CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Seroquel XR 50 mg, prolonged release tablets
Seroquel XR 200 mg, prolonged release tablets
Seroquel XR 300 mg, prolonged release tablets
Seroquel XR 400 mg, prolonged release tablets
AstraZeneca B.V., Zoetermeer, The Netherlands

quetiapine fumarate

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow–organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/0156/08-011/MR
Registration number in the Netherlands: RVG 34625-8

10 April 2008

Pharmacotherapeutic group:	antipsychotics; diazepines, oxazepines and thiazepines
ATC code:	N05AH04
Route of administration:	oral
Therapeutic indication:	schizophrenia and prevention of relapse in stable schizophrenic patients
Prescription status:	prescription only
Date of authorisation in NL:	21 August 2007
Concerned Member State:	Mutual recognition procedure with AT, BE, CY, DE, DK, EL, ES, FI, IE, IS, LU, MT, NO, PL, PT, SE
Application type/legal basis:	Directive 2001/83/EC, Article 8(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Seroquel XR 50/200/300/400 mg, prolonged release tablets from AstraZeneca B.V., the Netherlands. The products have been granted authorisation in the Netherlands on 21 August 2007. The products are indicated for the treatment of schizophrenia, and prevention of relapse in stable schizophrenic patients.

A comprehensive description of the indications and posology is given in the SPC.

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 ($5HT_2$) and dopamine D_1- and D_2- receptors. It is this combination of receptor antagonism with a higher selectivity for $5HT_2$ relative to D_2- receptors, which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal undesirable effect (EPS) liability of Seroquel. Additionally, N-desalkyl quetiapine has high affinity for the norepinephrine transporter (NET). Quetiapine and N-desalkyl quetiapine also have high affinity at histaminergic and adrenergic α1 receptors, with a lower affinity at adrenergic α2- and serotonin $5HT_1A$ receptors. Quetiapine has no appreciable affinity at cholinergic muscarinic or benzodiazepine receptors.

This mutual recognition procedure concerns an application made according to article 8.3 of Directive 2001/83/EEC. The Seroquel XR 50/200/300/400 mg, prolonged release tablets, are a line extension, a different pharmaceutical form, to the already existing Seroquel immediate release tablets, which have been authorised via MRP procedure NL/H/0156/01-07/MR. The Seroquel immediate release tablets have been registered since 27 April 1998 in the Netherlands.

The clinical development program for Seroquel XR has been discussed with the Medicines Evaluation Board (MEB), as reference member state for the MRP. Scientific advice in relation to the clinical development of the XR program was provided (April 2000 and March 2004).

Quetiapine IR (immediate release) tablets have been granted a licence for the indications schizophrenia and moderate to severe acute manic episode. For the treatment of schizophrenia the compound is administered twice a day. In order to reduce the frequency of quetiapine administration and simplifying the treatment initiation schedule, the MAH developed the Seroquel once daily XR (prolonged release) formulation. The drug release from the formulation is erosion-controlled and occurs over a 20-hour time period.

The marketing authorisation is granted based on article 8(3) of Directive 2001/83/EC, a dossier with full administrative, quality, preclinical and clinical data. This dossier also contained data already submitted in the dossier of Seroquel immediate release tablets NL/H/0156/01-07/MR (see below).

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for these product types at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisations.

Active substance and excipients
The active substance quetiapine is not described in the European Pharmacopoeia (Ph.Eur.*) or any other pharmacopoeia, but is a known drug substance as it has been used in quetiapine immediate release tablets (NL/H/0156/01-07/MR). The substance is a white to off-white crystalline non-hygroscopic powder that is soluble in dilute acidic and basic solutions, acetone, ethanol and methanol. Quetiapine is present as quetiapine fumarate and consists of two units quetiapine and one unit fumaric acid. The active substance specification is considered adequate to control the quality. The substance is tested for appearance, water content, sulphated ash, strength, related substances, residual solvents, heavy metals, identification and specific surface area. Batch analytical data demonstrating compliance with this specification have been provided for 29 commercial scale production batches.

Stability data on the active substance have been provided for 7 batches in accordance with applicable European guidelines demonstrating the stability of the active substance over 3 years, when stored below 30ºC in double polyethylene liners in fibreboard tubes/drums. The solid substance is stable with respect to degradation, temperature and light.

The excipients are usual for the dosage form in the concentrations used. All excipients comply with pharmacopoeial standards (Ph.Eur. or USP*). Additional in-house specifications are set for hypromellose. The additional specifications for hydroxypropoxy content and viscosity are adequate to control the quality of the excipient.

**Ph.Eur. and USP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU and USA, respectively.*

Medicinal Product

Composition
Seroquel XR 50, 200, 300 and 400 mg prolonged release tablets contain as active ingredient quetiapine fumarate (57.56, 230.26, 345.38 and 460.50 mg) corresponding to 50, 200, 300 and 400 mg of quetiapine, respectively. The different tablet strengths are qualitatively but not quantitatively identical and can be easily distinguished by their colour and inscription.

Seroquel XR 50 mg tablets are peach-coloured and engraved with “XR 50” on one side.
Seroquel XR 200 mg tablets are yellow and engraved with “XR 200” on one side.
Seroquel XR 300 mg tablets are pale yellow and engraved with “XR 300” on one side.
Seroquel XR 400 mg tablets are white and engraved with “XR 400” on one side.

The tablets are supplied in PVC+PCTFE blisters with aluminium backing. The blisters are packaged in a cardboard box.

