to demonstrate efficacy.

From these studies alone, there is no evidence to suggest any clinical benefit in increasing the dose to 800mg. However, this issue is discussed in section 3.7, pages 48-51, which justifies the approval of the 800mg posology.
3.2.2.2 Relapse Prevention Study D1444C00004

The primary objective of this study was to demonstrate the superior efficacy of quetiapine SR to placebo by evaluating relapse prevention in longer term use in patients with a DSM-IV diagnosis of schizophrenia as measured by the time to first psychiatric relapse up to one year. The study was designed as a multi-centre, randomised, double-blind, parallel group, placebo-controlled study involving 327 patients across 26 centres in Europe and India.

The secondary objectives were:

- To demonstrate superiority of quetiapine SR to placebo by evaluating the risk of relapse (defined as the proportion of relapses per treatment group) across a six month relapse rate.
- To document that quetiapine SR was superior to placebo in treating positive and negative symptoms by evaluating the PANSS total score and sub-scores.
- To document continuing stability of negative symptoms with quetiapine SR by evaluating the change in PANSS negative score from baseline to last visit before relapse.
- To document that the effect of quetiapine SR on global clinical status was superior to placebo by measuring the CGI severity of illness as a change from baseline to last visit.

Prior to randomisation, a 16 week stabilisation period ensured that the patients were clinically stable and received a stable dose of quetiapine SR. Patients were considered clinically stable when they met the following criteria:

- CGI score < 4 and a PANSS score <60 at enrolment and at point of randomisation
- Received a stable dose of quetiapine SR

At randomisation, patients were assigned to treatment with either quetiapine SR or placebo. The intended treatment period for each patient was one year or until relapse. During the stabilisation period, treatments were open label and were titrated as follows:

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing antipsychotic</td>
<td>75%*</td>
<td>50%*</td>
<td>25%*</td>
<td>0%</td>
</tr>
<tr>
<td>treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quetiapine SR</td>
<td>300 mg</td>
<td>600 mg</td>
<td>400, 600 or 800 mg</td>
<td>400, 600 or 800 mg</td>
</tr>
</tbody>
</table>

* Remaining dose
At randomisation, a double blind period of cross titration occurred, as follows:

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Open-label quetiapine SR</strong></td>
<td>75%*</td>
<td>50%*</td>
<td>25%*</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Doses in mg and number of tablets</strong></td>
<td>300 (2x50, 3x200)</td>
<td>200 (1x200)</td>
<td>100 (2x50)</td>
<td>0 mg</td>
</tr>
<tr>
<td></td>
<td>450 (1x50, 2x200)</td>
<td>300 (2x50, 1x200)</td>
<td>150 (3x50)</td>
<td>0 mg</td>
</tr>
<tr>
<td></td>
<td>600 (3x200)</td>
<td>400 (2x200)</td>
<td>200 (1x200)</td>
<td>0 mg</td>
</tr>
<tr>
<td><strong>Blinded quetiapine SR or placebo</strong></td>
<td>25%</td>
<td>50%</td>
<td>75%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Doses in mg and number of tablets</strong></td>
<td>100 (2x50)</td>
<td>200 (3x200)</td>
<td>300 (2x50, 1x200)</td>
<td>400 (2x200)</td>
</tr>
<tr>
<td></td>
<td>150 (3x50)</td>
<td>300 (2x50, 1x200)</td>
<td>450 (1x50, 2x200)</td>
<td>600 (3x200)</td>
</tr>
<tr>
<td></td>
<td>200 (1x200)</td>
<td>400 (2x200)</td>
<td>600 (3x200)</td>
<td>800 (4x200)</td>
</tr>
</tbody>
</table>

Tablets of 50 mg and 200 mg will be available

* Remaining dose

Patients randomised to quetiapine SR treatment were treated with a flexible dose of quetiapine SR at 400 – 800mg/day (mean dose of 669mg/day). In the case of deterioration in symptomatology, the investigator was advised to make dose adjustments of the investigational product, though tablets were matched to placebo to maintain the blind.

Two interim analyses were planned; one after 45 observed relapses and one after 60. The study was stopped after 45 relapses since the difference between SR and placebo had reached statistical significance.

The stabilisation period was completed by 197 patients who were randomised. Of those, 103 patients went on to receive placebo, and 94 received SR. The number of patients remaining in the trial when it was discontinued was 39 in the placebo group, and 78 in the active. 50 placebo patients discontinued due to relapse, and 11 did so in the active group.
The summary of results is as follows:

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>PLA</th>
<th>QTP SR</th>
<th>Hazard ratio / Estimated difference / Odds ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to schizophrenia relapse*</td>
<td>Number of relapses (%)</td>
<td>36 (41.4)</td>
<td>9 (10.7)</td>
<td>HR*: 0.16 (0.08, 0.34)</td>
</tr>
</tbody>
</table>

Secondary analyses (total ITT population):

- N: 103
- 94

Time to schizophrenia relapse*:

- Number of relapses (%): 30 (48.5) vs. 11 (11.7)
- HR*: 0.13 (0.07, 0.25) <0.001

Risk of schizophrenia relapse at 6 months:

- Proportion of patients (95% CI):
  - PLA: 68.2 (59.2, 77.2)
  - QTP SR: 14.3 (7.2, 21.3)
- Diff: -54.0 (-65.4, -42.5) <0.001

PANSS total score:

- LS mean(SE): PLA: 48.86 (0.51) vs. QTP SR: 47.15 (0.40)
- Diff: -1.71 (-2.34, -0.58) 0.0033

PANSS-P subscale score:

- LS mean(SE): PLA: 9.95 (0.30) vs. QTP SR: 9.48 (0.16)
- Diff: -0.47 (-0.93, -0.00) 0.0483

PANSS-N subscale score:

- LS mean(SE): PLA: 14.42 (0.25) vs. QTP SR: 13.89 (0.21)
- Diff: -0.53 (-1.01, -0.05) 0.0296

PANSS-G subscale score:

- LS mean(SE): PLA: 24.52 (0.31) vs. QTP SR: 23.69 (0.23)
- Diff: -0.83 (-1.15, -0.12) 0.0224

CGI-S:

- Patients with CGI-S ≤4 (%): PLA: 84 (84.0) vs. QTP SR: 87 (93.5)
- OR: 2.76 (1.03, 7.40) 0.0275

CGI-I:

- Mean score at last visit (95% CI): PLA: 4.5 (4.2, 4.8) vs. QTP SR: 3.7 (3.4, 4.0)
- Diff: -0.83 (-1.24, -0.42) <0.001

* The analysis of this variable was included in the confirmatory part of the study and a stepwise sequential testing procedure was pre-specified. The multiple level of significance of 0.01 was assured for this variable.

b Due to the low rate of relapse in the quetiapine SR group it is not possible to calculate a reliable median time to relapse. The number of relapses is presented for information. The p value relates to the analysis of time to schizophrenia relapse.

¹ Hazard ratio estimated by Cox proportional hazards model.

² significant at alpha level 0.00455

³ significant at alpha level 0.05

⁴ Cox regression estimate.

⁵ estimate of LS mean change during randomized period from a mixed effect repeated measures analysis of all post-baseline measurements from randomization up to, but not including, the relapse.

⁶ proportion of patients with CGI-S ≤4 at last assessment (including any relapse)

⁷ Mean CGI-I score at last assessment (including any relapse)

The applicant states that due to the low rate of relapse in the quetiapine SR group, it was not possible to calculate a reliable median time to relapse. Therefore, the number of relapses is presented, as opposed to time to relapse. Fewer patients experienced a relapse in the SR group (10.7%) compared to patients in the placebo group (41.4%), and the risk of a relapse was reduced by 84% (HR 0.16, p<0.0001) compared with placebo. All of the secondary outcome measures were met with statistical significance.

Assessor’s comment:

The primary objective here was to demonstrate the superior efficacy of quetiapine SR to placebo in relapse prevention as measured by the time to first psychiatric relapse up to one year.

The primary variable should be the variable capable of providing the most clinically relevant and convincing evidence of efficacy. What have been presented are data showing the number of relapses compared with placebo, with 41.4% of patients on
placebo relapsing versus 10.7% on active treatment. It is agreed that these data were met with statistical significance. The time to relapse data have not been presented because of the low rate of relapse in the quetiapine group. This is accepted.

There would appear to be a highly significant benefit in the long term continuation of treatment in order to prevent relapse.

3.2.2.3 IR to SR Switching Study D1444C00146

This study was conducted across 74 centres in 14 countries. The primary objective was to demonstrate that the efficacy of the SR formulation of quetiapine was not inferior to the IR formulation by evaluating the proportion of patients who discontinued study treatments due to lack of efficacy or whose PANSS total score increased 20% or more from randomisation to any visit. The secondary outcome variables were the proportion of patients discontinuing study treatment due to adverse events or lack of efficacy:

- Document maintained efficacy when switching from IR to SR as assessed by change in PANSS score.
- Document maintained stability in PANSS p, n and g sub-scores.
- Document maintained stability through maintenance of CGI scores.

The hypothesis to be shown was that these proportions, in patients switched to quetiapine SR, were lower than those proportions in patients remaining on quetiapine IR plus 6% (non-inferiority margin selected). Non-inferiority hypotheses were tested with 1 sided tests with a significance level of 2.5%. The selection of the 6% non-inferiority margin was based on results from a study of a different atypical antipsychotic (aripiprazole), in which a difference of 15 percentage points between active treatment and placebo in the relapse rates was observed at 6 weeks after randomisation. The selected non-inferiority margin of 6% represents a 60% preservation of the difference between active treatment and placebo.

Patients were to complete a 4 week run-in period to ensure clinical stability (CGI severity of illness score < 3 with no change form enrolment). Patients who were taking quetiapine IR 300-450mg/day at enrolment received quetiapine 400mg/day IR during the run-in period. Those taking 475-650mg/day were to receive 600mg/day and those taking 675-800mg/day received 800mg/day for the run-in.

The 6 week double blind phase of the trial started at randomisation. A total of 497 patients were randomised on day 1. Patients were randomised at a ratio of 1:2 to either switch to an SR dose equivalent to that taken during the run-in (400, 600 or 800mg/day), or to continue with their IR regimen. To maintain the blind, patients receiving the SR formulations also received a placebo in the evening. A total of 153 patients received 400mg/day SR (76 IR), 117 received 600mg/day (58 IR) and 61 received 800mg/day SR (32 IR). Of the randomised patients, 28 in the SR group and 10 in the IR group discontinued the study prematurely, equally for reasons of lack of therapeutic response and withdrawal of consent.

The patients recruited all had a DSM-IV diagnosis of schizophrenia. The majority were diagnosed with paranoid schizophrenia. At randomisation, the mean PANSS
total scores were 59.5 and 59.3 in the SR and IR groups respectively. Mean CGI severity of illness scores were 2.6 and 2.7 in the SR and the IR respectively.

The primary efficacy results were as follows:

MITT (modified intention to treat) population:

<table>
<thead>
<tr>
<th>Total patients with lack of efficacy* : n (%)</th>
<th>QTP SR N=330</th>
<th>QTP IR N=166</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinued study due to lack of efficacy : n (%)</td>
<td>7 (2.1)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>≥ 20% increase in PANSS score from randomization : n (%)</td>
<td>28 (8.5)</td>
<td>11 (6.6)</td>
</tr>
</tbody>
</table>

Difference QTP SR - QTP IR

- Estimated difference (%) = 1.86
- 95% CI = -3.78, 6.57
- p-value =$0.0431$

* Patients who discontinued study due to lack of efficacy whose PANSS total score increased ≥20% from baseline at any visit.

** The treatment switch from IR to SR is considered successful if the upper limit of the CI is lower than or equal to 0 (non-inferiority margin).

** The p-value belongs to the 1-sided non-inferiority test with margin 6%. A p-value <0.025 indicates non-inferiority of SR versus IR.

PP (per protocol) population: the PP population excluded the following from MITT:

- patients with significant protocol deviations; all data from patients deemed to be non-compliant.

Non inferiority was demonstrated in the PP population, only, where the point estimate for difference was -0.83%, p=0.0017, using a non-inferiority margin of 6%. The MITT analysis gave a treatment difference of 1.86%. The p-value was 0.0431 and the test was not significant compared to the significance level of 2.5%.
The secondary variable outcomes were:

**Proportion of patients discontinuing due to adverse events or lack of efficacy:**

**MITT:**

<table>
<thead>
<tr>
<th></th>
<th>QTP SR N=129</th>
<th>QTP IR N=146</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinued due to adverse events or lack of efficacy: n (%)</td>
<td>11 (9.1)</td>
<td>5 (3.5)</td>
</tr>
<tr>
<td>Discontinued due to adverse events: n (%)</td>
<td>4 (3.2)</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Discontinued due to lack of efficacy: n (%)</td>
<td>7 (5.4)</td>
<td>1 (0.7)</td>
</tr>
</tbody>
</table>

Difference¹: QTP SR - QTP IR:
- Estimated difference (%) 1.36
- 95% CI -2.55 to 5.27
- p-value 0.75
- Adjusted p-value 0.67

**PP population:**

<table>
<thead>
<tr>
<th></th>
<th>QTP SR N=263</th>
<th>QTP IR N=130</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinued due to adverse events or lack of efficacy: n (%)</td>
<td>3 (1.1)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Discontinued due to adverse events: n (%)</td>
<td>1 (0.4)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Discontinued due to lack of efficacy: n (%)</td>
<td>2 (0.8)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Difference¹: QTP SR - QTP IR:
- Estimated difference (%) 0.37
- 95% CI 0.21 to 0.53
- p-value 0.001
- Adjusted p-value 0.001

¹ Difference in discontinuation due to AEs or lack of efficacy.
² The p-value belongs to the 1-sided non-inferiority test with margin 5%.
³ Adjusted p-values according to the pre-specified fixed sequence approach. A p-value > 0.025 indicates non-inferiority of QTP SR versus QTP IR.

The IR and SR groups were similar in the proportion of patients withdrawing due to AEs or lack of efficacy.
Change in PANSS total score from randomisation to day 42 (MITT):

<table>
<thead>
<tr>
<th></th>
<th>QTP SR N=130</th>
<th>QTP IR N=166</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline mean (SD)*</td>
<td>59.3 (14.3)</td>
<td>59.3 (14.7)</td>
</tr>
<tr>
<td>Day 42: mean (SD)</td>
<td>55.4 (15.6)</td>
<td>54.8 (14.1)</td>
</tr>
<tr>
<td>Change from baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS mean (SE)</td>
<td>-3.7 (0.6)</td>
<td>-4.2 (0.9)</td>
</tr>
<tr>
<td>95% CI</td>
<td>-5.1 - -2.3</td>
<td>-5.0 - -2.5</td>
</tr>
</tbody>
</table>

* The assessment made at randomization was considered baseline.

Similar decreases in PANSS total score were observed for both treatment groups.

Change in PANSS positive, negative and general sub-scale scores from randomisation to day 42 (MITT):

**Table 30**

<table>
<thead>
<tr>
<th>PANSS positive subscale, change from baseline at Day 42 (LOCF, MITT population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTP SR N=130</td>
</tr>
<tr>
<td>Baseline mean (SD)*</td>
</tr>
<tr>
<td>Day 42: mean (SD)</td>
</tr>
<tr>
<td>Change from baseline</td>
</tr>
<tr>
<td>95% CI</td>
</tr>
</tbody>
</table>

**Table 31**

<table>
<thead>
<tr>
<th>PANSS negative subscale, change from baseline at Day 42 (LOCF, MITT population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTP SR N=130</td>
</tr>
<tr>
<td>Baseline mean (SD)*</td>
</tr>
<tr>
<td>Day 42: mean (SD)</td>
</tr>
<tr>
<td>Change from baseline</td>
</tr>
<tr>
<td>95% CI</td>
</tr>
</tbody>
</table>

**Table 32**

<table>
<thead>
<tr>
<th>PANSS general psychopathology subscale, change from baseline at Day 42 (LOCF, MITT population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTP SR N=130</td>
</tr>
<tr>
<td>Baseline mean (SD)*</td>
</tr>
<tr>
<td>Day 42: mean (SD)</td>
</tr>
<tr>
<td>Change from baseline</td>
</tr>
<tr>
<td>95% CI</td>
</tr>
</tbody>
</table>

* The assessment made at randomization was considered baseline.

Again, similar differences were seen in both treatment groups.
CGI Severity of illness score at Day 42:

<table>
<thead>
<tr>
<th></th>
<th>QTP SR N=130</th>
<th>QTP IR N=160</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline: mean (SD)</td>
<td>2.6 (0.6)</td>
<td>2.7 (0.6)</td>
</tr>
<tr>
<td>Day 42: mean (SD)</td>
<td>2.6 (0.8)</td>
<td>2.6 (0.8)</td>
</tr>
<tr>
<td>Change from baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>-0.0 (0.6)</td>
<td>-0.1 (0.6)</td>
</tr>
</tbody>
</table>

*The assessment made at randomisation was considered baseline.

There was an absence of deterioration seen in either group.

Overall, it was concluded that efficacy was maintained through the 6 week study period when patients were switched from IR to SR formulations.

Assessor’s comment
From the CPMP document CPMP/EWP/482/99, in a non-inferiority trial the full analysis set (MITT) and the PP analysis set have equal importance and their use should lead to similar conclusions for a robust interpretation. It is not sufficient to rely on one of the trials in isolation. The results from both trials are to be positive to conclude non-inferiority. In this instance, therefore, non-inferiority has not been demonstrated. This study has failed to meet its primary objective. This issue is discussed in section 3.6 (pages 46-47) and addressed by a statement in the SPC.

The approved SPC states that “For more convenient dosing, patients who are currently being treated with divided doses of immediate release Seroquel tablets may be switched to Seroquel SR at the equivalent total daily dose taken once daily. To ensure the maintenance of clinical response, a period of dose titration may be required.” This is satisfactory.

3.3 STATISTICAL ASSESSMENT OF EFFICACY

Seroquel (quetiapine) is already licensed as immediate release (IR) tablets for the treatment of schizophrenia and for the treatment of manic episodes associated with bipolar disorder. This application is to license a new prolonged release (SR) tablet formulation.

Seroquel immediate release tablets are taken twice daily. The licensed schizophrenia posology is 50mg/day (day 1), 100mg (day 2), 200mg (day 3) and 300mg (day 4). Following this, dependent upon clinical response and tolerability the dose may be adjusted within the range 150 to 750 mg/day. The usual effective dose is in the range 300-450 mg/day.

For the treatment of manic episodes associated with bipolar disorders, higher doses are recommended: 100mg/day (day 1), 200mg (day 2), 300mg (day 3) and 400mg (day 4). Depending on clinical response and tolerability the dose may be adjusted within the range 200 to 800 mg/day. The usual effective dose is in the range 400-800 mg/day.
The prolonged release tablet would be taken once daily. The SmPC for the prolonged release tablet has a virtually identical posology for both indications; 300mg on day 1, 600mg on day 2 and up to 800mg after day 2 (although enhanced efficacy at daily doses higher than 600mg has not been demonstrated in schizophrenia). Dependent upon clinical response and tolerability the dose should be adjusted within the range 400-800mg.

### 3.3.1 Acute schizophrenia

Three randomised, double-blind, double-dummy, placebo-controlled, parallel-group, clinical trials were conducted to investigate the efficacy of Seroquel prolonged release in patients with acute schizophrenia, studies 041, 132 and 133.

To be included in study 041, patients had to have a baseline Positive And Negative Syndrome Scale (PANSS) total score of at least 60 at randomisation with a score of at least 4 on one or more of delusions, conceptual disorganisation, hallucinatory behaviour, or suspiciousness/persecution; and a CGI severity of illness score of at least 4 (moderately ill).

For studies 132 and 133 the criteria were tightened up, with the threshold for the baseline PANSS score being increased to ≥ 70.

Each study compared a range of daily doses of the SR formulation with placebo and at least one dose of the already licensed IR product.

#### Dose groups in studies 041, 132 and 133 – mg/day

<table>
<thead>
<tr>
<th>Study</th>
<th>SR 300mg</th>
<th>400mg</th>
<th>600mg</th>
<th>800mg</th>
<th>IR 300mg</th>
<th>400mg</th>
<th>600mg</th>
<th>800mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>041</td>
<td>x</td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>132</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>133</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
</tbody>
</table>

The table below shows the doses of Seroquel that could be taken during the treatment phase of each study. Dosing with the SR formulation was once daily. The IR daily dose was received in 2 divided doses over the course of the day.

In study 041, titration of the prolonged release product was slower than the scheme in the proposed SPC, with titration to 600 and 800mg taking 5 and 8 days respectively. In studies 132 and 133 the titration was faster, in line with the proposed SPC, with all treatment groups reaching the planned dose in 3 days or less.

#### 3.3.2 Titration of Seroquel by treatment group (mg/day)

**Study 041**

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
<th>Day 8+</th>
</tr>
</thead>
<tbody>
<tr>
<td>SR 300mg</td>
<td>300mg</td>
<td>300mg</td>
<td>300mg</td>
<td>300mg</td>
<td>300mg</td>
<td>300mg</td>
<td>300mg</td>
<td>300mg</td>
</tr>
<tr>
<td>SR 600mg</td>
<td>300mg</td>
<td>300mg</td>
<td>300mg</td>
<td>300mg</td>
<td>300mg</td>
<td>600mg</td>
<td>600mg</td>
<td>600mg</td>
</tr>
<tr>
<td>SR 800mg</td>
<td>300mg</td>
<td>300mg</td>
<td>300mg</td>
<td>300mg</td>
<td>600mg</td>
<td>600mg</td>
<td>600mg</td>
<td>800mg</td>
</tr>
<tr>
<td>IR 300mg</td>
<td>50mg</td>
<td>100mg</td>
<td>200mg</td>
<td>300mg</td>
<td>300mg</td>
<td>300mg</td>
<td>300mg</td>
<td>300mg</td>
</tr>
<tr>
<td>IR 600mg</td>
<td>50mg</td>
<td>100mg</td>
<td>200mg</td>
<td>300mg</td>
<td>400mg</td>
<td>600mg</td>
<td>600mg</td>
<td>600mg</td>
</tr>
</tbody>
</table>
### Study 132 & 133

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7+</th>
</tr>
</thead>
<tbody>
<tr>
<td>SR 400mg</td>
<td>300mg</td>
<td>400mg</td>
<td>400mg</td>
<td>400mg</td>
<td>400mg</td>
<td>400mg</td>
<td>400mg</td>
</tr>
<tr>
<td>SR 600mg</td>
<td>300mg</td>
<td>600mg</td>
<td>600mg</td>
<td>600mg</td>
<td>600mg</td>
<td>600mg</td>
<td>600mg</td>
</tr>
<tr>
<td>SR 800mg</td>
<td>300mg</td>
<td>600mg</td>
<td>800mg</td>
<td>800mg</td>
<td>800mg</td>
<td>800mg</td>
<td>800mg</td>
</tr>
<tr>
<td>IR 400mg</td>
<td>50mg</td>
<td>100mg</td>
<td>200mg</td>
<td>300mg</td>
<td>400mg</td>
<td>400mg</td>
<td>400mg</td>
</tr>
<tr>
<td>IR 800mg</td>
<td>50mg</td>
<td>100mg</td>
<td>200mg</td>
<td>300mg</td>
<td>400mg</td>
<td>600mg</td>
<td>800mg</td>
</tr>
</tbody>
</table>

Patients were randomised in equal proportions to all treatment groups in each study.

A total of 1685 patients were randomised into the trials, with 951 being randomised into one of the Seroquel prolonged release groups. In study 041, only 222 (42%) patients completed the scheduled six weeks of treatment. In study 132 a more impressive 446/588 (76%) completed treatment, but in study 133 the rate was again low with only 333/565 (59%) completing treatment.

Lack of efficacy was the main reason for premature discontinuation in studies 041 and 132, while adverse events was the most common cause in 133. There were no obvious dose related trends for withdrawal for either adverse events or lack of efficacy, although the placebo group tended to have the most withdrawals for lack of efficacy.

The modified intent-to-treat (MITT) population was defined to include all randomised patients who received treatment, and had a baseline assessment for the primary efficacy endpoint and at least one valid post-baseline assessment. This was the primary population for efficacy analysis.

Ideally all randomised patients who were treated would be included in the efficacy analysis, with no requirement regarding efficacy assessments, but as this only affects 47 (3%) patients and there was no obvious difference between treatment groups, there is no real concern.

In addition all 22 patients from centre 0043 in study 041 were excluded, as the investigator had supplied false information in his licensure history, and his study participation was terminated. The primary analysis was repeated including these patients to demonstrate that removing these patients did not have undue impact on the results.

The conclusions were not altered by the exclusion of these patients.

### 3.3.3 Patient disposition – study 041

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>SR300</th>
<th>SR600</th>
<th>SR800</th>
<th>IR300</th>
<th>IR600</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised</td>
<td>84</td>
<td>91</td>
<td>92</td>
<td>89</td>
<td>90</td>
<td>86</td>
</tr>
<tr>
<td>Modified ITT</td>
<td>78 (93%)</td>
<td>83 (91%)</td>
<td>87 (95%)</td>
<td>85 (96%)</td>
<td>85 (94%)</td>
<td>80 (93%)</td>
</tr>
<tr>
<td>No post-baseline PANSS score</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Centre 0043</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Completed study</td>
<td>29 (35%)</td>
<td>35 (38%)</td>
<td>40 (43%)</td>
<td>44 (49%)</td>
<td>41 (46%)</td>
<td>33 (38%)</td>
</tr>
<tr>
<td>Discontinued treatment early</td>
<td>55</td>
<td>56</td>
<td>52</td>
<td>45</td>
<td>49</td>
<td>53</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>8</td>
<td>5</td>
<td>9</td>
<td>1</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>
3.3.4 Patient disposition – study 132

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>SR400</th>
<th>SR600</th>
<th>SR800</th>
<th>IR400</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised</td>
<td>118</td>
<td>113</td>
<td>113</td>
<td>121</td>
<td>123</td>
</tr>
<tr>
<td>Modified ITT</td>
<td>115 (97%)</td>
<td>111 (98%)</td>
<td>111 (98%)</td>
<td>117 (97%)</td>
<td>119 (97%)</td>
</tr>
<tr>
<td>No post-baseline PANSS score</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Completed study</td>
<td>85 (72%)</td>
<td>83 (73%)</td>
<td>92 (81%)</td>
<td>90 (74%)</td>
<td>96 (78%)</td>
</tr>
<tr>
<td>Discontinued treatment early</td>
<td>33</td>
<td>30</td>
<td>21</td>
<td>31</td>
<td>27</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>3</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Lack of Efficacy</td>
<td>17</td>
<td>13</td>
<td>7</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Eligibility criteria not fulfilled</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Subject not willing to continue</td>
<td>9</td>
<td>6</td>
<td>5</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

3.3.5 Patient disposition – study 133

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>SR400</th>
<th>SR600</th>
<th>SR800</th>
<th>IR800</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised</td>
<td>117</td>
<td>114</td>
<td>105</td>
<td>113</td>
<td>116</td>
</tr>
<tr>
<td>Modified ITT</td>
<td>111 (95%)</td>
<td>113 (99%)</td>
<td>101 (96%)</td>
<td>110 (97%)</td>
<td>109 (94%)</td>
</tr>
<tr>
<td>Not treated</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>No post-baseline PANSS score</td>
<td>6</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Completed study</td>
<td>68 (58%)</td>
<td>74 (65%)</td>
<td>61 (58%)</td>
<td>68 (60%)</td>
<td>62 (53%)</td>
</tr>
<tr>
<td>Discontinued treatment early</td>
<td>49</td>
<td>40</td>
<td>44</td>
<td>45</td>
<td>54</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>14</td>
<td>11</td>
<td>11</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Lack of Efficacy</td>
<td>15</td>
<td>6</td>
<td>9</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>4</td>
<td>6</td>
<td>3</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Eligibility criteria not fulfilled</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Subject not willing to continue</td>
<td>12</td>
<td>15</td>
<td>16</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Last observation carried forward (LOCF) was used to impute missing observations. This is generally appropriate in psychiatric disorders, where the trend is for improvement over the course of the trial meaning the imputed values are generally poor. However, a high proportion of patients did not provide data at week 6 in studies 041 and 133, and data were carried forward from very early visits.

3.3.6 Patients providing data at each visit – MITT population

Study 041

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=78)</th>
<th>SR300 (N=83)</th>
<th>SR600 (N=87)</th>
<th>SR800 (N=85)</th>
<th>IR300 (N=85)</th>
<th>IR600 (N=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 4</td>
<td>76 (97%)</td>
<td>81 (98%)</td>
<td>87 (100%)</td>
<td>84 (99%)</td>
<td>85 (100%)</td>
<td>80 (100%)</td>
</tr>
<tr>
<td>Day 8</td>
<td>65 (83%)</td>
<td>70 (84%)</td>
<td>76 (87%)</td>
<td>76 (89%)</td>
<td>68 (80%)</td>
<td>75 (94%)</td>
</tr>
<tr>
<td>Day 15</td>
<td>52 (67%)</td>
<td>53 (64%)</td>
<td>64 (74%)</td>
<td>61 (72%)</td>
<td>56 (66%)</td>
<td>55 (69%)</td>
</tr>
<tr>
<td>Week 4</td>
<td>35 (45%)</td>
<td>45 (54%)</td>
<td>49 (56%)</td>
<td>52 (61%)</td>
<td>47 (55%)</td>
<td>46 (58%)</td>
</tr>
<tr>
<td>Week 6</td>
<td>29 (37%)</td>
<td>36 (48%)</td>
<td>40 (46%)</td>
<td>42 (49%)</td>
<td>42 (49%)</td>
<td>36 (45%)</td>
</tr>
</tbody>
</table>
3.4 RESULTS

The primary efficacy endpoint was the change from baseline to week 6 in the PANSS total score. The PANSS is a 30 item scale where each item is rated on a severity scale ranging from 1 to 7. Patients with missing data had the data from their last available visit carried forward (LOCF). Differences between the SR formulation groups and placebo were analysed using analysis of covariance with baseline score and centre as covariates.

To account for the multiplicity of comparing three treatment groups to placebo the applicant used the Hochberg procedure. In this procedure the p-values are ordered. The study is positive if either (i) all three p-values are smaller than 0.05 (ii) the two smallest p-values are both less than 0.025 or (iii) the smallest p-value is less than 0.017.

3.4.1 Change from baseline to week 6 in PANSS total score – MITT LOCF

Study 041

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>SR300</th>
<th>SR600</th>
<th>SR800</th>
<th>IR300</th>
<th>IR600</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>91.1</td>
<td>91.5</td>
<td>92.4</td>
<td>89.0</td>
<td>89.5</td>
<td>88.6</td>
</tr>
<tr>
<td>Change from baseline (SE)*</td>
<td>-5.2 (2.3)</td>
<td>-5.0 (2.3)</td>
<td>-13.0 (2.2)</td>
<td>-11.2 (2.2)</td>
<td>-9.4 (2.2)</td>
<td>-7.0 (2.3)</td>
</tr>
<tr>
<td>Difference from placebo*</td>
<td>0.19</td>
<td>-7.82</td>
<td>-5.98</td>
<td>-4.23</td>
<td>-1.78</td>
<td></td>
</tr>
<tr>
<td>95% CI*</td>
<td>-5.9, 6.3</td>
<td>-13.8, -1.8</td>
<td>-12.0, 0.1</td>
<td>-10.3, 1.8</td>
<td>-7.9, 4.4</td>
<td></td>
</tr>
<tr>
<td>p-value*</td>
<td>0.952</td>
<td>0.011</td>
<td>0.052</td>
<td>0.169</td>
<td>0.569</td>
<td></td>
</tr>
</tbody>
</table>

* From ANCOVA with terms for treatment, centre and baseline

Only the 600mg dose of the SR product demonstrated superiority over placebo; the p-value of 0.011 was just below the Hochberg adjusted threshold of 0.017. The 800mg had a favourable trend over placebo but the 300mg did not separate from placebo at all. It is notable that the licensed immediate release product did not separate from placebo. This calls into question the sensitivity of this study to detect differences between treatments and places the results from the SR formulation into a slightly better context.
Study 132

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>SR400</th>
<th>SR600</th>
<th>SR800</th>
<th>IR400</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>96.2</td>
<td>95.8</td>
<td>96.8</td>
<td>97.3</td>
<td>96.5</td>
</tr>
<tr>
<td>Change from baseline (SE)*</td>
<td>-18.8 (2.5)</td>
<td>-24.8 (2.5)</td>
<td>-30.9 (2.5)</td>
<td>-31.3 (2.5)</td>
<td>-26.6 (2.4)</td>
</tr>
<tr>
<td>Difference from placebo*</td>
<td>-6.1</td>
<td>-12.1</td>
<td>-12.5</td>
<td>-7.8</td>
<td></td>
</tr>
<tr>
<td>95% CI*</td>
<td>-11.5, -0.6</td>
<td>-17.6, -6.7</td>
<td>-17.9, -7.1</td>
<td>-13.1, -2.4</td>
<td></td>
</tr>
<tr>
<td>p-value*</td>
<td>0.030</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.004</td>
<td></td>
</tr>
</tbody>
</table>

* From ANCOVA with terms for treatment, centre and baseline

All three p-values comparing the SR product to placebo were less than 0.05, so all three doses have demonstrated superiority over placebo. There seemed to be additional benefit for the 600mg dose over 400mg, but there was no obvious improvement from increasing the dose to 800 mg. The immediate release dose also showed superiority over placebo.

Study 133

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>SR400</th>
<th>SR600</th>
<th>SR800</th>
<th>IR800</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>90.8</td>
<td>91.1</td>
<td>93.1</td>
<td>92.6</td>
<td>93.0</td>
</tr>
<tr>
<td>Change from baseline (SE)*</td>
<td>-12.1 (1.9)</td>
<td>-13.8 (1.9)</td>
<td>-16.8 (2.0)</td>
<td>-14.8 (1.9)</td>
<td>-15.0 (1.9)</td>
</tr>
<tr>
<td>Difference from placebo*</td>
<td>-1.7</td>
<td>-4.7</td>
<td>-2.7</td>
<td>-3.0</td>
<td></td>
</tr>
<tr>
<td>95% CI*</td>
<td>-5.9, 2.5</td>
<td>-9.1, -0.4</td>
<td>-7.0, 1.6</td>
<td>-7.3, 1.3</td>
<td></td>
</tr>
<tr>
<td>p-value*</td>
<td>0.434</td>
<td>0.033</td>
<td>0.214</td>
<td>0.172</td>
<td></td>
</tr>
</tbody>
</table>

* From ANCOVA with terms for treatment, centre and baseline

The 600 mg dose of the SR product achieved a p-value of less than 0.05, however after adjusting for multiplicity this is not statistically significant as it does not beat the 0.017 threshold. None of the other treatment arms achieved statistical significance, although positive trends were seen for all groups. As with trial 041 the IR formulation did not demonstrate an advantage over placebo, calling into question the sensitivity of the trial.

There is fairly strong evidence of efficacy for the 600mg dose of the SR product. Statistical significance was achieved in two of the three studies, and a p-value less than 0.05 was also seen in the final trial. Considering the other doses, 400mg seems sub-optimal, while there is no evidence from these studies that using 800mg provides any additional benefit over 600mg.

The immediate release product only separated from placebo in study 132, which was also the study in which the SR formulation showed its best performance. As the already licensed IR formulation did not demonstrate efficacy in trials 041 and 133 there might be some question regarding the sensitivity of those trials to detect differences. This might be linked in some way to the high early withdrawal rate in these two trials. This strengthens the efficacy picture for the SR formulation as the less impressive results in those two trials could be a problem with the trials rather than the efficacy of the new formulation. It is useful to note that SR600 outperformed the IR dose(s) in all three trials.

As well as statistical significance, the clinical relevance of the differences must also be considered.
Consideration of responder rates can help to give some idea of the clinical relevance of a difference on the overall scales. It is also easy to use responder rates to get an idea of the influence of the handling of missing data on the results. This can be done by conducting an analysis where a patient with missing data is considered to be a non-responder.

A patient was classified as a responder if a reduction of 30% from baseline in the PANSS was achieved.