The excipients are:
core - cellulose microcrystalline, sodium citrate, lactose monohydrate, magnesium stearate, hypromellose.
coating – hypromellose, macrogol, titanium dioxide (E171), yellow iron oxide (E172) (50, 200 and 300 mg tablets), red iron oxide (E172) (50 mg tablets).

Pharmaceutical development
In order to reduce the frequency of quetiapine administration and simplifying the treatment initiation schedule, this quetiapine formulation was developed that had to be administered only once daily. All tablet strengths have a unique, but qualitatively related formulation. Two types of hypromellose are used to control the drug release from the tablet matrix. The dissolution rate is influenced by increasing the matrix viscosity by an increase in the hypromellose proportion. The formulation studies showed that differences in the proportion of hypromellose had an effect on the dissolution profile of the drug substance. The choice for the composition also involved the *in vivo* plasma profiles generated for different drug product compositions. A dose proportional mixture was examined, but it was found that the tablet size (surface area and volume) affected the drug release, therefore it was not possible to use a common granule for the different tablet strengths. The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The packaging is usual and suitable for the products at issue.

Manufacturing process and quality control of the medicinal product
The manufacturing process has been validated according to relevant European/ICH guidelines. Adequate in-process controls are included. Process validation data on the product have been presented for 6 batches of each strength in accordance with the relevant European guidelines.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specifications include tests for appearance, identification, assay, degradation products, dissolution, dose uniformity and microbial quality. Limits in the specifications have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data for 58 production-scaled batches have been provided, demonstrating compliance with the specification.

Stability tests on the finished product
Stability data on the product have been provided for 19 batches (4 batches of the 50 mg tablets, 5 batches of the 200 mg tablets, 6 batches of the 300 mg tablets, 4 batches of the 400 mg tablets) in accordance with applicable European guidelines demonstrating the stability of the product over 2 years. According to the Guideline on stability testing: stability testing of existing active substances and related finished products, extrapolation of the stability period up to 12 months is acceptable. Therefore, on the basis of the data submitted, a shelf life can be granted for all tablet strengths for 36 months when stored in the original packaging without any special storage condition.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal product has been satisfactorily demonstrated.

II.2 Non-clinical aspects

Quetiapine fumarate containing medicinal products have been marketed in many countries for many years. This application concerns a line extension to the already existing Seroquel immediate release tablets for which a full preclinical evaluation was performed. No new preclinical data have been submitted. Therefore this application has not undergone a formal preclinical assessment other than an environmental risk assessment (see below).

Environmental risk assessment
In line with current legislation, an environmental risk assessment has been undertaken for quetiapine. The use of quetiapine fumarate is likely to result mainly in metabolites and, to a lesser extent, the active moiety entering the environment, since it is almost completely metabolised after intake. Based on the physico-chemical and fate properties of quetiapine fumarate, it is predicted that most of the active moiety

(quetiapine) will be partitioned into the aqueous phase during wastewater treatment. The aqueous streams containing quetiapine will then, subsequently, be passed to the aquatic environment. In the aquatic environment, quetiapine is not likely to be hydrolytically degraded, and there is no evidence to suggest that biodegradation will be significant. However, as the octanol/water partition coefficient, log Dow is < 3, quetiapine is not likely to bioaccumulate in aquatic organisms.
The PEC/PNEC ratios for microorganisms, surface water and ground water are all below 0.1, and the risk of bioaccumulation is low. In addition, the fate analysis shows no reason for concern for the terrestrial compartment. In conclusion, the fate and effects analysis has not identified a potential risk to the environment as a consequence of the use of quetiapine. Since this application is a line extension of an already existing product for which an increase of the emission of quetiapine into the environment is not expected, no further action is needed.

The product does not contain any other component which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Scientific advice, and compliance with GCP
The clinical development program for Seroquel XR has been discussed with the Medicines Evaluation Board (MEB), as reference member state for the MRP, and scientific advice in relation to the clinical development of the XR program was provided (April 2000 and March 2004).

The MEB has been assured that the clinical trials used to support this application were designed, conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP, see Directive 2005/28/EC) regulations. All studies were conducted in accordance with the Declaration of Helsinki and recent revisions. The formulation of the batches used in key clinical studies is identical to those proposed for marketing.

Pharmacokinetics
The MAH developed a prolonged release (XR) formulation of quetiapine to enable once daily administration, with the objective to improve compliance with a QD regimen. The immediate-release (IR) tablets that are already marketed for the treatment of schizophrenia and mania have to be administered BID, because of the short half-life of the IR formulation (7 hours).

Quetiapine is well-absorbed. *In vitro* studies indicate that the cytochrome P450 3A4 iso-enzyme is involved in the metabolism of quetiapine to its active N-desalkyl quetiapine and other inactive metabolites. The major metabolic pathways of quetiapine are oxidation to the sulfoxide metabolite and an acid metabolite; both metabolites are pharmacologically inactive. N-desalkyl quetiapine, the major active metabolite, has steady-state molar C_{max} and AUC values that are 35% and 73%, respectively, of the values observed for quetiapine. For the IR form, the pharmacokinetics of quetiapine and N-desalkyl quetiapine are linear across the dose range of 50 mg to 800 mg.

The pharmacokinetic program comprised 7 studies. In pilot studies 036, 037 and 086 the optimal XR formulation was sought under fed and fasted conditions. Tablets to be marketed were tested in studies 097, 118, 001 and 003. Bioequivalence compared to the IR formulation was tested in study 097. Dose-proportionality and food-effect of a high fat meal was tested in study 118. In study 003, the effects of a light breakfast were tested in healthy volunteers and patients. For safety reasons, high doses > 50 mg were only applied in schizophrenic patients. Study 001 provides information regarding bioequivalence of metabolites when IR and XR are compared.