### 3.4.2 Responders (≥ 30% reduction in PANSS) – MITT

**Study 041**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=78)</th>
<th>SR300 (N=83)</th>
<th>SR600 (N=87)</th>
<th>SR800 (N=85)</th>
<th>IR300 (N=85)</th>
<th>IR600 (N=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOCF</td>
<td>11 (14%)</td>
<td>10 (12%)</td>
<td>21 (24%)</td>
<td>20 (24%)</td>
<td>16 (19%)</td>
<td>11 (14%)</td>
</tr>
<tr>
<td>Missing=Failure</td>
<td>11 (14%)</td>
<td>9 (11%)</td>
<td>17 (20%)</td>
<td>14 (16%)</td>
<td>12 (14%)</td>
<td>9 (11%)</td>
</tr>
</tbody>
</table>

**Study 132**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=115)</th>
<th>SR400 (N=111)</th>
<th>SR600 (N=111)</th>
<th>SR800 (N=117)</th>
<th>IR400 (N=119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOCF</td>
<td>35 (30%)</td>
<td>49 (44%)</td>
<td>67 (60%)</td>
<td>66 (56%)</td>
<td>63 (53%)</td>
</tr>
</tbody>
</table>

**Study 133**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=111)</th>
<th>SR400 (N=113)</th>
<th>SR600 (N=101)</th>
<th>SR800 (N=110)</th>
<th>IR800 (N=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOCF</td>
<td>23 (21%)</td>
<td>22 (19%)</td>
<td>27 (27%)</td>
<td>26 (24%)</td>
<td>25 (23%)</td>
</tr>
</tbody>
</table>

Consistent with the analysis of change from baseline the differences between treatments were small in studies 041 and 133. As this includes the IR doses as well, the sensitivity of these trials is questioned. In study 132 the difference from placebo for SR600 was 30%. This compares favourably with the 23% achieved by IR400. There was again no evidence of any additional benefit from going up to 800 mg.

A missing=failure analysis can provide an idea of the robustness of using LOCF to impute missing data. In study 041 the differences from placebo were smaller using this approach, but the analysis was not provided for the other two studies. Fortunately study 132 was less affected by missing data than the other studies, so the difference would not be as great in this trial.

### 3.5 LONG-TERM EFFICACY

A single trial, 0004, was conducted to assess the need for long-term treatment with Seroquel SR. This was a randomised, double-blind, placebo-controlled trial.

Patients initially were enrolled into a 16-week open-label stabilisation period using Seroquel SR. During this period patients were gradually down-titrated from their ongoing psychiatric medication and were titrated to a dose within the range of 400 to 800 mg/day of Seroquel SR (target dose 600 mg/day).

To be randomised into the trial patients must have been clinically stable before entering the stabilisation period and during the stabilisation period, i.e. CGI-S ≤ 4 and
PANSS ≤ 60 at enrolment and week 16, and no change of ≥10 in PANSS from enrolment to week 8 or week 16.

Patients were randomised in a 1:1 ratio to either switch to placebo or to continue on Seroquel SR for one year or until relapse. The randomised treatments were given double-blind. Over the course of the year patients could vary the dose across the 400-800 mg range (or placebo tablet equivalent) based upon efficacy and tolerability.

The switch to double-blind therapy was achieved over a 4 day “cross-titration” period where the open-label treatment was decreased (to 75% of total on day 1, 50% on day 2, 25% on day 3, 0% on day 4) while the double-blind treatment was increased (25% of total on day 1, 50% on day 2, 75% on day 3, 100% on day 4). This means that the total dose was never changed for those randomised to remain on Seroquel, while the dose was decreased in four equal increments for those receiving placebo.

It is appropriate that the dose of Seroquel was down-titrated rather than patients being abruptly switched to placebo.

Patients attended study visits at baseline (randomisation, day 1), day 14, day 30, and then every 30 days until month 12.

The primary efficacy endpoint was time to relapse. Relapse was defined as one or more of:

(i) hospitalisation due to worsening of schizophrenia
(ii) an increase on the PANSS score of more than 30% from randomisation
(iii) a rating of “much worse” or “very much worse” on the CGI-I
(iv) need of other antipsychotic medication to treat psychosis

This was to be analysed using a Cox proportional hazards model.

Based upon data from a trial with a similar design for aripiprazole, a hazard ratio of 0.50 was assumed. To provide 90% power to detect a difference at the 0.05 level, accounting for two interim analyses, at least 90 relapses needed to be observed.

It was anticipated that the 1-year relapse rate would be 52% and that around 75% of recruited patients would be randomised.

Therefore, the protocol planned that approximately 232 patients needed to be enrolled and approximately 174 randomised to obtain 90 patients with relapse for the final analysis.

The first patient was randomised in July 2005. By mid January 2006 about 280 patients were enrolled, 135 were randomised, and there had been 36 relapses. The
lower than expected relapse rate provoked an increase in the sample size to approximately 333 patients enrolled and 250 randomised.

Two interim analyses were planned – after 45 and 60 relapses had been observed. The final analysis was planned for when 90 relapses had been observed. A Data and Safety Monitoring Board (DSMB) was set up to look at the interim data, and personnel from the sponsor company did not have access to un-blinded data.

The O’Brien-Fleming method was used to account for these interim analyses. The critical value for stopping at the first interim analysis was set at p<0.004455.

This critical value was achieved and so the study was terminated early. After termination all patients were to be seen for their next scheduled visit to ascertain their status. Thus two sets of results are presented; the results from the interim analysis that led to study termination (interim ITT population); and the results after all patients had been seen following study termination (ITT population).

The results from the ITT population are the more complete data set and should be taken as primary. The applicant set the interim ITT population as primary.

**Patient accountability**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>SR</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled</td>
<td>358</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Started open-label treatment</td>
<td>327</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomised</td>
<td>103</td>
<td>94</td>
<td>197</td>
</tr>
<tr>
<td>ITT population</td>
<td>103 (100%)</td>
<td>94 (100%)</td>
<td></td>
</tr>
<tr>
<td>Interim ITT population</td>
<td>87</td>
<td>84</td>
<td></td>
</tr>
</tbody>
</table>

| Not discontinued     | 39 (38%) | 78 (83%) |
| Discontinued due to Relapse | 50 (49%) | 11 (12%) |
| Discontinued for other reason | 14 (14%) | 5 (5%)   |
| Adverse event        | 1       | 1    |
| Lost to follow-up    | 1       | 1    |
| Subject not willing to continue | 12 | 3 |

**Results**

**Time to schizophrenic relapse (and primary reason)**

<table>
<thead>
<tr>
<th>Population</th>
<th>Relapse rates</th>
<th>Hazard ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>SR</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>Interim ITT</td>
<td>36/87 (41%)</td>
<td>9/84 (11%)</td>
<td>0.16 (0.08, 0.34)</td>
</tr>
<tr>
<td>Hospitalisation</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>PASNSS ≥ 30% increase</td>
<td>12</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>CGI ≥ 6</td>
<td>18</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Antipsychotic medication</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>ITT</td>
<td>50/103 (49%)</td>
<td>11/94 (12%)</td>
<td>0.13 (0.07, 0.26)</td>
</tr>
<tr>
<td>Hospitalisation</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>PASNSS ≥ 30% increase</td>
<td>16</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>CGI ≥ 6</td>
<td>24</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Antipsychotic medication</td>
<td>6</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
There was a highly statistically significant difference between the treatments in the
time to relapse, with a hazard ratio of 0.13 in the overall ITT population. The
treatment effect was not restricted to one of the definitions of relapse but was evident
across all four of the criteria.

This provides strong evidence that patients who are stabilised after 12 weeks
treatment with Seroquel SR achieve continued benefit from remaining on treatment.

3.6 SWITCHING FROM IMMEDIATE TO PROLONGED RELEASE

A single study, study 146, was conducted to establish whether efficacy was
maintained when patients stabilised on the immediate release formulation were
switched to prolonged release.

This was a randomised, double-blind, double-dummy trial comparing Seroquel IR and
SR in patients who were stabilised on IR treatment.

Patients who were already receiving Seroquel IR were recruited into the trial. All
patients participated in a 4 week run-in period. The daily dose of Seroquel used in the
run-in period was based upon the dose already being received as shown in the table
below.

<table>
<thead>
<tr>
<th>Pre-trial dose</th>
<th>Dose for run-in period</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 – 450 mg/day</td>
<td>400 mg/day</td>
</tr>
<tr>
<td>475 – 650 mg/day</td>
<td>600 mg/day</td>
</tr>
<tr>
<td>675 – 800 mg/day</td>
<td>800 mg/day</td>
</tr>
</tbody>
</table>

Patients who were clinically stable throughout the 4-week run-in period (CGI severity
of illness \( \leq 3 \) with no change from enrolment) without altering their dose were
randomised in a 2:1 ratio to receive treatment with SR (once daily in the evening) or
IR (twice daily) for the next 6 weeks. The randomisation was stratified by the daily
dose being taken, which remained unchanged from the run-in period.

Almost all randomised patients were included in the modified ITT population and the
proportion of patients completing the study was high. Hence the trial conclusions
should be robust to issues relating to missing data.

<table>
<thead>
<tr>
<th>SR</th>
<th>IR</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled</td>
<td>331</td>
<td>166</td>
</tr>
<tr>
<td>Treated during run-in</td>
<td>263</td>
<td>130</td>
</tr>
<tr>
<td>Randomised</td>
<td>330 (99.7%)</td>
<td>166 (100%)</td>
</tr>
<tr>
<td>Modified ITT</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>No post randomisation data</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Per-protocol population</td>
<td>303 (92%)</td>
<td>156 (94%)</td>
</tr>
<tr>
<td>Completed study</td>
<td>28 (8%)</td>
<td>10 (6%)</td>
</tr>
<tr>
<td>Discontinued treatment early</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Lack of Efficacy</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Eligibility criteria not fulfilled</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Subject no willing to continue</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>
The primary variable was the proportion of patients who discontinued study treatment due to lack of efficacy or whose PANSS total score increased 20% or more from baseline at any visit.

Switching to SR was to be considered non-inferior to staying on IR if the 95% confidence interval for the difference between treatment groups excluded inferiority of greater than 6%. To demonstrate non-inferiority this should be achieved in both the ITT and per-protocol populations, as noted in the CHMP points to consider on switching between superiority and non-inferiority.

The confidence intervals were calculated using the Wilson score method for a single proportion without continuity correction.

### Lack of efficacy

<table>
<thead>
<tr>
<th>Population</th>
<th>SR</th>
<th>IR</th>
<th>Difference</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>MITT</td>
<td>30/330 (9.1%)</td>
<td>12/166 (7.2%)</td>
<td>1.86%</td>
<td>-3.78, 6.57</td>
</tr>
<tr>
<td>Discontinued</td>
<td>7 (2%)</td>
<td>1 (&lt;1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase in PANSS</td>
<td>28 (8%)</td>
<td>11 (7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per-protocol</td>
<td>14/263 (5.3%)</td>
<td>8/130 (6.2%)</td>
<td>0.83%</td>
<td>-6.75, 3.71</td>
</tr>
<tr>
<td>Discontinued</td>
<td>2 (&lt;1%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase in PANSS</td>
<td>13 (5%)</td>
<td>8 (6%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The criteria for non-inferiority were not met in the MITT population, where the confidence extended above the pre-defined non-inferiority margin of 6%. Therefore, it seems that the trial has not successfully demonstrated that switching to treatment with SR results in no important loss of efficacy compared to remaining on IR.

The primary objective of Study 146 was to demonstrate the non-inferiority of the efficacy of quetiapine XL versus quetiapine IR using the primary efficacy variable for the MITT population. Although the proportion of patients in the MITT population with lack of efficacy was similarly low in the 2 treatment groups, non-inferiority was narrowly missed statistically. Using the PP population, the treatment difference for the primary efficacy variable was statistically significantly lower than the non-inferiority margin, indicating the non-inferiority of quetiapine XL compared to quetiapine IR.

Despite non-inferiority in the full analysis set being narrowly missed, the results from the full analysis set and the PP analysis set in Study 146 lead to similar conclusions, in line with the CPMP guideline requirement. Although the primary variable did not achieve statistical non-inferiority for the margin selected, analyses of key secondary efficacy variables demonstrated similar results in the MITT and PP populations suggesting no notable loss of efficacy on switching from IR to XL formulations in either population.

To summarise, in the trial to support switching from IR to SR the non-inferiority criteria was achieved for the PP population but not for the MITT population. Therefore, strictly, the trial has failed, as successful results in both populations are required. In view of this, the approved SmPCs have appropriate wording to reflect the need for ensuring maintained efficacy when switching from the IR to the XL formulation, and this issue is satisfactorily resolved. The issue of switching will be further addressed in the pharmacoepidemiology program contained in the Risk Management Plan (RMP).
3.7 JUSTIFICATION FOR POSOLOGY INCLUDING TITRATION UP TO 800MG IN SCHIZOPHRENIA

Seroquel XL is a line extension to the immediate-release (IR) formulation which was developed to facilitate once daily dosing of quetiapine and also to simplify the titration schedule. Seroquel IR has been approved in Europe for over 10 years. There are approximately 20 000 patients in the Seroquel clinical safety database and more than 25 million patients worldwide have taken Seroquel to date. The new formulation had been approved in the dose range of up to 800 mg in 24 of the 27 EU Member States at the time of these applications.

In the UK, the currently approved SmPC for Seroquel IR allows for dose adjustments of up to 750 mg per day. According to a market research in the UK from 2006 (Adelphi diary study in 240 patients), 20% of patients were prescribed doses above 600 mg per day. Corresponding figures from a market research study in 252 patients in the UK, Germany, Italy and Spain (Seroquel Dosing Diary 2006 Wave 3) showed that approximately 30% of patients reached a final maintenance dose of more than 700 mg/day. These data from the real-life setting indicates that some patients require doses in the higher end of the range. The use of higher doses in real-life setting is further reported in published articles (J Clin Psychiatry 2003; 64 (suppl 12; “Guideline 2”)) and (Citrome et al 2005) where over 50% of patients using quetiapine in New York State in 2004 were reported to use doses higher than 500 mg. In the management of psychiatric illness it is important that treatment is individualised to each patient. As demonstrated with other marketed atypical antipsychotics, it is difficult to define a single dose level which would effectively treat all patients. It is of great importance to offer treatment opportunities for all patients, including those that would require treatment in the higher dose range with the immediate-release formulation, to have the option to utilize the once-daily formulation. Thus, the prescribing information should provide the flexibility for physicians to titrate to a dose that is both safe and effective.

It should be noted that the proposed prescribing information does not mandate that patients treated with quetiapine XL be titrated directly to 800 mg as an initial target dose. The intention is that patients will receive the effective dose of 600 mg on Day 2 of treatment but after Day 2 will only progress up to 800 mg depending on individual response. As such, the recommended dose is 600mg per day, while the 800mg dose is included in the label to represent a maximum dose. This is reflected in the SmPC.

Based on the results of Study 5077IL/0097, which compared the steady-state pharmacokinetics of equivalent total daily doses of quetiapine (administered as Seroquel IR; given twice daily) and Seroquel XL (administered once daily), both formulations are similar with respect to AUC over a 24-hour time period. Additionally, in Studies 5077IL/0086 and 5077IL/0118 both dose and dose unit proportionality have been demonstrated up to total daily doses of 800 mg with respect to Cmax and AUC. Thus, with repeated dosing, the bioavailability of a once-daily dose of Seroquel XL is expected to be similar to that of the same total daily dose of Seroquel IR administered in divided doses every 12 hours. The currently approved SmPC for Seroquel IR allows for dose adjustments of up to 750 mg per day and AstraZeneca believes that the pharmacokinetic similarities between the formulations justify that similar dose adjustments should be allowed with the prolonged-release formulation.
The Seroquel XL schizophrenia clinical programme was not designed to compare doses. However, the clinical programme for the prolonged-release formulation gives support for the use of daily doses of up to 800 mg. In the acute efficacy Study 132, larger treatment effects were observed at the higher fixed doses of 600 mg/day and 800 mg/day than for the lower 400 mg/day dose in patients with acute schizophrenia. Specifically, quetiapine XL 400 mg/day, 600 mg/day, and 800 mg/day showed statistically significant improvement in PANSS total score at Day 42 of 6.1, 12.1, and 12.5 points, respectively, compared with placebo. Although an incremental benefit of 800 mg versus the 600 mg dose was not seen in Study 132, both the 600 and 800 mg doses had numerical advantages over the 400 mg XL and IR doses.

However, additional evidence for the value of the 800 mg maximum dose was shown in the long-term relapse prevention Study D1444C00004 (Study 004). In this study patients were dosed flexibly in 200 mg increments between 400 mg and 800 mg per day. Results demonstrated that quetiapine XL significantly prolonged time to first schizophrenic relapse in clinically stable patients treated for up to approximately 9 months. The average dose of quetiapine XL selected by investigators during the randomized treatment phase was 669 mg/day, and in this study nearly half (48.9%) of the patients were dosed at 800 mg/day based on the investigator’s judgment. All dose strata demonstrated significant efficacy versus placebo. This indicates that individual patients may require the higher dose to achieve the maximal clinical benefit.

Regarding the safety and tolerability profiles of quetiapine XL 600 mg and 800 mg/day, these were generally similar in the 6-week, placebo controlled studies (Studies 132, 133, and 041). In particular, pooled data from the 6-week placebo-controlled studies showed the incidence of adverse events leading to discontinuation was similar for 600 mg and 800 mg treatment groups (Table 1) and that there were no dose-related trends in common adverse events (nor any dose-related trends in the specific safety data for EPS, diabetes mellitus, neutropenia, suicidality, weight increase and lipid laboratory data). The data from these studies confirmed that tolerability was not compromised at the 800 mg dose and as such the benefit: risk ratio of the 800 mg dose is considered to be positive.

### Table 1 Various categories of adverse events in quetiapine XL dose groups

<table>
<thead>
<tr>
<th>(safety population): Placebo-controlled pool</th>
<th>QTP XL 300 mg N=91</th>
<th>QTP XL 400 mg N=227</th>
<th>QTP XL 600 mg N=310</th>
<th>QTP XL 800 mg N=323</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events&lt;sup&gt;a&lt;/sup&gt;</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Serious adverse events&lt;sup&gt;b&lt;/sup&gt;</td>
<td>78 (85.7)</td>
<td>141 (62.1)</td>
<td>228 (73.5)</td>
<td>214 (66.3)</td>
</tr>
<tr>
<td>Serious adverse events leading to death&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2 (2.2)</td>
<td>12 (5.3)</td>
<td>17 (5.5)</td>
<td>11 (3.4)</td>
</tr>
<tr>
<td>Serious adverse events not leading to death&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Drug-related adverse events&lt;sup&gt;b&lt;/sup&gt;</td>
<td>53 (58.2)</td>
<td>87 (38.5)</td>
<td>145 (46.8)</td>
<td>127 (39.3)</td>
</tr>
<tr>
<td>Adverse events leading to discontinuation&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5 (5.5)</td>
<td>17 (7.5)</td>
<td>23 (7.4)</td>
<td>16 (5.0)</td>
</tr>
<tr>
<td>Total number of adverse events</td>
<td>350</td>
<td>392</td>
<td>808</td>
<td>776</td>
</tr>
<tr>
<td>Adverse events</td>
<td>350</td>
<td>392</td>
<td>808</td>
<td>776</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>3</td>
<td>15</td>
<td>20</td>
<td>16</td>
</tr>
<tr>
<td>Drug-related adverse events&lt;sup&gt;b&lt;/sup&gt;</td>
<td>197</td>
<td>195</td>
<td>442</td>
<td>434</td>
</tr>
</tbody>
</table>

<sup>a</sup> Patients with multiple events in the same category are counted only once in that category.

<sup>b</sup> As judged by the investigator.


Note: Placebo-controlled pool is the studies D1444C00013, D1444C00113 and 5077E0041.

In summary, the applicant believes that individual patients may show an enhanced treatment response in the upper dose range. Market research has shown that approximately 20-30% of patients taking Seroquel IR use doses above 600 mg per day. The same option to use higher doses when needed should be available with the new formulation.

Statistical Assessor’s Comment:

From studies 041, 132 and 133, there is no definitive proof of additional benefit from using 800mg compared to using 600mg.

The MAH points to the facts that the current IR posology allows doses up to 750mg/day, and that research shows that a certain percentage of patients make use of doses above 600mg/day. However, it is difficult to make direct comparisons with data from the IR formulation as the proposed titration schemes are so different. For sustained release the proposal is to take 300mg on day 1 and 600mg on day 2, and then choose a final dose in the 400-800mg range. This is very different from the titration used for IR where patients increase the dose across 50, 100, 200 and 300mg/day over 4 days, before choosing a final dose in the 150-750mg/day range. The usual effective dose is stated to be in the 300-450mg/day range.

It seems difficult to bridge from one formulation to another when the dosing schemes proposed are so different. In addition, the scheme proposed for the SR formulation has a much more aggressive titration and proposes generally higher doses - even with a highest dose of 600mg (a usual effective dose of 400-600mg compared to 300-450mg/day).

The best evidence for comparing doses is from the 3 randomised controlled fixed dose trials performed by the applicant which use the proposed sustained release formulation.

The studies submitted were self evidently sensitive to detect differences between doses, as they show that the 400mg dose is sub-optimal. Yet the same studies that show the benefits of increasing the dose above 400mg do not show that there is any reason to go beyond 600mg. In fact, if anything, there is a suggestion that the results are a little worse as the dose is pushed up as the point estimates tend to favour 600mg over 800mg, with generally fewer responders and a smaller change from baseline.

If there is a sub-group of patients that respond to 800mg and not to 600mg it would have been expected that this would create some kind of trend in favour of 800mg over 600mg – no such trend is evident.

Change from baseline to week 6 in PANSS total score difference from placebo

<table>
<thead>
<tr>
<th>Study</th>
<th>400mg*</th>
<th>600mg</th>
<th>800mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>041</td>
<td>0.19</td>
<td>-7.82</td>
<td>-5.98</td>
</tr>
<tr>
<td>132</td>
<td>-6.1</td>
<td>-12.1</td>
<td>-12.5</td>
</tr>
<tr>
<td>133</td>
<td>-1.7</td>
<td>-4.7</td>
<td>-2.7</td>
</tr>
</tbody>
</table>
**Responder rates (≥ 30% reduction in PANSS)**

<table>
<thead>
<tr>
<th>Study</th>
<th>400mg*</th>
<th>600mg</th>
<th>800mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>041</td>
<td>10/83 (12%)</td>
<td>21/87 (24%)</td>
<td>20/85 (24%)</td>
</tr>
<tr>
<td>132</td>
<td>49/111 (44%)</td>
<td>67/111 (60%)</td>
<td>66/117 (56%)</td>
</tr>
<tr>
<td>133</td>
<td>22/113 (19%)</td>
<td>27/101 (27%)</td>
<td>26/110 (24%)</td>
</tr>
</tbody>
</table>

*The lowest dose was 300mg rather than 400mg in study 041.

Finally the applicant points to the relapse prevention trial which employed flexible dosing rather than randomising patients to the different doses. In this trial 48.9% of patients were dosed at 800mg. However the fact that patients took 800mg does not mean that they needed to. This trial does not have the appropriate design to allow any assessment of the dose response.

In consideration of the fact that the 800mg strength SR formulation presents no additional safety concerns in comparison to the 600mg SR formulation, and that some market experience indicate benefits of a dose above 600mg for the treatment of schizophrenia in some patients, the titration to 800mg is accepted in the posology. The approved SmPCs contain appropriate wording to reflect this.

**Clinical Assessor’s Comment:**

As detailed in the statistical assessment, there was no clinically or statistically significant separation between dosing at the 600mg and 800mg dose strengths. The applicant acknowledges this, but their arguments are considered valid to support the use of the higher posology, and the approved SmPCs address this issue.

Experience from the immediate release preparation shows that there is clearly a clinical need in support of higher dose strengths in some patients. The applicant asserts that around 20% of patients treated with immediate release preparations of Seroquel require dosing >700mg. They also identify that compliance with medication can be an issue in this patient group. It is agreed that a once a day dosing regime would be of assistance in this area.

There were no particular dose related safety issues seen in any of the clinical trials, as the applicant outlines above. Therefore, there is seen to be a need for treatment at doses higher than 600mg of quetiapine in some patients and any risks associated with the use of higher doses would appear to have been minimised through restriction of the SPC and through the proposed pharmacoepidemiology programme. Furthermore, the use of the 800mg SR posology has precedence through a previous MRP (NL/H/0156/08-011/MR).

Overall, it is assessed that there can be concluded a positive risk-benefit for the inclusion of the 800mg dose strength.
3.8 TREATMENT OF MANIC EPISODES ASSOCIATED WITH BIPOLAR DISORDER

In the current label for quetiapine IR there are some differences between the approved posology for schizophrenia and bipolar mania with the immediate-release formulation. The approved dose range for mania patients is 200-800 mg/day, and the effective dose range for mania patients is 400-800 mg/day, compared with a dose range of 150-750 mg/day and an effective dose range of 300-450 mg/day for schizophrenia patients. These differences are due to the fact that the clinical programs supporting the two indications were done at different times. When the mania studies were planned, experience from the clinical use of quetiapine in schizophrenic patients was considered. Therefore, when designing the mania studies, the different dose interval was investigated.

The available data for quetiapine XL have shown that initiation of treatment with 300 mg/day is safe and well tolerated. A key benefit of the new quetiapine formulation is, therefore, simplification of treatment initiation so that patients can safely achieve a therapeutically effective dose sooner. Patients with mania would be treated similarly to those with schizophrenia with the XL formulation; that is, treatment would begin with a dose of 300 mg on Day 1, followed by escalation to 600 mg on Day 2, and subsequently up to 800 mg after Day 2 if required. The proposed dose range of 400 mg/day to 800 mg/day is the same as the effective quetiapine IR dose range for the treatment of mania. In patients with acute bipolar mania, compliance is especially important and problematic and provides a strong rationale for reducing the frequency of administration and simplifying the dose-titration regimen. The XL formulation of quetiapine has been developed to provide sustained exposure to the drug when administered once daily. Once-daily administration of quetiapine as an XL formulation will potentially facilitate patient compliance. Further, simplified dosing will allow a patient to achieve a dose in the effective range sooner. Hence, the proposed titration scheme and 300 mg starting dose, shown to be a safe and tolerable in schizophrenia patients, and as with schizophrenia patients is thought to convey clinical benefit in facilitating patients with mania reaching an effective dose as early as possible.

Quetiapine XL mania Study D144CC00004 (Study 004)

Study 004 examines the efficacy of the XL formulation in patients with bipolar mania. Results from this study validate the kinetic bridge between IR and XL in bipolar mania. On the basis of the bridging principles and the extent of data already available in the mania indication, the applicant believes that the positive data from mania Study 004 are sufficient to confirm efficacy with this formulation in this population.

Study Design and Patients

Mania Study 004 was a 3-week, multicentre, randomized, parallel-group, double-blind, placebo-controlled, Phase III study of the efficacy and safety of quetiapine XL with flexible doses in the range of 400 to 800 mg or placebo given once a day (QD) in the evening in the treatment of patients with bipolar I disorder with an acute manic episode. This study consisted of an enrolment period of up to 35 days and a 3-week treatment period with 1 of 2 treatment regimens (quetiapine XL 400 to 800 mg QD or placebo). A total of 316 patients were randomized, 155 in the quetiapine XL group and 161 in the placebo group. Overall, 72% of patients in each treatment group...
completed the study. More patients in the placebo group discontinued due to AEs and lack of therapeutic response (7.5% and 9.3%, respectively) compared with those in the quetiapine XL group (2.6% and 3.9%) whereas the quetiapine XL group had more discontinuations due to patients being lost to follow-up compared with placebo (7.7% versus 2.5%).

The majority of patients in both treatment groups had only manic episode (versus mixed) at baseline (58% and 55% in the quetiapine XL and placebo groups, respectively); approximately 30% and 33% of patients in the quetiapine XL and placebo groups, respectively, had a rapid cycling course. Mean baseline YMRS (Young Mania Rating Scale) scores were similar (28.8 and 28.4 for the quetiapine XL and placebo groups, respectively). Study patients in both treatment groups had greater severity of illness for mania in comparison with depression. In this study quetiapine XL was administered orally, once daily in the evening. The initial dose was 300 mg, adjusted on Day 2 to 600 mg and continuing on 600 mg on Day 3 or adjusted to 400 mg or 800 mg, depending on tolerability. The therapeutic dose was subsequently adjusted as necessary throughout the treatment period to 400 mg, 600 mg, or 800 mg but was not to be less than 400 mg or higher than 800 mg per day. The expected therapeutic dose was 600 mg per day. A flexible dose regimen rather than fixed doses was chosen to mimic clinical practice. The mean daily dose of quetiapine over the course of the study was approximately 604 mg. In the comparative group, placebo to match the quetiapine XL formulation was given.

### Efficacy Results

Key efficacy results for mania Study 004 are presented for the MITT population in Table 1.

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Quetiapine XL (N=149)</th>
<th>Placebo (N=159)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 4</td>
<td>Week 3</td>
</tr>
<tr>
<td>YMRS change, LS mean (SE)</td>
<td>-9.89 (0.79)</td>
<td>-14.34 (0.91)</td>
</tr>
<tr>
<td>Proportion with ≥50% YMRS response, n (%)</td>
<td>33 (22.6)</td>
<td>82 (55.0)</td>
</tr>
<tr>
<td>Proportion with YMRS remission (total score &lt;=12), n (%)</td>
<td>27 (18.5)</td>
<td>62 (41.6)</td>
</tr>
<tr>
<td>CGI-BP-S overall LS mean change from baseline (SE)</td>
<td>-0.81 (0.09)</td>
<td>-1.51 (0.11)</td>
</tr>
<tr>
<td>CGI-BP-C overall, LS mean (SE)</td>
<td>2.86 (0.09)</td>
<td>2.58 (0.12)</td>
</tr>
<tr>
<td>CGI-BP-C “much improved” or “very much improved”, n (%)</td>
<td>44 (30.1)</td>
<td>80 (53.7)</td>
</tr>
</tbody>
</table>

**CGI-BP-S** Clinical Global Impression - Bipolar - Severity of Illness. **CGI-BP-C** Clinical Global Impression – Bipolar – Change. **LOCF** Last observation carried forward. **LS** Least square. **MITT** Modified intention-to-treat. **N** Number of patients in treatment group. **SE** Standard error. **XL** Extended-release. **YMRS** Young Mania Rating Scale.
Quetiapine XL monotherapy at a dose of 400 to 800 mg QD for 3 weeks of treatment in patients with bipolar I mania (both manic and mixed at baseline) was superior to placebo in reducing the level of mania symptoms as measured by the change from baseline on the YMRS total score as early as Day 4 and continuing through to the end of treatment. The therapeutic effects of quetiapine XL were not restricted to any subgroup examined (gender, age group, race, manic/mixed episode, rapid/non-rapid cycling). Analysis of other secondary outcome variables also supported the superiority of quetiapine XL 400 to 800 mg QD over placebo in the treatment of mania in patients with bipolar disorder.

**Safety results**

For patients treated with quetiapine XL, the mean daily dose over the treatment period was 603.8 mg with 47% of patients having a final dose level of 600 mg/day; approximately 22% and 29% of patients had final dose levels of 400 and 800 mg/day, respectively.

A summary of AEs is presented in Table 2.

Table 2 Overview of adverse events in mania Study 004 (safety population)

<table>
<thead>
<tr>
<th>AE category</th>
<th>Number (% of patients)(^a)</th>
<th>Quetiapine XL (N=151)</th>
<th>Placebo (N=160)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td></td>
<td>128 (84.8)</td>
<td>107 (66.9)</td>
</tr>
<tr>
<td>Any AE with an outcome of death</td>
<td>0</td>
<td>1</td>
<td>(0.6)</td>
</tr>
<tr>
<td>Any SAE</td>
<td></td>
<td>6 (4.0)</td>
<td>13 (8.1)</td>
</tr>
<tr>
<td>Any SAE leading to discontinuation of treatment</td>
<td>4</td>
<td>9</td>
<td>(5.6)</td>
</tr>
<tr>
<td>Any non-serious AE leading to discontinuation of treatment</td>
<td>3</td>
<td>4</td>
<td>(2.5)</td>
</tr>
<tr>
<td>Any other significant AE(^b)</td>
<td>0</td>
<td>1</td>
<td>(0.6)</td>
</tr>
</tbody>
</table>

AE  Adverse event. N Number of patients in treatment group. SAE Serious adverse event. XL Extended-release.

\(^a\) Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

\(^b\) Any AE that led to dose of treatment being temporarily stopped, or deemed by the sponsor to be significant, excluding AEs reported as SAEs or led to discontinuation of treatment.

The percentage of patients with AEs was higher in the quetiapine XL (84.8%) than the placebo group (66.9%); however, the incidences of SAEs and discontinuations due to SAEs were higher in the placebo group (8.1% and 5.6%, respectively) compared with the quetiapine XL group (4.0% and 2.6%, respectively). The percentages of patients with discontinuation of treatment due to non-serious AEs were comparable between the 2 treatment groups (2.0% in the quetiapine XL group and 2.5% in the placebo group). There was one “unexplained” death (placebo group).

The most common AEs were sedation, dry mouth, and somnolence, and all were reported more frequently in the quetiapine XL group (34.4%, 33.8%, and 16.6%, respectively) compared with placebo (7.5%, 6.9%, and 4.4%, respectively). Among AEs reported by >5% of patients in any group, AEs reported by at least twice as many patients in the quetiapine XL group compared to placebo included sedation, dry mouth, somnolence, constipation, dizziness, and weight increased.
An increase in the incidence in the composite of AEs potentially related to EPS was noted for the quetiapine XL group compared with the placebo group (6.6% vs. 3.8%). The incidences of individual AEs potentially related to EPS were low in both treatment groups. No AEs were encoded to QT prolongation. There were no AEs potentially related to neutropenia/agranulocytosis during the study; however, clinically laboratory assessments showed that 3 patients (2 quetiapine XL and 1 placebo) had shifts in neutrophil values from non-clinically significant at baseline to clinically-important low values (<1.5 x 10^9/L) at the end of treatment.

It was concluded from this study that Quetiapine XL 400 to 800 mg given QD in the evening, flexibly dosed, as monotherapy is superior to placebo in treatment of mania in patients with bipolar disorder. Quetiapine XL, at a dose of 400 to 800 mg given QD, flexibly dosed, was generally safe and well-tolerated in patients with bipolar disorder who were experiencing a manic episode.

Based on the previously demonstrated kinetic similarities between the two formulations together with the positive results from mania Study 004, the applicant believes the proposed wording, including the starting dose and proposed titration, regarding the use of quetiapine XL in the treatment of manic episodes can now be supported.

**Assessor’s Comment:**

This was a 3-week, multicentre, randomized, parallel-group, double-blind, placebo-controlled, Phase III study of the efficacy and safety of quetiapine XL as monotherapy in the treatment of patients with bipolar I disorder with acute bipolar mania. It was expected that the 3-week treatment duration would be sufficient for clinical effects to be observed in patients with acute bipolar mania without exposing patients randomized to placebo to undue risk or prolongation of risk. This 3-week treatment duration is also accepted by the Committee for Proprietary Medicinal Products (CPMP).

The primary objective of this study was to demonstrate superior efficacy of quetiapine XL formulation administered QD as monotherapy at a dose of 400 to 800 mg per day compared to placebo in decreasing the manic symptoms in patients with bipolar manic or mixed episode, after 3 weeks of treatment. This was assessed as the change from baseline (randomization) to final visit in the YMRS total score.

The secondary efficacy objectives of this study were as follows:

- To evaluate the efficacy and time course of quetiapine XR given QD compared to placebo in decreasing the manic symptoms in patients with bipolar mania at each visit, including Day 4;
- To evaluate the efficacy of quetiapine XT given QD compared to placebo in decreasing agitation and aggression in patients with bipolar mania;
- To evaluate the efficacy of quetiapine XR given QD compared to placebo in decreasing psychotic symptoms in patients with bipolar mania;
- To evaluate the efficacy of quetiapine XR QD compared to placebo in decreasing depressive symptoms in patients with bipolar mania.
The two treatment groups were matched in respect to age, race, and weight. 60.1% were male. Both groups were also matched with respect to baseline disease characteristics, with baseline YMRS scores at 28.8 and 28.4 for quetiapine and placebo groups respectively. The inclusion criteria were provided and were satisfactory.