Pharmacokinetic studies were performed under steady-state conditions for safety and ethical reasons, in order to prevent long-term periods of non-treatment. As the uptitration schedule is completely different than for the IR tablets, and the new dosing schedule with the XR formulation is extensively tested clinically, the lack of single-dose studies is acceptable.

A 13-50% lower C_{max} may allow a higher initial dose and a faster uptitration schedule with the XR

formulation compared to IR formulation.

Dose-linearity of XR tablets was tested in patients using a dosage range of 50 - 400 mg given as a single-dose. Visual inspection of the Dose—AUC scatterplot as well as statistical tests on linearity indicate that the pharmacokinetics of quetiapine XR were linear and proportional to dose. As the pharmacokinetic profile of the IR product is linear, it can be assumed that this also applies to the XR formulation.

The AUC values of the parent drug and sum of active moieties at a 300 mg and 400 Seroquel tablet QD regimen were bioequivalent to a daily dose of 150-200 mg IR tablets BID, at steady state. This means that conclusions regarding the bioequivalence study with the 300 mg Seroquel tablet can in principle be extrapolated to other strengths.

There was a significant food effect when a high fat meal was given, although the effect was minor after a light breakfast. C_{max} significantly increased with 50% after a high fat meal, and side effects may be related to high C_{max}. Seroquel XR should therefore be taken without food.

Pharmacodynamics

The MAH developed a new and much faster uptitration schedule for Seroquel XR. In the titration schedule for Seroquel IR, patients received a 50 mg at Day 1, 100 mg at Day 2, 200 mg at Day 3 and 300 mg at Day 4.

In studies 087 and 098, the maximal tolerated starting dose was sought with doses up to 800 mg. In studies 109 and 145, dose escalation schemes were investigated; schedules of uptitration to 800 mg within 3-9 days were studied. In these studies, participating patients discontinued former antipsychotic therapy two days before start of this study, except for lithium and valproate.

Study 087 and 098

Study 087: is a double-blind, randomised parallel group study. Patients received either IR or XR tablets. For the XR tablets, 1 day titration schedule was applied for doses ranging 50/100/200/300 mg QD. In the IR arms, doses were uptitrated from Day 1-4 according to the regular schedule (see Table P-2 below).

Table P-2 Quetiapine SR and quetiapine IR dosing schedules for Study 087

	Total daily quetiapine dose (mg)							
	Quetiapine SR[a]				Quetiapine IR[a]			
Dose	Day 1[b]	Day 2	Day 3	Day 4	Day 1[b]	Day 2	Day 3	Day 4
50 mg	50	50	50	50	50	50	50	50
100 mg	100	100	100	100	50	100	100	100
200 mg	200	200	200	200	50	100	200	200
300 mg	300	300	300	300	50	100	200	300

[a] Quetiapine SR was given once daily (morning), quetiapine IR was given twice daily.

For safety reasons, the lower starting doses of the XR tablets were tested first. 87 patients were randomised. Each XR study arm consisted of 15-18 subjects, and the IR arms of 5-6 subjects.

Study 098: In this study, it was planned to study feasibility of starting doses of 400, 600 and 800 mg XR in a study of similar design as study 087. The study was interrupted after the 400 mg Seroquel dose, as dose-limiting adverse events occurred (tachycardia).

Measures

In both studies, key assessments were adverse events, vital signs, ECG and laboratory evaluations. Systolic and diastolic blood pressures and pulse rates were recorded 15 minutes before quetiapine administration, and 4 and 6 hours after quetiapine administration. No pharmacokinetic data were sampled.

Results
In short, patients could tolerate initial dosages of one 300 mg XR tablet as well as the traditional 50 mg IR starting dose. A starting dose of 400 mg XR tablet could not be tolerated. Dose limiting factor was tachycardia, probably as a compensatory mechanism for orthostatic hypotension. Most frequently observed adverse events in the dose-finding studies were headache, somnolence or opposite, insomnia. There was no relationship between dose and incidence of these adverse events. E.g. in study 087, somnolence was reported for 38% of patients in the 50-mg/day quetiapine XR group and no patients in the 300-mg/day quetiapine XR group. In study 087, 1 serious adverse event (a TIA) was reported after 300 mg Seroquel at Day 2, but this was not thought to be drug related.

Initial doses above 200 mg caused hypotension. The blood pressure declined, but this did not lead to clinical symptoms. The effects of quetiapine on vital signs were more explicit at Day 1 than at Day 4 (in other words, tolerance occurred). No significant changes in QTc and chemistry occurred.

Studies 109 and 145
In these double-blinded pilot studies, a dose escalation schedule of Seroquel XR tablets was compared to a fixed dose regimen of 300 mg XR tablets QD. All patients discontinued antipsychotic medication (except for lithium and valproate) two days before study. In both studies, key assessments were adverse events, vital signs, an ECG.
In study 109, patients were up-titrated till 800 mg within 9 days. In study 145, uptitration occurred at a faster pace: patients were up-titrated till 800 mg QD within 3 and 4 days, respectively.

Results

Adverse events

Table P-11 Commonly reported adverse events of interest during study treatment (Study 145)

	Number (%) of patients with an adverse event		
Adverse event[a] (MedDRA)	**Quetiapine SR dose escalated to 800 mg by Day 4 N=19**	**Quetiapine SR dose escalated to 800 mg by Day 3 N=17**	**Quetiapine SR fixed dose N=16**
Somnolence	3 (15.8)	4 (23.5)	2 (12.5)
Sedation	5 (26.3)	7 (41.2)	5 (31.3)
Dizziness	3 (15.8)	6 (35.3)	4 (25.0)
Insomnia	2 (10.5)	1 (5.9)	0
Hypertension	0	1 (5.9)	0
Tachycardia	1 (5.3)	2 (11.8)	1 (6.3)

The data in table P-11 show that compared to the fixed dosing regimen of 300 mg XR, the 800 mg regimen caused more adverse events. However, the incidence of adverse events was not related to the rate of dose-titration (within 3-9 days).