Following a 28 day washout period from any previous medication, patients were randomised to receive either Quetiapine XL or matching placebo orally, once daily in the evening. The tablets were swallowed whole with fluid, starting with 300 mg on Day 1 and 600 mg on Day 2. Beginning on Day 3, the investigator could adjust the dose at a range between 400 and 800 mg per day depending on the effect and tolerance. However, the expected therapeutic dose was 600 mg per day. The investigator prescribed doses of 400, 600, or 800 mg per day. Quetiapine XL was not down-titrated at the end of the study.

The majority of patients in each treatment group completed the study (71.6% in the quetiapine XR group and 72.0% in the placebo group). Withdrawal due to lack of therapeutic response was more frequent in the placebo group (9.3%) compared to quetiapine XR (3.9%) and more placebo patients discontinued study treatment due to AEs (7.5%) compared to quetiapine XR (2.6%). There was a higher frequency of patients being lost to follow-up in the quetiapine XR group (7.7%) compared to placebo (2.5%). Approximately 99% of patients in each group were classified as being compliant on the basis of tablet counts that were consistent with ≥70% consumption of doses. Of the 89 patients who discontinued the study, 5 patients actually discontinued prior to receiving any study treatment. The reasons for discontinuation for these 5 patients included voluntary discontinuation (2 patients in the quetiapine XR group and 1 patient in the placebo group), incorrect enrolment (1 patient in the quetiapine XR group), and lost to follow-up (1 patient in the quetiapine XR group).

There can be seen a highly statistically significant improvement in YMRS (see Table 1, page 71) from baseline, along with statistically significant improvements in the clinical global impression scores. The percentage of patients with AEs was higher in the quetiapine XL (84.8%) than the placebo group (66.9%); however, the incidences of SAEs and discontinuations due to SAEs were higher in the placebo group (8.1% and 5.6%, respectively) compared with the quetiapine XL group (4.0% and 2.6%, respectively).

**Statistical assessor’s comment**

This was a randomised, placebo-controlled trial to investigate the efficacy of Seroquel prolonged release in patients with bipolar I disorder with an acute manic episode.

To be included in the study patients had to have a YMRS total score of at least 20 at enrolment and randomisation with a score of at least 4 on two of the four core items (irritability, speech, content, disruptive/aggressive behaviour); and a CGI-BP score of at least 4 (moderately ill). Patients must also have experienced at least one (but not more than eight) manic or mixed episodes in the last 5 years.

Patients were randomised in equal proportions to receive flexible dose Seroquel extended release or placebo. Dosing was once daily in the evening.
Titration of Seroquel XR (mg/day)

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3-21</th>
</tr>
</thead>
<tbody>
<tr>
<td>300mg</td>
<td>600mg</td>
<td>400-800mg</td>
</tr>
</tbody>
</table>

There were 316 patients randomised into the trial, and 227 (72%) patients completed the scheduled three weeks of treatment.

The modified intent-to-treat (MITT) population was defined to include all randomised patients who received treatment, had a baseline assessment for the primary efficacy endpoint and at least one valid post-baseline assessment. This was the primary population for efficacy analysis.

Ideally all randomised patients who were treated would be included in the efficacy analysis, with no requirement regarding efficacy assessments, but as this only affects 8 (2.5%) patients there is no real concern, especially as most of these withdrew before taking treatment – which is not a concern in a blinded trial.

Patient disposition

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Seroquel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised</td>
<td>161</td>
<td>155</td>
</tr>
<tr>
<td>Modified ITT</td>
<td>159 (99%)</td>
<td>149 (96%)</td>
</tr>
<tr>
<td>Not treated</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>No post-baseline YMRS score</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Completed study</td>
<td>116 (72%)</td>
<td>111 (72%)</td>
</tr>
<tr>
<td>Discontinued treatment early</td>
<td>45</td>
<td>44</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Severe non-compliance with protocol</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Condition worsened</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Lack of therapeutic response</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>Voluntary discontinuation</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Incorrect enrolment</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Last observation carried forward (LOCF) was used to impute missing observations. This is generally appropriate in psychiatric disorders, where the trend is for improvement over the course of the trial meaning the imputed values are generally poor.

Results

The primary efficacy endpoint was the change from baseline to week 3 in the YMRS total score. The YMRS is an 11 item scale where seven items are rated on a scale of 0 to 4 and four items on a scale from 0 to 8, giving a maximum total of 60 points. Patients with missing data had the data from their last available visit carried forward (LOCF). Differences between the SR formulation groups and placebo were analysed using analysis of covariance with baseline score and centre as covariates. Baseline score was treated as a fixed effect and centre as a random effect.
Change from baseline to week 3 in YMRS total score – MITT LOCF

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Seroquel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>90.8</td>
<td>28.8</td>
</tr>
<tr>
<td>Change from baseline (SE)*</td>
<td>-10.52 (0.88)</td>
<td>-14.34 (0.91)</td>
</tr>
<tr>
<td>Difference from placebo*</td>
<td></td>
<td>-3.83</td>
</tr>
<tr>
<td>95% CI*</td>
<td></td>
<td>-5.66, -2.00</td>
</tr>
<tr>
<td>p-value*</td>
<td></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* From ANCOVA with terms for treatment, centre and baseline

The results were highly statistically significant.

As well as statistical significance, the clinical relevance of the differences must also be considered. Consideration of responder rates can help to give some idea of the clinical relevance of a difference on the overall scales. Two definitions were used, both showing large differences from placebo.

Responders (≥ 50% reduction in YMRS) – MITT

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=159)</th>
<th>Seroquel (N=149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>53 (33%)</td>
<td>82 (55%)</td>
<td></td>
</tr>
</tbody>
</table>

Remission (YMRS ≤ 12)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=159)</th>
<th>Seroquel (N=149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>44 (28%)</td>
<td>62 (42%)</td>
<td></td>
</tr>
</tbody>
</table>

This trial provides robust evidence of the efficacy of the sustained release formulation used in the range 400-800mg. The trial design does not make it possible to investigate the dose response. In particular, considering the results of the schizophrenia trial, we cannot assess the additional benefit of the 800mg dose. However higher doses are generally needed in this indication, as reflected in the IR posology where the usual effective dose was in the same 400-800mg/day range as is recommended here. Therefore for this indication there seems no compelling reason to restrict the dose.

Overall, it is assessed that the applicant has adequately demonstrated that treatment with Quetiapine XL in a dose range between 400 and 800mg is more efficacious than placebo in the treatment of mania. There are no particular safety concerns raised.
4 ASSESSORS’ OVERALL CONCLUSIONS ON CLINICAL EFFICACY

Statistical assessor conclusion

There is fairly strong evidence that Seroquel SR is efficacious for the treatment of Schizophrenia at a dose of 600 mg/day. Statistical significance was achieved in two of the three studies, and a p-value less than 0.05 (not significant after adjustment for multiplicity) was also seen in the final trial.

This evidence is strengthened when it is considered that the two trials with the smallest effect for 600 mg were also the two trials where the licensed IR formulation did not separate from placebo, suggesting there may be some problem with the sensitivity of those studies. There is no evidence for additional efficacy from dosing above 600mg/day, but this issue has been discussed, and the points presented support the full proposed posology, including the 800mg dose.

The applicant has provided data which demonstrate that if a patient is stabilised by treatment with SR, there is benefit from continued treatment.

The study testing switching from IR to SR formulations without a dose adjustment showed some positive data but failed in its primary objective to demonstrate that there is no important loss of efficacy. This issue has been satisfactorily resolved in the approved SmPCs, which reflect the need for ensuring maintained efficacy when switching from the IR to the XL formulation.

With regards to the treatment of manic episodes associated with bipolar disorder, the Phase III study (Study 004) presented provides robust evidence of the efficacy of the sustained release formulation used in the range 400-800mg.

Clinical assessor conclusion

All studies were conducted according to the key requirements for Good Clinical Practice (GCP).

Initially, there was considered to be insufficient evidence of efficacy to support a dose strength any higher than 600mg of the new sustained release preparation of quetiapine. Of three Phase III trials examining efficacy in comparison to placebo, two (Study 041 and study 132) demonstrated a greater effect with statistical significance at the 600mg strength. Study number 0132 showed statistical significance at 800mg also, though the actual clinical improvement seen was no better than that at 600mg.

In those trials where the IR formulation also failed to demonstrate significant efficacy, it could be considered that the assay sensitivity of these trials was poor. If those studies were disregarded then this could be argued to lend support to a ‘single pivotal trial’ regarding Study 0132. In this case, the 600mg strength could be said to demonstrate efficacy. However, there is no evidence to suggest any clinical benefit in increasing to 800mg.

Overall, as discussed, and in view of the arguments presented by the applicant identifying a clear clinical need for a posology greater than 600mg in some cases, and
the fact that there were no dose-related safety issues or specific safety concerns attributed to the 800mg dose, it was concluded that there is a positive risk-benefit for the inclusion of the 800mg dose strength.

As regards the relapse prevention study, the data presented show the *number of relapses* compared with placebo, with 41.4% of patients on placebo relapsing versus 10.7% on active treatment. It is agreed that these data were met with statistical significance. The *time* to relapse data have not been presented because of the low rate of relapse in the quetiapine group. This is accepted. There would appear to be a highly significant benefit in the long term continuation of treatment in order to prevent relapse.

The data presented regarding switching between IR and SR formulations are not decisive. From the CPMP document CPMP/EWP/482/99, in a non-inferiority trial the full analysis set and the PP analysis set have equal importance and their use should lead to similar conclusions for a robust interpretation. It is not sufficient to rely on one of the trials in isolation. The results from *both* trials are to be positive to conclude non-inferiority. In this instance, therefore, non-inferiority has not been demonstrated. This is reflected in the approved SmPCs, which reflect a required period of dose titration when switching between IR and SR formulations.

With regards to the treatment of manic episodes associated with bipolar disorder, the primary objective of Study 004 was to demonstrate superior efficacy of quetiapine XL formulation administered QD as monotherapy at a dose of 400 to 800 mg per day compared to placebo in decreasing the manic symptoms in patients with bipolar manic or mixed episode, after 3 weeks of treatment. This objective was clearly met.
5 CLINICAL SAFETY

5.1 INTRODUCTION
Quetiapine IR has a well-established safety and tolerability in the treatment of schizophrenia and bipolar mania. The safety programme in the development of the SR formulation aimed to demonstrate comparable safety and tolerability to the IR preparation, and to also show comparison to placebo in this respect.

5.2 PATIENT EXPOSURE
During Phase III of the clinical development programme, a total of 1677 patients were exposed to quetiapine SR.

The 3 placebo-controlled studies in patients with acute schizophrenia, which included a total of 951 patients treated with quetiapine SR for up to 42 days, provided safety data for 4 fixed doses of quetiapine SR: 300 mg/day (91 patients), 400 mg/day (227 patients), 600 mg/day (310 patients), and 800 mg/day (323 patients). In addition, 319 patients were treated with placebo, and 414 patients were treated with quetiapine IR (300 mg/day to 800 mg/day). Total exposure to quetiapine SR in these studies was 82.9 patient years. The mean duration of exposure to drug for patients treated with quetiapine SR was 31.8 days. Median exposure to quetiapine SR 400 mg/day, 600 mg/day, and 800 mg/day was 42 days. Median exposure to quetiapine SR 300 mg/day was 22 days; this dose was included only in Study 041, in which early withdrawals in the study as a whole were more frequent than in Studies 132 and 133.

Longer-term placebo-controlled safety data for clinically stable patients with schizophrenia were provided by Study 004. In this relapse-prevention study, 327 minimally symptomatic patients were enrolled and began 16 weeks of open-label treatment with quetiapine SR to confirm their clinical stability before they were randomized to either continue treatment with quetiapine SR in the dose range 400 mg/day to 800 mg/day or switch to placebo for up to 1 year of additional treatment. At the beginning of the stabilization period, quetiapine SR treatment was phased in over 4 days, while a patient’s current antipsychotic treatments were being phased out. A total of 197 patients completed the stabilization period and were randomized (94 patients to quetiapine SR, and 103 patients to placebo). Thus, this study provides additional safety information regarding treatment initiation with quetiapine SR. Total open-label exposure to quetiapine SR was 78.5 patient-years. Because the study was stopped early, the maximum duration of randomized treatment was approximately 9 months (mean 4 months), and total randomized quetiapine SR exposure was 30.9 patient-years. The average dose of quetiapine SR during randomized treatment was 669 mg/day, and the most frequently used doses were 600 mg/day and 800 mg/day.

Study 146 provided data on the safety and tolerability of switching 331 clinically stable patients from treatment with quetiapine IR to the same total daily dose of quetiapine SR (400 mg/day, 600 mg/day, or 800 mg/day) for 42 days of randomized treatment. The 166 patients in the study who continued treatment with quetiapine IR provided a comparison group.
5.3 DEATHS

There was 1 death during the 6-week placebo-controlled studies, in Study 132. The patient died of unknown causes on Day 41 of treatment with Quetiapine IR 400mg/day. The death was considered unrelated to study treatment by the investigators.

There was a further death during the relapse prevention study. This patient died following suicide on Day 173 of randomised treatment. The patient was receiving placebo medication at the time.

5.4 SERIOUS ADVERSE EVENTS

In the 6-week placebo-controlled pool, the number of SAEs was low in all quetiapine SR groups, and similar to placebo. In all quetiapine SR groups the majority of SAEs fell under the MedDRA preferred terms psychotic disorders, schizophrenia and agitation, and were due to worsening of patients’ underlying disorders. No clinically-important differences were seen between the quetiapine SR treatment groups and the quetiapine IR treatment groups. No clear dose-relationships could be observed across SR treatment groups. The type and incidence of SAEs was consistent with the SAEs that were anticipated based on the pharmacological profile of quetiapine IR.

In the relapse prevention study (Study 004), there were no other (non-fatal) SAEs in the quetiapine SR group during randomized treatment, and 1 SAE (peritonsillar abscess) in the placebo group. There were no SAEs during the open-label stabilization period of Study 004.

5.5 COMMON ADVERSE EVENTS

In the 6-week placebo-controlled studies, common AEs associated with quetiapine SR treatment were sedation, dry mouth, and somnolence. There were no AEs associated only with quetiapine SR treatment, and in general there was no dose relationship with any common AE associated with drug across the dose range (300–800 mg).

In Study 004, insomnia, headache, irritability, and neutrophil count decrease were the AEs in the quetiapine SR group most frequently judged to be causally related to treatment; 4 patients (4.3%) each for insomnia and headache, and 2 patients (2.1%) each for irritability and neutrophil count decreased. In the placebo group, 11 patients (10.7%), 3 patients (2.9%), and 2 patients (1.9%) had the AEs of insomnia, headache and irritability, respectively, judged by the investigator to be drug-related.

The profile of AEs identified by investigators to be related to quetiapine SR treatment for patients in Study 146 was similar to those in the 6-week placebo-controlled trials, but overall AE rates were generally lower than the corresponding treatment groups in the 6-week placebo-controlled studies. These lower rates are primarily due to the 4 weeks of run-in treatment with quetiapine IR before randomization in Study 146.

The incidence of combined somnolence and sedation ranged from 22.5% to 28.6% in patients treated with quetiapine SR compared to 10.3% in placebo-treated patients. Somnolence and sedation AEs were generally rated as mild to moderate in intensity. The incidence rates for events were lower in quetiapine SR treatment
groups compared to most of the quetiapine IR groups, with the exception of the quetiapine IR 400 mg group (incidence of 8.1%). The mean time to onset of sedation and somnolence was similar in patients treated with quetiapine SR (4.7 days) compared to quetiapine IR (4.2 days) and placebo (5.8 days).

In the study of relapse prevention (Study 004), the proportion of patients with adverse events potentially associated with somnolence emerging during randomized treatment was low in both the quetiapine SR and placebo groups (1 and 2 patients, respectively). None of the AEs emerged within the first 14 days of randomized treatment. During the open-label treatment period, there were 74 patients (22.6%) with AEs associated with somnolence. In 57 (77.0%) of these 74 patients, the AE started within 14 days after enrolment.

The incidence of tachycardia in the 6-week placebo-controlled pool ranged from 1.3% to 7.7% in patients treated with quetiapine SR compared to a range of 0% to 15.1% in patients treated with quetiapine IR, and 1.3% in placebo-treated patients. The incidence rates were comparable across quetiapine formulations, although two of the quetiapine IR treatment groups (300 and 600 mg) had higher incidence rates of 11.1% and 15.1%, respectively. Tachycardia AEs were all rated as mild to moderate in intensity. The mean time to onset of tachycardia AEs was less in the quetiapine SR treatment groups (range 3.4 to 5.4 days) compared to the quetiapine IR groups (range 8.0 to 9.8 days, although the 800 mg group had no tachycardia AEs and thus no time to onset value), and placebo (12.3 days).

In the study of relapse prevention (Study 004), the only AE associated with tachycardia reported during the randomized treatment period was a “sinus tachycardia” in the placebo group, emerging within 14 days after randomization. There was 1 AE with preferred term “tachycardia” reported in the open-label period.

The incidence of dizziness ranged from 8.4% to 11.9% in patients treated with quetiapine SR compared to a range of 5.7% to 11.6% in patients treated with quetiapine IR, and 3.8% in placebo-treated patients. The incidence rates were comparable across quetiapine formulations. Dizziness AEs were generally rated as mild to moderate in intensity. The mean time to onset of dizziness AEs was variable but similar in the quetiapine SR treatment groups (range 3.0 to 10.2 days) compared to the quetiapine IR groups (range 3.2 to 11.1 days) and placebo (7.3 days).

In the study of relapse prevention (Study 004), the proportion of patients with adverse events potentially associated with dizziness emerging during randomized treatment was low in both quetiapine SR and placebo groups (2 and 1 patients, respectively). None of the AEs emerged within the first 14 days of randomized treatment. During the open-label treatment period, there were 21 patients (6.4%) with AEs associated with dizziness. In 9 (2.8% of total) of these patients on open-label treatment, the AE started within 14 days after enrolment.

The incidence of orthostatic hypotension in the 6-week placebo-controlled pool was from 1.3% to 24.2% in patients treated with quetiapine SR compared to a range of 1.6% to 24.4% in patients treated with quetiapine IR, and 5.6% in placebo-treated patients. The incidence rates were variable but comparable across quetiapine formulations when pooled across dose within each formulation. Orthostatic
hypotension AEs were generally rated as mild to moderate in intensity. The mean time to onset of orthostatic hypotension AEs was varied across treatment groups but similar in quetiapine SR treatment groups (range 3.1 to 13.7 days) compared to the quetiapine IR groups (range 5.0 to 11.5 days), all of which were somewhat higher than placebo (2.4 days). Comparison of placebo and quetiapine treatment groups within individual studies did not reveal any clinically relevant AE data not seen in the pooled data.

In the study of relapse prevention (Study 004), there were no reports of patients with postural hypotension AEs at any time during the study.

The incidence of syncope in the 6-week placebo-controlled pool was very low throughout all of the studies: 3 reports in patients treated with quetiapine SR compared to 1 report in patients treated with quetiapine IR, and 1 report in placebo-treated patients. The incidence rates were comparable across quetiapine formulations. Syncope AEs were all rated as mild to moderate in intensity. For patients treated with quetiapine 3 syncopal events were noted within the first week of treatment (2 for SR and 1 for IR) and 1 (for SR) in the second week. The single event in the placebo group occurred after 28 days of treatment. One patient reported an event that the investigator described as “loss of consciousness” in Study 133 that occurred immediately after the patient’s first dose of 400 mg quetiapine SR. Neither the event nor any underlying aetiology could be confirmed. One patient treated with quetiapine SR reported mild syncope on Day 2 of treatment as 1 of 10 AEs that led to discontinuation.

5.6 DISCONTINUATION DUE TO ADVERSE EVENTS

In the 6-week placebo-controlled pool, discontinuations due to adverse events occurred at rates of 5.0% to 11.3% across treatment groups with no apparent difference between placebo and quetiapine groups. The majority of AEs leading to discontinuation fell under the MedDRA preferred terms psychotic disorders, schizophrenia and agitation and were due to worsening of patients’ underlying disorders, and some patients had multiple AEs leading to discontinuation. Psychotic disorders and schizophrenia were observed in placebo-treated patients and in quetiapine-treated patients, irrespective of formulation. Some patients discontinued with more than 1 AE, and 1 patient, treated with quetiapine SR 600 mg, reported 10 AEs at discontinuation. The mean time to discontinuation due to AEs was similar in the quetiapine SR treatment groups (range 8.0 to 14.8 days) compared to the quetiapine IR groups (range 10.2 to 16.0 days), all of which were somewhat less than placebo (17.0 days).

In the relapse prevention study (Study 004), there was 1 discontinuation due to an adverse event in the quetiapine SR treatment group (1.1%): the patient in the quetiapine SR group had an event of decreased neutrophil count reported on Day 1 of randomized treatment and was discontinued from treatment on Day 14. In the placebo group, there was a completed suicide (1.0%) that was reported as an SAE leading to discontinuation: The patient had committed suicide on Day 173 of randomized treatment. There were also 4 discontinuations due to AEs during the open-label stabilization period, 1 each for the terms “dyspepsia”, “epilepsy”, “neutrophil count decreased”, and “somnolence”.

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5.7 LABORATORY FINDINGS

5.7.1 Biochemistry

There were no clinically relevant differences between the treatment groups or quetiapine formulations with respect to mean change from baseline in electrolyte data in any of the studies performed. All quetiapine treatment groups exhibited slight mean and median increases in fasting glucose compared to placebo. However, no dose response trend was apparent within the treatment groups for either quetiapine formulation.

5.7.2 Haematology

There were no clinically relevant differences between the treatment groups or quetiapine formulations with respect to mean change from baseline for any haematology assessments.

5.7.3 ECG and QTc

In the 6-week placebo-controlled pool, small dose-related increases in mean heart rate were observed in the quetiapine-treated groups at the end of treatment. There was no increase in mean heart rate in the placebo group. The increases observed in quetiapine SR treatment groups were similar to those seen with quetiapine IR treatment (5 to 9 bpm). Consistent with the increase in heart rate during the course of the study, decreases in QT interval were observed in the quetiapine SR and quetiapine IR groups. The results from both groups were consistent with the changes that were anticipated based on the pharmacological profile of quetiapine IR. Small mean changes in QTcF were observed in all quetiapine treatment groups at end of treatment, with no systematic or clinically meaningful effects.

In the relapse prevention study (Study 004), a small increase in mean heart rate (3.15 bpm) was observed in the quetiapine SR group at the end of treatment, compared to a small decrease in mean heart rate (-7.53 bpm) in the placebo group. Consistent with the increase in heart rate during the course of the study, a decrease in the QT interval was observed in the quetiapine SR group (-6.65 ms). A small decrease in mean QTcF was observed in the quetiapine SR group (-3.30 ms) at end of treatment, and this change was similar to that observed in the placebo group (-1.43 ms).

Patients switched to quetiapine SR in Study 146 exhibited similar changes in ECG parameters as did those maintained on quetiapine IR.

In the 6-week placebo-controlled pool, the incidence of shifts to clinical importance in ECG assessments was small and similar among the treatment groups. Shifts to a QTc ≥450 msec were reported with a 0.8% incidence in the placebo patients, a 0.6% incidence in the quetiapine SR patients and a 0.6% incidence in quetiapine IR patients. Shifts to a QTc ≥60 msec increase from baseline were reported with a null incidence in the placebo patients, a 0.3% incidence in the quetiapine SR patients and a 0.3% incidence in quetiapine IR patients.

In the relapse prevention study (Study 004), the incidence of clinically important increases in heart rate was higher in the quetiapine SR group (16 patients, 19.0%) compared to 1 patient (1.2%) in the placebo group; while the incidence of decreases in
heart rate was lower in the quetiapine SR group (5 patients, 6.0%) compared to 24 patients (29.6%) in the placebo group. The only registered clinically important value for an ECG interval was a ≥60 ms increase in QT in 1 patient (1.2%) in the placebo group.

Patients switched to quetiapine SR in Study 146 exhibited similar rates of shifts to clinically important ECG parameters as did those maintained on quetiapine IR.

5.8 SAFETY IN SPECIAL POPULATIONS

5.8.1 Elderly

Study 5077IL/0115

This was an exploratory, multicentre, double blind, double dummy, randomised, parallel group, controlled phase III study designed to evaluate the safety and tolerability of SR quetiapine in the treatment of elderly subjects with Alzheimer’s disease with symptoms of psychosis and/or agitation. The study was conducted across 14 centres.

Male and female patients with Alzheimer’s disease, mean age of 80 years (65-94 years), resident in nursing homes and requiring a neuroleptic for symptoms of psychosis and/or agitation were selected for investigation. The primary variable was the incidence of adverse events for the SR formulation for quetiapine compared with that for the IR formulation. 100 patients were randomised to receive study treatment: 68 to the SR group, and 32 to the IR group. 9 patients in the SR group and 1 in the IR group discontinued following randomisation. In the SR group, 1 patient developed aggression prior to dosing; 2 patients had a lack of therapeutic response; 4 patients were non-compliant with medication; 1 withdrew consent; and 1 refused to provide a blood pressure measurement. The 1 withdrawal in the IR group was due to a lack of therapeutic response.

On day 1, quetiapine SR was initiated at a dose of 50mg/day and the IR at 25mg/day (based on current recommended prescribing information). The IR dose was increased to 50mg on day 2. Both groups were titrated up to 100mg/day on Day 4. From day 8 onwards, the dose was individually adjusted up to a maximum of 300mg/day or downwards to a minimum of 50mg/day at the discretion of the investigator on the basis of tolerability and clinical response to the symptoms of psychosis/agitation. The mean daily dosage was 143.6mg/day for the SR group, and 142.0mg/day for the IR group. Overall the safety results were as follows:
The percentage of patients with at least 1 AE was similar in the 2 treatment groups. One death due to pneumonia was reported by the end of the 30 day follow-up period in a patient treated with the IR formulation. Four patients experienced serious adverse events during the 30 day follow-up period. Two patients in the SR group suffered a subdural haemorrhage and pneumonia respectively. Two patients in the IR group suffered a urinary tract infection and complete atrioventricular block respectively. There was one withdrawal due to an adverse event (agression), as mentioned before.

Both treatment groups had a similar occurrence of both the type and frequency of AEs. The most common AEs in the SR group, in decreasing order of frequency, were somnolence, vomiting, headache, urinary tract infections, sedation, dry mouth, fatigue and nausea:

Overall, there were no new safety issues arising in this population, and the SR formulation was generally well tolerated.

5.8.2 Age

No trials have been performed in any patients less than 18 years of age.
5.8.3 Gender/Ethnicity
No differences with respect to adverse events were observed between males and females or race.

5.8.4 Extrinsic Factors
No extrinsic factors of relevance to the schizophrenia population have been identified.

5.8.5 Pregnancy
There were no instances where quetiapine SR was administered to pregnant patients.

5.9 DRUG-SPECIFIC SAFETY CONSIDERATIONS
There is no evidence from the AE reports that quetiapine interacted with other medications during the clinical studies. This is in keeping with current PK knowledge of the IR formulation.

5.10 SAFETY RELATED TO INTERACTIONS
There are no new data provided.

5.11 POST MARKETING EXPERIENCE
As quetiapine SR has not been marketed, there are no post marketing data.

5.12 PROPOSALS FOR POST MARKETING SURVEILLANCE / STUDIES
The Safety Specification, Pharmacovigilance Plan, and Risk Minimisation Plan have been provided and are satisfactory.

6 EXPERT REPORTS
A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

7 PRODUCT INFORMATION:
7.1 Summary of Product Characteristics (SmPC)
The approved SmPCs are satisfactory.

7.2 Patient Information Leaflet (PIL)
The PIL is in line with the approved SmPCs and is satisfactory.

7.3 Labelling
Colour mock-ups of the labelling have been provided. The labelling is satisfactory and fulfils the statutory requirements for Braille.
8 OVERALL CONCLUSIONS

8.1 PHARMACOKINETICS

The pharmacokinetic profile of quetiapine is well known. The applicant has provided data outlining the major features of the sustained release formulation. From these data, it can be seen that the bioavailability, in terms of AUC, is similar following administration of equivalent total daily doses of either the SR or IR formulation. Under fasting conditions, peak plasma quetiapine concentrations are achieved approximately 6 hours after administration of Quetiapine SR. The Tmax of the IR formulation is around 1 hour. The SR formulation can be seen to exhibit unit dose proportionality and linear pharmacokinetics.

Study 5077IL/0118 established statistically significant increases in Cmax and AUC following a high fat meal. Study D1444C00003 demonstrated no significant changes in absorption following a light meal (approx. 300 calories). In modified release products, the investigation of the effect of food on bioavailability should be performed with a high fat meal. In the absence of such, it remains difficult to interpret the clinical significance of the food effect. In view of this, the approved SmPCs state that the medicine should be administered ‘once daily, without food (at least one hour before a meal’).

8.2 PHARMACODYNAMICS

It is agreed that an acceptable level of safety was demonstrated in both of the rapid dose escalation regimes, when compared to a fixed dose patient group. To this end, Study 5077IL/0145 has provided a justification for a similar regime to be used in Phase III trials.

Tolerability has not been adequately demonstrated, particularly in subjects not previously exposed to atypical antipsychotics. The assessment of ‘tolerability’ in the healthy volunteers engaged a patient centred, subjective approach, supported by physiological variables. It was found that dose initiation at 150mg was clinically intolerable. Even the low initial dose escalation study was considered to fail to achieve tolerability, though it is agreed that any side effects were not considered to exhibit dose proportionality. The proposed products cannot be considered to be without risk. The approved SmPCs addresses this by stating that the dose should be adjusted ‘depending on the clinical response and tolerability of the patient.’ and by giving appropriate warnings.

The concerns are alleviated by the general consideration that healthy volunteers are more sensitive to antipsychotic medications than patients with psychotic illness (Cutler 2001). Additionally, evidence from patients in the 3 large scale efficacy trials (Studies 132, 133 and 041) suggests that the safety and tolerability issues described in the healthy volunteer studies are not replicated in patients with psychotic illness.

It is accepted that there were no particular safety signals raised in the Phase III trials provided by the applicant, and there were no clinically significant differences seen between IR and SR formulations in the frequency of adverse events. This offers some reassurance. It is concluded that no particular restriction in use need be applied.
8.3 Efficacy

In Study 146, the trial to support switching from IR to SR, the non-inferiority criteria was achieved for the PP population but not for the MITT population. Therefore, strictly, the trial has failed, as successful results in both populations are required. The approved SmPCs contain appropriate wording in relation to switching from the IR to the XL formulation.

Initially, there was considered to be insufficient evidence of efficacy to support any higher than the 600mg dose strength of the new sustained release preparation of quetiapine. Of three Phase III trials examining efficacy in comparison to placebo, two (Study 041 and study 132) demonstrated a greater effect with statistical significance at the 600mg strength. Study number 0132 showed statistical significance at 800mg also, though the actual clinical improvement seen was no better than that at 600mg.

Experience from the immediate release preparation shows that there is clearly a clinical need in support of higher dose strengths in some patients. It should be noted that the proposed prescribing information does not mandate that patients treated with quetiapine XL be titrated directly to 800 mg as an initial target dose. The intention is that patients will receive the effective dose of 600 mg on Day 2 of treatment but after Day 2 will only progress up to 800 mg depending on individual response. As such, the recommended dose is 600mg per day, while the 800mg dose is included in the label to represent a maximum dose. This is reflected in the SmPC.

Regarding the safety and tolerability profiles of quetiapine XL 600 mg and 800 mg/day, these were generally similar in the 6-week, placebo controlled studies (Studies 132, 133, and 041). In particular, pooled data from the 6-week placebo-controlled studies showed the incidence of adverse events leading to discontinuation was similar for 600 mg and 800 mg treatment groups and that there were no dose-related trends in common adverse events. The data from these studies confirmed that tolerability was not compromised at the 800 mg dose and as such the benefit: risk ratio of the 800 mg dose is considered to be positive.

The applicant has provided data which demonstrate that if a patient is stabilised by treatment with SR, there is benefit from continued treatment.

For the treatment of manic episodes associated with bipolar disorder, the Phase III study (Study 004) presented provides robust evidence of the efficacy of the sustained release formulation used in the range 400-800mg.

8.4 Safety

It is reassuring that there were no particular safety signals raised during Phase III of clinical development. However, there were some issues regarding safety and tolerability relating to Phase II.

In assessing safety, the PK/PD Phase II studies performed in pre-exposed patients have confirmed possible signals – namely tachycardia and syncope/syncope-like events – upon treatment initiation. The main signal here was an unacceptably high frequency of heart rate increases in the 400mg SR treatment initiation group. This was the basis for selecting a lower treatment initiation dose. In the dose escalation initiated
at 300mg when compared with a fixed dose, this group displayed a 21% greater frequency of tachycardias. Therefore the proposed product cannot be considered to be without risk. The approved SmPCs address this by stating that the dose should be adjusted ‘depending on the clinical response and tolerability of the patient.’ and by giving appropriate warnings.

The concerns are lessened by the general consideration that healthy volunteers are more sensitive to antipsychotic medications than patients with psychotic illness (Cutler 2001). Additionally, evidence from patients in the 3 large scale efficacy trials (Studies 132, 133 and 041) suggests that the safety and tolerability issues described in the healthy volunteer studies are not replicated in patients with psychotic illness.

Overall, the safety profile of the products was considered to be satisfactory and the proposed post-marketing surveillance / studies with regards to safety have been discussed (Safety Specification, Pharmacovigilance Plan, and Risk Minimisation Plan have been provided).

8.5  RISK BENEFIT

Sufficient clinical information has been submitted to support these applications. All issues have been adequately addressed by the applicant.

The risk-benefit for the sustained release preparation of quetiapine is considered to be positive.

Marketing Authorisations were, therefore, recommended to be granted on medical grounds.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Seroquel XL 50mg, 200mg, 300mg and 400mg 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 applications of this type.

EFFICACY
The efficacy of the products has been demonstrated through a series of clinical studies.

The safety profiles of the products are considered to be acceptable.

PRODUCT LITERATURE
The approved SmPCs, PIL and labelling are satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet 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.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label. The Marketing Authorisation Holder (MAH) has stated that not all pack sizes may be marketed. However, they have committed to submitting mock-ups for all packaging for assessment before they are commercially marketed.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The clinical studies undertaken demonstrate the efficacy and safety of the products. Extensive clinical experience with quetiapine hydrochloride is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit is considered to be positive.
STEPs TAKEN FOR ASSESMENT

1 The MHRA received the marketing authorisation applications on 26th October 2006

2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 30th January 2007

3 Following assessment of the applications, the MHRA sought advice from the Commission on Human Medicines (CHM) with regards to issues raised during assessment.

4 The MHRA requested further information relating to the quality dossiers on 1st August 2007.

5 The CHM met on 6th December 2007 and issued their advice. Further information relating to the clinical dossiers was requested on 7th December 2007. The applications were determined on 3rd September 2008

6 The applicant responded to the MHRA’s requests, providing further information for the quality and clinical sections on 1st September 2008

7 The applications were determined on 10th September 2008
### STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>13/10/2008</td>
<td>Variation Medical Type II - National</td>
<td>To update section 5.2 (Pharmacokinetic properties) of the SPC as requested by the MHRA.</td>
<td>Application granted 16/10/2008</td>
</tr>
</tbody>
</table>

This was a bulk variation submitted for all 4 licences, 17901/0249 - 0252.
SUMMARY OF PRODUCT CHARACTERISTICS
The UK Summary of Product Characteristics (SmPC) for Seroquel XL 50 mg prolonged-release tablets is as follows:

1 NAME OF THE MEDICINAL PRODUCT
Seroquel XL 50 mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 50 mg tablet contains 50 mg quetiapine (as quetiapine fumarate).
Excipient: 125.72 mg lactose monohydrate per tablet.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Prolonged-release tablet

Peach, bi-convex, capsule shaped tablets, marked with XR50.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Seroquel XL is indicated for:
- the treatment of schizophrenia
- the treatment of manic episodes associated with bipolar disorder.