Vital signs

Table P-13 Standing vital signs: mean change from baseline at 6 hours postdose (Study 145)

	Dose escalated to 800 mg/day by Day 4					Dose escalated to 800 mg/day by Day 3					Fixed dose				
Day	QTP SR dose (mg)	N	Mean change in SBP (mmHg)	Mean change in DBP (mmHg)	Mean change in pulse (bpm)	QTP SR dose (mg)	N	Mean change in SBP (mmHg)	Mean change in DBP (mmHg)	Mean change in pulse (bpm)	QTP SR dose (mg)	N	Mean change in SBP (mmHg)	Mean change in DBP (mmHg)	Mean change in pulse (bpm)
1	200	18	–11.6	–3.7	9.0	300	17	–18.9	–12.9	3.1	300	16	–21.9	–12.6	5.0
2	400	19	–14.7	–7.1	6.5	600	17	–11.2	–8.7	9.8	300	15	–16.4	–8.4	14.1
3	600	18	–14.7	–8.5	8.2	800	17	–11.4	–6.4	13.7	300	14	–12.1	–8.1	11.6
4	800	19	–10.9	–8.4	14.5	800	17	–15.2	–8.2	17.7	300	15	–7.3	–6.2	5.5

bpm Beats per minute. DBP Diastolic blood pressure. QTP Quetiapine. SBP Systolic blood pressure. SR Sustained release.

Table P-13 shows that there were no relevant differences between fast and more gradual uptitration schedules for the vital signs.

These small-scaled studies indicated that a starting dose of 300 mg and an uptitration schedule till 800 mg within 3 days may be feasible for the XR formulation. This was further investigated in clinical safety and efficacy studies.

Clinical efficacy

Flexible-dose studies suggested that the clinically optimal dose for the quetiapine IR formulation is in the range of 500 mg/day to 600 mg/day. Therefore, in the clinical program for quetiapine XR, efficacy was evaluated for the dose range 400 mg/day to 800 mg/day. In short-term and long-term studies efficacy in the treatment of acute exacerbation of schizophrenia and in the prevention of schizophrenic relapse was investigated, respectively. In comparison to the IR tablet, the maximal recommended dose is extended from 750 to 800 mg for both indications, and the usual effective dose ranges from 300-450 mg to 400-800 mg daily for schizophrenia.

Short-term efficacy

Three well-designed short-term (duration 6 weeks) efficacy placebo-controlled studies were submitted (studies 132, 133, and 041). These studies were conducted in acutely ill schizophrenic patients. One study was conducted in EU/Asia (study 132; Greece, Bulgaria, Russia, Romania, India, Indonesia, Philippines, South Africa), while the other two were conducted in the US (study 133) and US/Canada (study 041). Efficacy assessment was performed using the reliable and validated PANSS (Positive and Negative Syndrome Scale).

The PANSS consists of 30 items, with the total score consisting of the sum of the seven positive items (P1-P7), seven negative items (N1-N7), and 16 general psychopathology items (G1-G16). The PANSS Negative Subscale Score was the sum of the seven negative items. For each of the 30 items, the possible rating ranged from 1 (symptom not reported) to 7 (symptom very severe).

Studies	double-blind period	Diagnosis /demographics	treatments	N (MITT population)	Mean baseline PANSS (SD)	Discontinuation		
						total	insufficient response	adverse events
132	6 weeks	Acute exacerbation of schizophrenia (DSM IV) East-EU/Asia study 76% hospitalised at randomisation	XR 400 mg XR 600 mg XR 800 mg IR 400 mg Placebo	111 111 117 119 115	95.8 (13.9) 96.8 (14.1) 97.3 (14.7) 96.5 (16.0) 96.2 (13.3)	25% 17% 23% 19% 26%	12% 6% 10% 9% 15%	5% 2% 3% 4% 3%
133	6 weeks	Acute exacerbation of schizophrenia (DSM IV) US study 78% hospitalised at randomisation	XR 400 mg XR 600 mg XR 800 mg IR 800 mg Placebo	113 101 110 109 111	91.1 (13.4) 93.1 (14.0) 92.6 (13.2) 93.0 (13.5) 90.8 (11.9)	35% 40% 38% 43% 39%	5% 9% 9% 10% 13%	10% 10% 9% 11% 13%
041	6 weeks	Acute exacerbation of schizophrenia (DSM IV) US/CA study All patients were required to be hospitalised.	XR 300 mg XR 600 mg XR 800 mg IR 300 mg IR 600 mg Placebo	83 87 85 85 80 78	91.5 (19.2) 92.4 (17.2) 89.0 (14.9) 89.5 (15.7) 88.6 (17.3) 91.1 (16.3)	59% 55% 51% 52% 59% 67%	30% 22% 29% 24% 21% 33%	6% 9% 1% 7% 9% 9%

Studies/ Treatments		Mean change from baseline on the PANSS	Differences in mean change from baseline medication vs. placebo on the PANSS (95% CI)	Response (%)	Comment
132	XR 400 mg XR 600 mg XR 800 mg IR 400 mg Placebo	-24.8* -30.9* -31.3* -26.6* -18.8*	-11.5 -0.6 -17.6 -6.7 -17.9 -7.1 -13.1 -2.4	44.1* 60.4* 56.4* 52.9* 30.4	Study 132 clearly is a positive study showing a statistically significant effect for both primary outcome measures in favour of XR 400 mg, 600 mg, 800 mg and IR 400 mg compared to placebo. Moreover, remarkably low discontinuation rates and high placebo response
133	XR 400 mg XR 600 mg XR 800 mg IR 800 mg Placebo	-13.8 -16.8 -14.8 -15.0 -12.1	-5.9 2,5 -9.1 -0.4 -7.0 1.6 -7.3 1.3	19.5 26.7 23.6 22.9 20.7	Study 133 is a failed study (= lack of assay sensitivity in the study ≠ negative study). XR 300 mg, 600 mg, 800 mg as well as IR 300 and 600 mg did not separate from placebo for the two primary outcome measures
041	XR 300 mg XR 600 mg XR 800 mg IR 300 mg IR 600 mg Placebo	-5.0 -13.0* -11.3 -9.4 -7.0 -5.2	-5.9 6.2 -13.8 -1.8 -12.0 0.06 -10.3 1.8 -7.9 4.4	12.0 24.1 23.5 18.8 13.8 14.1	Study 041 is more or less also a failed study. For the outcome measure “mean improvement from baseline” only XR 600 mg separated from placebo, while 300 mg and 800 mg as well as 300 mg and 600 mg IR did not. Considering the primary outcome measure “responders” all treatment groups did not separate from placebo. A normal low placebo response in this study, but high discontinuation rate.

* statistically significant superior compared to placebo

In these short-term studies response was defined as 30% or more change in PANSS scale from baseline. In studies 133 and 041 active treatments did not separate from placebo (table above). Study 041 should be considered as a failed study, because of design failures causing massive early withdrawal. Therefore, changes in design were made in studies 132 and 133. Moreover, it turned out in study 133 that 50% of the patients were moderately ill. Including less ill patients in study 133 may have resulted in a strong and continuing placebo effect, which may have caused the lack of statistically significance difference between active compound and placebo.

Short-term treatment effects and dose

There was no linear dose-effect relation in the studies. In study 132 the magnitude of effect was larger on average in 600 mg/800 mg XR treatment groups compared to the 400 mg XR group. Study 133 failed due to lack of assay sensitivity and in study 041 only the XR 600 mg XR separated from placebo, while the 300 mg XR and 800 mg XR did not. On basis of these short-term data, it is difficult to draw a definite conclusion about optimal dose.

Long-term efficacy

Study 004 had an open phase of 16 weeks (Phase I), and in addition (Phase II) a classic placebo-controlled withdrawal design with a duration of 1-year. The study has been performed in 26 centres divided over 5 countries: Bulgaria, Poland, Russia, Ukraine and India (Table 16).

Table 16 Number of sites and randomized patients by country

Country	N of centres	N of enrolled patients	N of patients randomized to PLA	N of patients randomized to QTP SR	Total N of randomized patients
Bulgaria	2	13	1	1	2
Poland	4	24	7	9	16
Russia	9	129	37	32	69
Ukraine	6	99	30	29	59
India	5	93	28	23	51

N Number of. PLA Placebo. QTP Quetiapine. SR Sustained release.
Note: Additional centers did not enroll any patients.
Study:D1444C00004, Source document: ST_COUNTRY731.SAS. Generated: 15:45:33 29Aug2006 DB version prod: 6.

The objective of the study was to evaluate prevention of relapse in clinically stable patients with schizophrenia, who were treated with either quetiapine XR (flexible dosing in 200 mg increments (XR 400 mg/day, 600 mg/day, or 800 mg/day) or placebo. The protocol-specified interim analysis in study 004 performed by the independent Data Safety Monitoring Board (DSMB) after 45 reported relapses showed that quetiapine XR significantly prolonged time to relapse compared with placebo. Based on these results that met prespecified stopping criterion, the independent DSMB recommended the study be terminated and the MAH accepted the DSMB's advice. The study was terminated after 9 months.

Relapse was not defined completely unequivocally: hospitalization due to worsening schizophrenia, increase in PANSS score ≥30% from baseline, score of 6 or 7 on CGI-I scale or need for any other antipsychotic medication to treat psychosis despite study drug dose adjustments. In advance of the submission the MEB advised the company to present the results broken down into the individual components of the relapse, because it is the opinion of regulatory agencies that relapse should be defined by means of a threshold value on a specific rating scale only (e.g. *increase in PANSS score ≥ 30% from baseline*). All vaguely defined relapse definitions are considered as secondary outcome measures (e.g. hospitalization may be initiated by social circumstances and not per se because of psychotic relapse).

Relapses did not occur predominantly in the first weeks of randomized treatment in either group. For each broken down relapse criterion including, increase in PANSS score ≥30% from baseline, active treatment (= XR quetiapine) was superior to placebo treatment with regard to relapse (Table O-6). Therefore, this study has shown unequivocally the need for continuation of XR quetiapine.

Table O- 6 Primary criteria for schizophrenic relapse for Study 004 (interim ITT population)

	PLA N=87 n (%)	QTP SR N=84 n (%)
Number of patients with schizophrenic relapse	36 (100.0)	9 (100.0)
Hospitalization[a]	3 (8.3)	0
PANSS ≥ 30% increase[b]	12 (33.3)	4 (44.4)
CGI ≥6[c]	18 (50.0)	4 (44.4)
Antipsychotic medication[d]	3 (8.3)	1 (11.1)

[a] Hospitalization due to worsening of schizophrenia.
[b] An increase on PANSS score of 30% or more from baseline (randomization).
[c] A rating of much worse or very much worse (score 6 or 7) on the CGI-I scale.
[d] Need for any other antipsychotic medication to treat psychosis.
CGI Clinical Global Impression. ITT Intention-to-treat. N Number of patients in treatment group. n Number of patients. PAl Positive and Negative Syndrome Scale. PLA Placebo. QTP Quetiapine. SR Sustained-release.
Study: D1444C00004 Source document: ETI_RELAPSE203.SAS. Generated: 11:49:24 30Aug2006 DB version prod: 6.