Seroquel XL is effective in preventing relapse in stable schizophrenic patients who have been maintained on Seroquel XL (See Section 5.1).

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.

**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.

**Children and Adolescents:**
The safety and efficacy of Seroquel XL have not been evaluated in children and adolescents.

**Renal and hepatic impairment:**
The oral clearance of quetiapine is reduced by approximately 25% in patients with renal or hepatic impairment. Quetiapine is extensively metabolized by the liver. Therefore, Seroquel XL should be used with caution in patients with known hepatic impairment.

 Patients with hepatic or renal impairment should be started on 50 mg/day. The dose should 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.

4.4 **SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

**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).

**Tardive Dyskinesia:**
If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of Seroquel XL should be considered. (see Section 4.8)

**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 Seroquel clinical trials. Most cases of severe neutropenia have occurred within a couple of months of starting therapy with Seroquel. There is no apparent dose relationship. Possible risk factors for neutropenia include pre-existing low white cell count (WBC) and history of drug induced neutropenia. Quetiapine should be discontinued in patients with a neutrophil count <1.0 X 10^9/L. 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 4.8 Undesirable effects).

**Interactions:**
See also section 4.5 Interactions with other medicinal products and other forms of interactions.
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).

**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) 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).

**Withdrawal:**

Acute withdrawal symptoms such as nausea, vomiting, and insomnia have been described after abrupt cessation of antipsychotic drugs including quetiapine. Gradual withdrawal is advisable.

**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.

**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 and 5.1). 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 (CYP) 3A4 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 Special precautions for Use).

The pharmacokinetics of quetiapine were not significantly altered by co-administration of the antidepressants imipramine (a known CYP 2D6 inhibitor) or fluoxetine (a known CYP 3A4 and CYP 2D6 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 with 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, 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).

The frequencies of adverse events are ranked according to the following: Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000) and very rare (<1/10,000).

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Common: Leucopenia</td>
<td></td>
</tr>
<tr>
<td>Uncommon: Eosinophilia</td>
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</table>

<table>
<thead>
<tr>
<th>Immune system disorders</th>
<th></th>
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<tbody>
<tr>
<td>Uncommon: Hypersensitivity</td>
<td></td>
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<table>
<thead>
<tr>
<th>Metabolism and nutritional disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare: Diabetes Mellitus</td>
<td>1, 5, 6</td>
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</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Common: Dizziness, somnolence, headache</td>
<td></td>
</tr>
<tr>
<td>Common: Syncope</td>
<td>4</td>
</tr>
<tr>
<td>Uncommon: Seizure</td>
<td>1</td>
</tr>
<tr>
<td>Very rare: Tardive dyskinesia</td>
<td>6</td>
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<table>
<thead>
<tr>
<th>Cardiac disorders</th>
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</thead>
<tbody>
<tr>
<td>Common: Tachycardia</td>
<td>4</td>
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</table>

<table>
<thead>
<tr>
<th>Vascular disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Common: Orthostatic hypotension</td>
<td>4</td>
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<table>
<thead>
<tr>
<th>Respiratory, thoracic and mediastinal disorder</th>
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<tbody>
<tr>
<td>Common: Rhinitis</td>
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</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>Very Common: Dry mouth</td>
<td></td>
</tr>
<tr>
<td>Common: Constipation, dyspepsia</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Hepato-biliary disorders</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Rare: Jaundice</td>
<td>6</td>
</tr>
<tr>
<td>Very rare: Hepatitis</td>
<td>6</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Skin and subcutaneous tissue disorders</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Very rare: Angioedema, Stevens-Johnson syndrome</td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reproductive system and breast disorders</th>
<th></th>
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<tbody>
<tr>
<td>Rare: Priapism</td>
<td></td>
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<table>
<thead>
<tr>
<th>General disorders and administration site conditions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Common: Mild asthenia, peripheral oedema</td>
<td></td>
</tr>
<tr>
<td>Rare: Neuroleptic malignant syndrome</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Investigations</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Common: Weight gain, elevations in serum transaminases (ALT, AST), decreased neutrophil count, blood glucose increased to hyperglycaemic levels</td>
<td></td>
</tr>
<tr>
<td>Uncommon: Elevations in gamma-GT levels, elevations in non-fasting serum triglyceride levels, elevations in total cholesterol (predominantly LDL cholesterol)</td>
<td></td>
</tr>
</tbody>
</table>
(1) See Section 4.4 Special Warnings and Special 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. These elevations were usually reversible on continued quetiapine treatment.

(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 Special precautions for Use).

(5) Exacerbation of pre-existing diabetes has been reported in very rare cases.

(6) Calculation of Frequency for these ADR’s have only been taken from postmarketing data with the immediate release formulation of Seroquel

(7) In placebo-controlled monotherapy trials in patients with a baseline neutrophil count ≥1.5 x 10^9/L, the incidence of at least one occurrence of neutrophil count <1.5 x 10^9/L was 1.72% in patients treated with quetiapine compared to 0.73% in placebo-treated patients. In all clinical trials (placebo-controlled, open-label, active comparator; patients with a baseline neutrophil count ≥1.5 x 10^9/L), the incidence of at least one occurrence of neutrophil count <0.5 x 10^9/L was 0.21% in patients treated with quetiapine and 0% in placebo-treated patients and the incidence ≥0.5 - <1.0 x 10^9/L was 0.75% in patients treated with quetiapine and 0.11% in placebo-treated patients.

(8) Occurs predominantly during the early weeks of treatment.

(9) Fasting blood glucose ≥ 7.0 mmol/L or a non fasting blood glucose ≥ 11.1 mmol/L on at least one occasion.

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 three-arm, short-term placebo-controlled clinical trials of Seroquel XL for schizophrenia, the aggregate incidence of EPS adverse events was 7.5% for Seroquel XL, 7.7% for Seroquel IR and 4.7% for placebo and without evidence of dose response. The incidence rates of the individual EPS adverse events (eg, akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness and muscle rigidity) were generally low and did not exceed 3% in any treatment group.

In a relapse prevention trial in which schizophrenia patients were treated with Seroquel XL for 16 weeks and then randomized to Seroquel XL or placebo, the incidence of EPS adverse events with Seroquel XL was no different to that of placebo (1.1% Seroquel XL; 1.0% placebo).

In short-term, placebo-controlled clinical trials of Seroquel IR for bipolar mania the aggregate incidence of EPS events was no different than 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 Seroquel treatment, with no further reduction during long-term treatment. In nearly all cases, cessation of Seroquel 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.

4.9 OVERDOSE

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 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 special precautions for use: Concomitant illness).

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

There is no specific antidote to quetiapine. In cases of severe signs, the possibility of multiple drug involvement should be considered, and intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system. Whilst the prevention of absorption in overdose has not been investigated, 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, N-desalkyl quetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and N-desalkyl quetiapine 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. Additionally, N-desalkyl quetiapine has high affinity at serotonin 5HT1 receptors. Quetiapine and N-desalkyl quetiapine 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 N-desalkyl quetiapine 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 standard 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. The results of these tests predict that Seroquel XL should have minimal EPS liability, and it has been hypothesised that agents with a lower EPS liability may also have a lower liability to produce tardive dyskinesia (See Section 4.8).

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, ie, who discontinued study treatment due to lack of efficacy or whose PANSS total score increased 20% or more from randomization to any visit. In patients stabilised on Seroquel 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.

Lack of induction of EPS is considered a feature of atypical antipsychotics.

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.

Unlike many other antipsychotics, quetiapine does not produce sustained elevations in prolactin, which is considered a feature of atypical agents. In a multiple fixed-dose clinical trial, there were no differences in prolactin levels at study completion, for quetiapine across the recommended dose range, and placebo.

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.

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 N-desalkyl quetiapine are 35% of that observed for quetiapine.

The pharmacokinetics of quetiapine and N-desalkyl quetiapine 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 N-desalkyl quetiapine 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 N-desalkyl quetiapine 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 with 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).

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

Quetiapine and several of its metabolites (including N-desalkyl quetiapine) 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.

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
Hypermellose
Macrogol 400
Titanium dioxide (E171)
Ferric oxide, yellow (E172)
Ferric oxide, red (E172)

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 17901/0249

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
10/09/2008

10 DATE OF REVISION OF THE TEXT
16/10/2008
SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Seroquel XL 200 mg prolonged-release tablets is as follows:

1 NAME OF THE MEDICINAL PRODUCT
Seroquel XL 200 mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 200 mg tablet contains 200 mg quetiapine (as quetiapine fumarate).
Excipient: 52.87 mg lactose monohydrate per tablet.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Prolonged-release tablet
Yellow, bi-convex, capsule shaped tablets, marked with XR200.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Seroquel XL is indicated for:
- the treatment of schizophrenia
- the treatment of manic episodes associated with bipolar disorder.
Seroquel XL is effective in preventing relapse in stable schizophrenic patients who have been maintained on Seroquel XL (See Section 5.1).

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.

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.

**Children and Adolescents:**
The safety and efficacy of Seroquel XL have not been evaluated in children and adolescents.

**Renal and hepatic impairment:**
The oral clearance of quetiapine is reduced by approximately 25% in patients with renal or hepatic impairment. Quetiapine is extensively metabolized by the liver. Therefore, Seroquel XL should be used with caution in patients with known hepatic impairment.

Patients with hepatic or renal impairment should be started on 50 mg/day. The dose should 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.

### 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

**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).

**Tardive Dyskinesia:**
If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of Seroquel XL should be considered. (see Section 4.8)

**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 Seroquel clinical trials. Most cases of severe neutropenia have occurred within a couple of months of starting therapy with Seroquel. There is no apparent dose relationship. Possible risk factors for neutropenia include pre-existing low white cell count (WBC) and history of drug induced neutropenia. Quetiapine should be discontinued in patients with a neutrophil count <1.0 X 10^9/L. 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 4.8 Undesirable effects).

**Interactions:**
See also section 4.5 Interactions with other medicinal products and other forms of interactions.
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).

**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) 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).

**Withdrawal:**

Acute withdrawal symptoms such as nausea, vomiting, and insomnia have been described after abrupt cessation of antipsychotic drugs including quetiapine. Gradual withdrawal is advisable.

**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.

**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 and 5.1). 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 (CYP) 3A4 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 Special precautions for Use).

The pharmacokinetics of quetiapine were not significantly altered by co-administration of the antidepressants imipramine (a known CYP 2D6 inhibitor) or fluoxetine (a known CYP 3A4 and CYP 2D6 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 with 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, 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).

The frequencies of adverse events are ranked according to the following: Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000) and very rare (<1/10,000).

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common: Leucopenia</td>
</tr>
<tr>
<td>Uncommon: Eosinophilia</td>
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<table>
<thead>
<tr>
<th>Immune system disorders</th>
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</thead>
<tbody>
<tr>
<td>Uncommon: Hypersensitivity</td>
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<table>
<thead>
<tr>
<th>Metabolism and nutritional disorders</th>
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</thead>
<tbody>
<tr>
<td>Very rare: Diabetes Mellitus¹, ⁵, ⁶</td>
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</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Common: Dizziness⁴, somnolence², headache</td>
</tr>
<tr>
<td>Common: Syncope⁴</td>
</tr>
<tr>
<td>Uncommon: Seizure¹</td>
</tr>
<tr>
<td>Very rare: Tardive dyskinesia⁶</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiac disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common: Tachycardia⁴</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common: Orthostatic hypotension⁴</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiratory, thoracic and mediastinal disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common: Rhinitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Common: Dry mouth</td>
</tr>
<tr>
<td>Common: Constipation, dyspepsia</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Hepato-biliary disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare: Jaundice⁶</td>
</tr>
<tr>
<td>Very rare: Hepatitis⁶</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Skin and subcutaneous tissue disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare: Angioedema⁶, Stevens-Johnson syndrome⁶</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Reproductive system and breast disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare: Priapism</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General disorders and administration site conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common: Mild asthenia, peripheral oedema</td>
</tr>
<tr>
<td>Rare: Neuroleptic malignant syndrome¹</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common: Weight gain⁸, elevations in serum transaminases (ALT, AST)³, decreased neutrophil count⁷, blood glucose increased to hyperglycaemic levels⁹</td>
</tr>
<tr>
<td>Uncommon: Elevations in gamma-GT levels³, elevations in non-fasting serum triglyceride levels, elevations in total cholesterol (predominantly LDL cholesterol)</td>
</tr>
</tbody>
</table>
(10) See Section 4.4 Special Warnings and Special Precautions for Use.

(11) Somnolence may occur, usually during the first two weeks of treatment and generally resolves with the continued administration of quetiapine.

(12) Asymptomatic elevations 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.

(13) 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 Special precautions for Use).

(14) Exacerbation of pre-existing diabetes has been reported in very rare cases.

(15) Calculation of Frequency for these ADR’s have only been taken from postmarketing data with the immediate release formulation of Seroquel.

(16) 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.

(17) Occurs predominantly during the early weeks of treatment.

(18) Fasting blood glucose \( \geq 7.0 \text{ mmol/L} \) or a non fasting blood glucose \( \geq 11.1 \text{ mmol/L} \) on at least one occasion.

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 three-arm, short-term placebo-controlled clinical trials of Seroquel XL for schizophrenia, the aggregate incidence of EPS adverse events was 7.5\% for Seroquel XL, 7.7\% for Seroquel IR and 4.7\% for placebo and without evidence of dose response. The incidence rates of the individual EPS adverse events (e.g., akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness and muscle rigidity) were generally low and did not exceed 3\% in any treatment group.

In a relapse prevention trial in which schizophrenia patients were treated with Seroquel XL for 16 weeks and then randomized to Seroquel XL or placebo, the incidence of EPS adverse events with Seroquel XL was no different to that of placebo (1.1\% Seroquel XL; 1.0\% placebo).

In short-term, placebo-controlled clinical trials of Seroquel IR for bipolar mania the aggregate incidence of EPS events was no different than 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 Seroquel treatment, with no further reduction during long-term treatment. In nearly all cases, cessation of Seroquel 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.

4.9 OVERDOSE

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 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 special precautions for use: 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.

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, N-desalkyl quetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and N-desalkyl quetiapine 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. Additionally, N-desalkyl quetiapine has high affinity at serotonin 5HT1 receptors. Quetiapine and N-desalkyl quetiapine 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 N-desalkyl quetiapine 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 standard 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-naïve Cebus monkeys after acute and chronic administration. The results of these tests predict that Seroquel XL should have minimal EPS liability, and it has been hypothesised that agents with a lower EPS liability may also have a lower liability to produce tardive dyskinesia (See Section 4.8).

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 randomization 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.

Lack of induction of EPS is considered a feature of atypical antipsychotics.

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.

Unlike many other antipsychotics, quetiapine does not produce sustained elevations in prolactin, which is considered a feature of atypical agents. In a multiple fixed-dose clinical trial, there were no differences in prolactin levels at study completion, for quetiapine across the recommended dose range, and placebo.

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.

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 N-desalkyl quetiapine are 35% of that observed for quetiapine.

The pharmacokinetics of quetiapine and N-desalkyl quetiapine 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 N-desalkyl quetiapine 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 N-desalkyl quetiapine 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 with 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).

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

Quetiapine and several of its metabolites (including N-desalkyl quetiapine) 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.

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
Hypermellose
Macrogol 400
Titanium dioxide (E171)
Ferric oxide, yellow (E172)

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 17901/0250

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
10/09/2008

10 DATE OF REVISION OF THE TEXT
16/10/2008
SUMMARY OF PRODUCT CHARACTERISTICS
The UK Summary of Product Characteristics (SmPC) for Seroquel XL 300 mg prolonged-release tablets is as follows:

1 NAME OF THE MEDICINAL PRODUCT
Seroquel XL 300 mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 300 mg tablet contains 300 mg quetiapine (as quetiapine fumarate).
Excipient: 49.31 mg lactose monohydrate per tablet.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Prolonged-release tablet
Pale yellow, bi-convex, capsule shaped tablets, marked with XR300.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Seroquel XL is indicated for:
- the treatment of schizophrenia
- the treatment of manic episodes associated with bipolar disorder.
Seroquel XL is effective in preventing relapse in stable schizophrenic patients who have been maintained on Seroquel XL (See Section 5.1).

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.

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.

**Children and Adolescents:**
The safety and efficacy of Seroquel XL have not been evaluated in children and adolescents.

**Renal and hepatic impairment:**
The oral clearance of quetiapine is reduced by approximately 25% in patients with renal or hepatic impairment. Quetiapine is extensively metabolized by the liver. Therefore, Seroquel XL should be used with caution in patients with known hepatic impairment.

Patients with hepatic or renal impairment should be started on 50 mg/day. The dose should 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.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

**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).

**Tardive Dyskinesia:**
If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of Seroquel XL should be considered. (see Section 4.8)

**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 10⁹/L) has been uncommonly reported in Seroquel clinical trials. Most cases of severe neutropenia have occurred within a couple of months of starting therapy with Seroquel. There is no apparent dose relationship. Possible risk factors for neutropenia include pre-existing low white cell count (WBC) and history of drug induced neutropenia. Quetiapine should be discontinued in patients with a neutrophil count <1.0 X 10⁹/L. Patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed 1.5 X 10⁹/L). (See section 4.8 Undesirable effects).

**Interactions:**
See also section 4.5 Interactions with other medicinal products and other forms of interactions.
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).

**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) 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).

**Withdrawal:**

Acute withdrawal symptoms such as nausea, vomiting, and insomnia have been described after abrupt cessation of antipsychotic drugs including quetiapine. Gradual withdrawal is advisable.

**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.

**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 and 5.1). 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 (CYP) 3A4 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 Special precautions for Use).

The pharmacokinetics of quetiapine were not significantly altered by co-administration of the antidepressants imipramine (a known CYP 2D6 inhibitor) or fluoxetine (a known CYP 3A4 and CYP 2D6 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 with 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, 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).

The frequencies of adverse events are ranked according to the following: Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100, rare (>1/10,000, <1/1000) and very rare (<1/10,000).