Short-term switching study 146

In study 146 clinically stable patients, patients who were clinically stable on treatment with twice-daily quetiapine IR at enrolment were switched to treatment with the same once-daily dose of quetiapine XR, switched from quetiapine IR to quetiapine XR. After 4 weeks of run-in treatment with quetiapine IR 400 mg, 600 mg, or 800 mg/day, patients were randomized to 6 weeks of treatment with quetiapine IR or XR at the same total daily dose used during run-in treatment. Randomized treatment continued for up to 6 weeks.

The primary variable in study 146 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 at any visit. This composite variable was chosen to assess lack of efficacy both in overall terms (discontinuations) and in terms of objectively determined, clinically relevant change in psychotic symptoms (PANSS scores).

A total of 630 patients were enrolled in the study and treated with quetiapine IR for 4 weeks. 497 patients completed the run-in period, 133 were not randomised.

	Quetiapine XR	Quetiapine IR	95% CI in difference between XR and IR
All randomised patients (MITT population)	331	166	
Completed the randomisation phase	303 (91.5%)	156 (94%)	
Withdrawal due to lack of efficacy	30 (9.1%)	12 (7.2%)	MITT population analysis: -3.78, 6.57 PP population analysis: -6.75, 3.71
Withdrawal due to lack of therapeutic response	7 (2.1%)	1 (0.6%)	
Withdrawal due to an AE	(1.5%)	(1.2%)	

Chosen margin for demonstrating non-inferiority: 6%

Maintenance of treatment effect in clinically stable patients was observed in both quetiapine groups over the course of the study, with all efficacy measures remaining stable or showing improvement. The proportion of patients with lack of efficacy after switching to quetiapine XR was 9.1%, compared to 7.2% of patients maintained on quetiapine IR. The point estimate for the treatment difference between quetiapine XR and quetiapine IR in the MITT population was 1.86% (95% CI -3.78, 6.57, p-value for 1-sided test = 0.0431). As the upper limit of 95% CI exceeded the selected margin of 6%, non-inferiority could not be shown in this population.

However, the per protocol analysis provided further support that efficacy is maintained on switching from quetiapine IR to quetiapine XR. In this analysis the proportions of patients with lack of efficacy were 5.3% and 6.2% in the quetiapine XR and quetiapine IR groups, respectively, with a treatment difference of -0.83%. The upper limit of the 95% CI was lower than the selected margin of 6% (95% CI -6.75, 3.71: p-value for 1-sided test = 0.0017), demonstrating non-inferiority.

Therefore it was concluded that the effect of quetiapine after switching from the IR formulation to the XR formulation was maintained, and the study considered positive.

Mania

The indication in bipolar mania, which has been approved for the already authorised immediate release tablets, was refused as there were no clinical data submitted with the current formulation to support this indication.

Overall conclusions on clinical efficacy

Two of the short-term placebo-controlled studies failed due to design failures that caused massive early withdrawals in one study, and the inclusion of an unusually high proportion of moderately ill patients in the other study. The third short-term study clearly showed short-term efficacy. The switching study convincingly showed that switching from quetiapine IR to quetiapine XR did not result in lack of efficacy. Moreover, the well-conducted long-term study was showing that active treatment (= XR quetiapine) was superior to placebo treatment with regard to time to relapse indicating the need for continuation of Seroquel XR in schizophrenic patients who had an initial response.
Therefore, efficacy (including short-term and long-term efficacy) has been shown for Seroquel XR for the indications *"schizophrenia"* and *"prevention of relapse in stable schizophrenic patients"*.

Clinical safety

Adverse events

Common adverse events in short-term studies

The common adverse events are presented in table O-7. There seems to be no difference in incidence of some well-known quetiapine adverse events (sedation, dry mouth, somnolence) between the XR and IR formulation. Moreover the type, frequency and intensity of adverse events observed in the quetiapine XR and quetiapine IR groups were similar, with no apparent dose-response relationship. There were no adverse events associated only with quetiapine XR treatment, and in general, there was no dose relationship with any common adverse event associated with drug across the dose range (300 mg/day to 800 mg/day).
The combined data for placebo-controlled studies in quetiapine XR show that the incidence rates for hyperglycemia are 0.1% and hepatitis also 0.1%.

Table O- 7 Common adverse events for placebo-controlled studies in patients with acute schizophrenia (safety population)

MedDRA Preferred term[a]	PLA[b] N=319 n (%)	QTP SR[b] N=951 n (%)	QTP IR[b] N=414 n (%)	SCHIZ[c] PLA N=206 n (%)	SCHIZ[c] QTP N=510 n (%)
Sedation	21 (6.6)	121 (12.7)	65 (15.7)	8 (3.9)	53 (10.4)
Dry mouth	4 (1.3)	115 (12.1)	38 (9.2)	6 (2.9)	32 (6.3)
Somnolence	12 (3.8)	115 (12.1)	55 (13.3)	12 (5.8)	48 (9.4)
Dizziness	12 (3.8)	93 (9.8)	37 (8.9)	9 (4.4)	60 (11.8)
Headache	47 (14.7)	92 (9.7)	42 (10.1)	40 (19.4)	112 (22.0)
Insomnia	46 (14.4)	71 (7.5)	28 (6.8)	40 (19.4)	73 (14.3)
Orthostatic hypotension	15 (4.7)	70 (7.4)	39 (9.4)	2 (1.0)	10 (2.0)
Constipation	15 (4.7)	61 (6.4)	25 (6.0)	11 (5.3)	53 (10.4)
Nausea	22 (6.9)	52 (5.5)	19 (4.6)	11 (5.3)	27 (5.3)
Dyspepsia	7 (2.2)	44 (4.6)	20 (4.8)	5 (2.4)	29 (5.7)
Agitation	16 (5.0)	35 (3.7)	14 (3.4)	48 (23.3)	119 (23.3)
Heart rate increased	4 (1.3)	34 (3.6)	16 (3.9)	2 (1.0)	12 (2.4)
Vomiting	13 (4.1)	32 (3.4)	7 (1.7)	11 (5.3)	33 (6.5)
Fatigue	6 (1.9)	28 (2.9)	16 (3.9)	3 (1.5)	15 (2.9)
Tachycardia	3 (0.9)	27 (2.8)	26 (6.3)	6 (2.9)	27 (5.3)
Hypotension	3 (0.9)	26 (2.7)	17 (4.1)	2 (1.0)	6 (1.2)
Weight increased	5 (1.6)	23 (2.4)	20 (4.8)	2 (1.0)	14 (2.7)
Diarrhoea	10 (3.1)	16 (1.7)	12 (2.9)	4 (1.9)	10 (2.0)
Blood pressure diastolic decreased	2 (0.6)	13 (1.4)	10 (2.4)	0	0
Dizziness postural	2 (0.6)	13 (1.4)	6 (1.4)	6 (2.9)	30 (5.9)
Stomach discomfort	5 (1.6)	13 (1.4)	11 (2.7)	1 (0.5)	7 (1.4)
Blood pressure systolic decreased	3 (0.9)	10 (1.1)	8 (1.9)	0	0
Lethargy	0	6 (0.6)	6 (1.4)	2 (1.0)	4 (0.8)
Alanine aminotransferase increased	1 (0.3)	3 (0.3)	1 (0.2)	3 (1.5)	35 (6.9)

[a] Patients with multiple events falling under the same preferred term are counted only once in that term.
[b] Studies D1444C00132, D1444C00133 and 5077IL/0041.
[c] Studies 5077IL/0004, 5077IL/ 0006, 5077IL/0008 and 5077IL/0013, conducted to support the marketing approval of QTP IR
IR Immediate release. QTP Quetiapine. SCHIZ Schizophrenia. SR Sustained release.
Note: Common adverse event: an adverse event occurring at an incidence of ≥ 5% in any randomized treatment group within the individual placebo controlled studies.
Note: Sorted by descending frequency in QTP SR column.

Adverse events leading to death, serious non-fatal adverse events, and adverse events leading to discontinuation

These events are given in the following table.

AE	Incidence	Comment
death	1 patient in the 400 mg IR group	Considered as unrelated to study treatment
Serious adverse events	1 x dizziness with quetiapine 800 mg	Considered as unrelated to study treatment
Discontinuation due to adverse events	5-11% in all treatment groups	No apparent difference between placebo and quetiapine groups

Clinical laboratory test results, vital signs, and ECG data

Both IR and XR formulation were showing changes in glucose regulation, lipid, thyroid, and prolactin laboratory data. Both the IR and XR formulation presented increases in glucose as compared to placebo. There was no apparent relationship to quetiapine dose or formulation for shifts in glucose and glycated hemoglobin concentrations. No important differences were noted among groups of patients who were classified as having diabetes, at risk for diabetes, or non-diabetic.
Triglyceride concentrations decreased by a mean of 0.09 mmol/L (8.38 mg/dL) in placebo-treated patients and increased by a mean of 0.02 to 0.51 mmol/L (2.04 to 45.45 mg/dL) in quetiapine-treated patients. Treatment-emergent shifts to clinical importance in triglyceride concentrations (≥2.26 mmol/L [200 mg/dL]) occurred at overall rates of 5.1% for placebo, 17.9% for quetiapine XR, and 15.9% for quetiapine IR. The increases in triglycerides did not show a systematic dose response and were not differentially affected by quetiapine formulation. Increases in triglyceride concentration following quetiapine treatment have been observed in previous clinical studies and are consistent with labelling for quetiapine IR.
There were no clinically relevant changes in mean total cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) levels in patients treated with quetiapine XR or quetiapine IR.
Changes in thyroxine and thyroid-stimulating hormone were consistent with those previously seen in clinical studies with quetiapine, with no important differences between quetiapine formulations and no systematic relationship to dose.
Decreases of 6.00 to 24.09 ng/mL in mean prolactin concentration were observed in all treatment groups. 5.6% for quetiapine XR-treated patients and 6.7% for quetiapine IR-treated patients.

Vital signs
Changes in vital signs in patients treated with quetiapine XR, e.g., increases in pulse rate and orthostatic decreases in blood pressure, were consistent with the known effects of quetiapine. A dose-related increase of 1.1 to 5.7 bpm in mean supine pulse rate was observed at the end of treatment in the quetiapine-treated groups. Changes in mean systolic and diastolic blood pressure were similar between quetiapine formulations, with no clear dose relationship. Treatment-emergent shifts to clinical importance (according to predefined criteria) were generally similar for quetiapine XR and quetiapine IR. Orthostatic changes in vital signs did not show any important differences between quetiapine XR and quetiapine IR.