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
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</thead>
<tbody>
<tr>
<td>Common: Leucopenia</td>
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<tr>
<td>Uncommon: Eosinophilia</td>
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<table>
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<tr>
<th>Immune system disorders</th>
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<tbody>
<tr>
<td>Uncommon: Hypersensitivity</td>
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<table>
<thead>
<tr>
<th>Metabolism and nutritional disorders</th>
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</thead>
<tbody>
<tr>
<td>Very rare: Diabetes Mellitus¹,⁵,⁶</td>
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<table>
<thead>
<tr>
<th>Nervous system disorders</th>
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</thead>
<tbody>
<tr>
<td>Very Common: Dizziness⁴, somnolence², headache</td>
</tr>
<tr>
<td>Common: Syncope⁴</td>
</tr>
<tr>
<td>Uncommon: Seizure¹</td>
</tr>
<tr>
<td>Very rare: Tardive dyskinesia⁶</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Cardiac disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common: Tachycardia⁴</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common: Orthostatic hypotension⁴</td>
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</table>

<table>
<thead>
<tr>
<th>Respiratory, thoracic and mediastinal disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common: Rhinitis</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Common: Dry mouth</td>
</tr>
<tr>
<td>Common: Constipation, dyspepsia</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Hepato-biliary disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare: Jaundice⁶</td>
</tr>
<tr>
<td>Very rare: Hepatitis⁶</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Skin and subcutaneous tissue disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare: Angioedema⁶, Stevens-Johnson syndrome⁶</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Reproductive system and breast disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare: Priapism</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General disorders and administration site conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common: Mild asthenia, peripheral oedema</td>
</tr>
<tr>
<td>Rare: Neuroleptic malignant syndrome¹</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common: Weight gain⁶, elevations in serum transaminases (ALT, AST)³, decreased neutrophil count⁷, blood glucose increased to hyperglycaemic levels⁹</td>
</tr>
<tr>
<td>Uncommon: Elevations in gamma-GT levels³, elevations in non-fasting serum triglyceride levels, elevations in total cholesterol (predominantly LDL cholesterol)</td>
</tr>
</tbody>
</table>
(19) See Section 4.4 Special Warnings and Special Precautions for Use.

(20) Somnolence may occur, usually during the first two weeks of treatment and generally resolves with the continued administration of quetiapine.

(21) Asymptomatic elevations 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.

(22) 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 Special precautions for Use).

(23) Exacerbation of pre-existing diabetes has been reported in very rare cases.

(24) Calculation of Frequency for these ADR’s have only been taken from postmarketing data with the immediate release formulation of Seroquel.

(25) 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.

(26) Occurs predominantly during the early weeks of treatment.

(27) Fasting blood glucose \( \geq 7.0 \text{ mmol/L} \) or a non-fasting blood glucose \( \geq 11.1 \text{ mmol/L} \) on at least one occasion.

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 three-arm, short-term placebo-controlled clinical trials of Seroquel XL for schizophrenia, the aggregate incidence of EPS adverse events was 7.5% for Seroquel XL, 7.7% for Seroquel IR and 4.7% for placebo and without evidence of dose response. The incidence rates of the individual EPS adverse events (eg, akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness and muscle rigidity) were generally low and did not exceed 3% in any treatment group.

In a relapse prevention trial in which schizophrenia patients were treated with Seroquel XL for 16 weeks and then randomized to Seroquel XL or placebo, the incidence of EPS adverse events with Seroquel XL was no different to that of placebo (1.1% Seroquel XL; 1.0% placebo).

In short-term, placebo-controlled clinical trials of Seroquel IR for bipolar mania the aggregate incidence of EPS events was no different than 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 Seroquel treatment, with no further reduction during long-term treatment. In nearly all cases, cessation of Seroquel 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.

4.9 OVERDOSE

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
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 special precautions for use: 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.

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, N-desalkyl quetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and N-desalkyl quetiapine 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. Additionally, N-desalkyl quetiapine has high affinity at serotonin 5HT₁ receptors. Quetiapine and N-desalkyl quetiapine 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 N-desalkyl quetiapine 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 standard 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-naïve Cebus monkeys after acute and chronic administration. The results of these tests predict that Seroquel XL should have minimal EPS liability, and it has been hypothesised that agents with a lower EPS liability may also have a lower liability to produce tardive dyskinesia (See Section 4.8).

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, ie, who discontinued study treatment due to lack of efficacy or whose PANSS total score increased 20% or more from randomization to any visit. In patients stabilised on Seroquel 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.

Lack of induction of EPS is considered a feature of atypical antipsychotics.

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.

Unlike many other antipsychotics, quetiapine does not produce sustained elevations in prolactin, which is considered a feature of atypical agents. In a multiple fixed-dose clinical trial, there were no differences in prolactin levels at study completion, for quetiapine across the recommended dose range, and placebo.

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.

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 N-desalkyl quetiapine are 35% of that observed for quetiapine.

The pharmacokinetics of quetiapine and N-desalkyl quetiapine 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 N-desalkyl quetiapine 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 N-desalkyl quetiapine 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 with 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).

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

Quetiapine and several of its metabolites (including N-desalkyl quetiapine) 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.

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)
Ferric oxide, yellow (E172)

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 17901/0251

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
10/09/2008

10 DATE OF REVISION OF THE TEXT
16/10/2008
SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Seroquel XL 400 mg prolonged-release tablets is as follows:

1 NAME OF THE MEDICINAL PRODUCT
Seroquel XL 400 mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 400 mg tablet contains 400 mg quetiapine (as quetiapine fumarate).
Excipient: 15.50 mg lactose monohydrate per tablet.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Prolonged-release tablet
400mg White, bi-convex, capsule shaped tablets, marked with XR400.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS
Seroquel XL is indicated for:
- the treatment of schizophrenia
- the treatment of manic episodes associated with bipolar disorder.
Seroquel XL is effective in preventing relapse in stable schizophrenic patients who have been maintained on Seroquel XL (See Section 5.1).

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.

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.

Children and Adolescents:
The safety and efficacy of Seroquel XL have not been evaluated in children and adolescents.

Renal and hepatic impairment:
The oral clearance of quetiapine is reduced by approximately 25% in patients with renal or hepatic impairment. Quetiapine is extensively metabolized by the liver. Therefore, Seroquel XL should be used with caution in patients with known hepatic impairment.

Patients with hepatic or renal impairment should be started on 50 mg/day. The dose should 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.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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).

Tardive Dyskinesia:
If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of Seroquel XL should be considered. (see Section 4.8)

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 Seroquel clinical trials. Most cases of severe neutropenia have occurred within a couple of months of starting therapy with Seroquel. There is no apparent dose relationship. Possible risk factors for neutropenia include pre-existing low white cell count (WBC) and history of drug induced neutropenia. Quetiapine should be discontinued in patients with a neutrophil count <1.0 X 10^9/L. 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 4.8 Undesirable effects).

Interactions:
See also section 4.5 Interactions with other medicinal products and other forms of interactions.
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).

**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) 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).

**Withdrawal:**
Acute withdrawal symptoms such as nausea, vomiting, and insomnia have been described after abrupt cessation of antipsychotic drugs including quetiapine. Gradual withdrawal is advisable.

**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.

**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 and 5.1). 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 (CYP) 3A4 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 Special precautions for Use).

The pharmacokinetics of quetiapine were not significantly altered by co-administration of the antidepressants imipramine (a known CYP 2D6 inhibitor) or fluoxetine (a known CYP 3A4 and CYP 2D6 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 with 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, 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).

The frequencies of adverse events are ranked according to the following: Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000) and very rare (<1/10,000).

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
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<tbody>
<tr>
<td>Common: Leucopenia</td>
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<tr>
<td>Uncommon: Eosinophilia</td>
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<tr>
<th>Immune system disorders</th>
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</thead>
<tbody>
<tr>
<td>Uncommon: Hypersensitivity</td>
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<tr>
<th>Metabolism and nutritional disorders</th>
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<tbody>
<tr>
<td>Very rare: Diabetes Mellitus&lt;sup&gt;1, 5, 6&lt;/sup&gt;</td>
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<tr>
<th>Nervous system disorders</th>
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<tbody>
<tr>
<td>Very Common: Dizziness&lt;sup&gt;4&lt;/sup&gt;, somnolence&lt;sup&gt;2&lt;/sup&gt;, headache</td>
</tr>
<tr>
<td>Common: Syncope&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Uncommon: Seizure&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Very rare: Tardive dyskinesia&lt;sup&gt;6&lt;/sup&gt;</td>
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<tr>
<th>Cardiac disorders</th>
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<tbody>
<tr>
<td>Common: Tachycardia&lt;sup&gt;4&lt;/sup&gt;</td>
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<tr>
<th>Vascular disorders</th>
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<tbody>
<tr>
<td>Common: Orthostatic hypotension&lt;sup&gt;4&lt;/sup&gt;</td>
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<tr>
<th>Respiratory, thoracic and mediastinal disorder</th>
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<tr>
<td>Common: Rhinitis</td>
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<table>
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<tr>
<th>Gastrointestinal disorders</th>
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<tbody>
<tr>
<td>Very Common: Dry mouth</td>
</tr>
<tr>
<td>Common: Constipation, dyspepsia</td>
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<thead>
<tr>
<th>Hepato-biliary disorders</th>
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<tbody>
<tr>
<td>Rare: Jaundice&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Very rare: Hepatitis&lt;sup&gt;6&lt;/sup&gt;</td>
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<tr>
<th>Skin and subcutaneous tissue disorders</th>
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<tbody>
<tr>
<td>Very rare: Angioedema&lt;sup&gt;6&lt;/sup&gt;, Stevens-Johnson syndrome&lt;sup&gt;6&lt;/sup&gt;</td>
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<table>
<thead>
<tr>
<th>Reproductive system and breast disorders</th>
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<tbody>
<tr>
<td>Rare: Priapism</td>
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</table>

<table>
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<tr>
<th>General disorders and administration site conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common: Mild asthenia, peripheral oedema</td>
</tr>
<tr>
<td>Rare: Neuroleptic malignant syndrome&lt;sup&gt;1&lt;/sup&gt;</td>
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</tbody>
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<tr>
<th>Investigations</th>
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<tr>
<td>Common: Weight gain&lt;sup&gt;6&lt;/sup&gt;, elevations in serum transaminases (ALT, AST)&lt;sup&gt;3&lt;/sup&gt;, decreased neutrophil count&lt;sup&gt;7&lt;/sup&gt;, blood glucose increased to hyperglycaemic levels&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td>Uncommon: Elevations in gamma-GT levels&lt;sup&gt;3&lt;/sup&gt;, elevations in non-fasting serum triglyceride levels, elevations in total cholesterol (predominantly LDL cholesterol)</td>
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</tbody>
</table>
(28) See Section 4.4 Special Warnings and Special Precautions for Use.

(29) Somnolence may occur, usually during the first two weeks of treatment and generally resolves with the continued administration of quetiapine.

(30) Asymptomatic elevations 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.

(31) 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 Special precautions for Use).

(32) Exacerbation of pre-existing diabetes has been reported in very rare cases.

(33) Calculation of Frequency for these ADR’s have only been taken from postmarketing data with the immediate release formulation of Seroquel.

(34) In placebo-controlled monotherapy trials in patients with a baseline neutrophil count ≥1.5 x 10^9/L, the incidence of at least one occurrence of neutrophil count <1.5 x 10^9/L was 1.72% in patients treated with quetiapine compared to 0.73% in placebo-treated patients. In all clinical trials (placebo-controlled, open-label, active comparator; patients with a baseline neutrophil count ≥1.5 x 10^9/L), the incidence of at least one occurrence of neutrophil count <0.5 x 10^9/L was 0.21% in patients treated with quetiapine and 0% in placebo-treated patients and the incidence ≥0.5 - <1.0 x 10^9/L was 0.75% in patients treated with quetiapine and 0.11% in placebo-treated patients.

(35) Occurs predominantly during the early weeks of treatment.

(36) Fasting blood glucose ≥7.0 mmol/L or a non fasting blood glucose ≥11.1 mmol/L on at least one occasion.

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 three-arm, short-term placebo-controlled clinical trials of Seroquel XL for schizophrenia, the aggregate incidence of EPS adverse events was 7.5% for Seroquel XL, 7.7% for Seroquel IR and 4.7% for placebo and without evidence of dose response. The incidence rates of the individual EPS adverse events (eg, akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness and muscle rigidity) were generally low and did not exceed 3% in any treatment group.

In a relapse prevention trial in which schizophrenia patients were treated with Seroquel XL for 16 weeks and then randomized to Seroquel XL or placebo, the incidence of EPS adverse events with Seroquel XL was no different to that of placebo (1.1% Seroquel XL; 1.0% placebo).

In short-term, placebo-controlled clinical trials of Seroquel IR for bipolar mania the aggregate incidence of EPS events was no different than 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 Seroquel treatment, with no further reduction during long-term treatment. In nearly all cases, cessation of Seroquel 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.

4.9 OVERDOSE

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 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 special precautions for use: Concomitant illness).

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

There is no specific antidote to quetiapine. In cases of severe signs, the possibility of multiple drug involvement should be considered, and intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system. Whilst the prevention of absorption in overdose has not been investigated, 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, N-desalkyl quetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and N-desalkyl quetiapine 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. Additionally, N-desalkyl quetiapine has high affinity at serotonin 5HT1 receptors. Quetiapine and N-desalkyl quetiapine 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 N-desalkyl quetiapine 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 standard 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-naïve Cebus monkeys after acute and chronic administration. The results of these tests predict that Seroquel XL should have minimal EPS liability, and it has been hypothesised that agents with a lower EPS liability may also have a lower liability to produce tardive dyskinesia (See Section 4.8).

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, ie, who discontinued study treatment due to lack of efficacy or whose PANSS total score increased 20% or more from randomization to any visit. In patients stabilised on Seroquel 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.

Lack of induction of EPS is considered a feature of atypical antipsychotics.

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.

Unlike many other antipsychotics, quetiapine does not produce sustained elevations in prolactin, which is considered a feature of atypical agents. In a multiple fixed-dose clinical trial, there were no differences in prolactin levels at study completion, for quetiapine across the recommended dose range, and placebo.

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.

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 N-desalkyl quetiapine are 35% of that observed for quetiapine.

The pharmacokinetics of quetiapine and N-desalkyl quetiapine 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 N-desalkyl quetiapine 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 N-desalkyl quetiapine 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 with 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).

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

Quetiapine and several of its metabolites (including N-desalkyl quetiapine) 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.

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
Hypermellose
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>
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</thead>
<tbody>
<tr>
<td>10 tablets</td>
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<tr>
<td>30 tablets</td>
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<tr>
<td>50 tablets</td>
<td>10 blisters of 5 tablets</td>
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<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 17901/0252

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
10/09/2008

10 DATE OF REVISION OF THE TEXT
16/10/2008
PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Seroquel XL 50 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 anti-psychotics. 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’.

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)

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.
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).
- Medicines for an infection (like erythromycin or ketoconazole).
- High blood pressure medicines.
- Rifampicin (for tuberculosis).
- Barbital (for difficulty sleeping).
- Thoridazine (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. This will depend on your illness.

The starting dose is usually:
- 300 mg on the first day and 600 mg on the second day.
After this your doctor will tell you how many Seroquel XL tablets to take each day. The dose can be between 400 mg and 800 mg each day. It depends on your illness and needs. Please read the label on the container. It will also tell you how many tablets to take and when to take them. Ask your doctor or pharmacist if you are not sure.
- 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 4 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.
If you are elderly, or have liver problems, your doctor may give you a lower dose. Ask your doctor or pharmacist if you are unsure.
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 happens, 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 (weals), swelling of the skin and swelling around the mouth.

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.
- Jaundice (yellowing of the skin and eyes).
- Priapism (a long-lasting and painful erection).

Very rare (affects less than 10,000 people):
- 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, headache, dry mouth.
- Feeling sleepy (this may go away with time, as you keep taking Seroquel XL).

Common (affects less than 1 in 100 people):
- Rapid heartbeat.
- Stuffy nose.
- Constipation, upset stomach (indigestion).
- Feeling weak, fainting.
- Swelling of arms or legs.
- Putting on weight, mainly in the first weeks of treatment.
- Low blood pressure when standing up. This may make you feel dizzy or faint.
- High blood sugar.

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.

You may get abnormal muscle movements. These include difficulty starting muscle movements, shaking, feeling restless or muscle stiffness without pain. If you get any of these, contact your doctor.

Some side effects are only seen when a blood test is taken. These include increases in the amount of fats in the blood and decreases in the number of certain types of blood cells. Your doctor may ask you to have blood tests from time to time.
If you have to take Seroquel XL for a long time, it could cause uncontrollable movements, mainly of your face or tongue. Tell your doctor if this happens.
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.
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, 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 400, titanium dioxide (E171). The 50mg, 200mg and 300mg tablets also contain ferric oxide (E172).

What Seroquel XL looks like and contents of the pack

All tablet strengths are capsule shaped and marked with the XR and the strength. 50 mg tablets are peach 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 and AstraZeneca AB, S-151 85 Södertälje, Sweden.

This leaflet was last updated in July 2008

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): MindInfoLine: 0845 7660163
- RETHINK (Formerly the National Schizophrenia Fellowship) Advice Service: 0208 9746914
- National Schizophrenia Fellowship (Scotland): 0131 5578969. CareLinkLine: 01224 213034 (for Grampian)
- 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:

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<thead>
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<th>Product name</th>
<th>Reference number</th>
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<td>Seroquel XL prolonged release tablets 50 mg</td>
<td>PL 17901/0249</td>
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<td>Seroquel XL prolonged release tablets 400 mg</td>
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This is a service provided by the Royal National Institute of Blind People.
LABELLING

Blister cartons

Seroquel XL 50mg prolonged-release tablets - Carton for blisters, with Braille
Seroquel XL 200mg prolonged-release tablets - Carton for blisters, with Braille
Seroquel XL 300mg prolonged-release tablets - Carton for blisters, with Braille
Seroquel XL 400mg prolonged-release tablets - Carton for blisters, with Braille
Blister foils

Seroquel XL 50mg prolonged-release tablets
Seroquel XL 200mg prolonged-release tablets
Seroquel XL 300mg prolonged-release tablets
Seroquel XL 400mg prolonged-release tablets