ECG data and QT prolongation
ECG results were similar for quetiapine XR and quetiapine IR. Small increases in mean heart rate were consistent with the changes that were anticipated, based on the pharmacological profile of quetiapine IR. There were no systematic or clinically meaningful changes in QTcF intervals.
The data did not indicate an association between quetiapine XR and QT prolongation. The frequency of shifts to clinical importance (according to predefined criteria) seen during treatment with quetiapine XR was similar to that seen during placebo treatment. There were no adverse events associated with QT prolongation.

Diabetes mellitus
Assessment of clinical laboratory data and adverse events classified as associated with diabetes revealed no pattern of emergent or worsening diabetes mellitus with quetiapine XR treatment. There were small, highly variable increases in mean glucose concentrations with quetiapine XR and quetiapine IR treatment compared with placebo. The mean changes were generally similar across all quetiapine XR groups, with no suggestion of a dose relationship. Increases in insulin concentrations were also observed, but interpretation of the observed changes was obscured by the large standard deviations in mean concentrations. Overall, there were no clinically relevant findings to suggest that progression of diabetes had occurred in patients with a baseline diagnosis of diabetes. Examination of data for patients without diabetes or only at-risk for diabetes, showed no clinically relevant findings to suggest that diabetes was emergent in these patients. These data were in accordance with the lack of adverse events that might suggest the development of diabetic symptoms.

Agranulocytosis and neutropenia
The results from these studies indicate that quetiapine XR treatment demonstrate no association with treatment-emergent agranulocytosis. Shifts to a neutrophil count of <1.5 x 109 cells/L were reported at rates of 1.5% in patients treated with quetiapine XR, 1.5% in patients treated with quetiapine IR, and 0.8% in patients treated with placebo. Neutropenia is already an adverse reaction described in the approved prescribing information for Seroquel.

Weight
Increases in mean weight from baseline were observed in the quetiapine XR and quetiapine IR treatment groups, with no apparent differences across formulations. Among patients who completed the studies, mean weight increases were 0.26 kg in the placebo group, 1.77 kg in the quetiapine XR group, and 2.19 kg in the quetiapine IR group. The percentage of patients completing the studies with weight increases of ≥7% was lower in patients treated with quetiapine XR (13.7%) than in patients treated with quetiapine IR (19.5%) and higher than in patients treated with placebo (6.7%).

Metabolic syndrome
The 6-week study duration permitted a limited assessment of possible changes in factors relevant to metabolic syndrome. Among patients who had fewer than 3 metabolic risk factors at baseline, the incidence of 3 or more risk factors (aggregate criteria) at the end of treatment was as follows: 10.2% for placebo, 12.9% for quetiapine XR, and 13.4% for quetiapine IR. There was no clear dose response relationship or difference by formulation. When triglyceride shifts (5.1% for placebo, 17.9% for quetiapine XR, and 15.9% for quetiapine IR) were excluded from the aggregate criteria, there was little difference between placebo and quetiapine: placebo 7.6%, quetiapine XR 8.7%, quetiapine IR 9.3%.

Specific safety areas in patients with acute schizophrenia

Extrapyramidal symptoms
Extrapyramidal symptoms (EPS) were assessed by adverse events and rating scales (SAS total score and BARS Global Assessment score). The most common adverse events potentially associated with EPS in the quetiapine treatment groups were “tremor”, “akathisia” and “restlessness”. The incidence rates for individual adverse events did not exceed 3% in any quetiapine XR treatment group. Most adverse events were reported as mild to moderate in intensity, and infrequently led to discontinuation from study treatment. The aggregate incidence of EPS events was 7.5% for quetiapine XR, 7.7% for quetiapine IR, and 4.7% for placebo. While EPS-related adverse events were more frequent for quetiapine-treated patients, changes in SAS and BARS scores demonstrated that most patients either did not worsen or remained unchanged. Worsening of SAS and BARS scores from baseline occurred at similar rates for quetiapine XR, quetiapine IR, and placebo. For SAS total score, the percentages of patients with worsening were 13.7% for quetiapine XR, 13.4% for quetiapine IR, and 12.7% for placebo. For BARS Global Assessment score, the percentages of patients with worsening were 6.4% for quetiapine XR, 8.1% for quetiapine IR, and 7.5% for placebo. The use of anticholinergic medication was infrequent throughout the studies and was similar across treatment groups. The incidence of EPS did not increase with dose of

quetiapine XR. In conclusion, the evidence from adverse event reports, SAS and BARS scores, and anticholinergic medication use suggest that tolerance for quetiapine XR was similar to the known profile of quetiapine IR.

Suicidality
The incidence of adverse events classified as suicidality was low and similar across treatment groups in the placebo-controlled pool. The Columbia University-type analysis of suicidality revealed relative risk estimates for all quetiapine-treated groups in the placebo-controlled pool that were not statistically separable from placebo. Rates of suicidal behavior/ideation were 0.6% for quetiapine XR, 1.0% for quetiapine IR, and 0.9% for placebo. Estimates of relative risk (95% CI) for quetiapine XR versus placebo were as follows: 1.0 (0.204 to 4.993) for 300 mg/day and 400 mg/day (combined data), 0.69 (0.115 to 4.078) for 600 mg/day, and 0.33 (0.034 to 3.148) for 800 mg/day.
There was one completed suicide in a patient treated with placebo in the relapse-prevention study (004). The scores of the patient's PANSS scale did not show any worsening leading up to the event. According to the CGI-I scores this patient was mildly ill throughout randomized treatment.

Overall conclusions on clinical safety
There seems to be no difference in incidence of adverse events between the XR and IR formulation. Moreover the type, frequency and intensity of adverse events observed in the quetiapine XR and quetiapine IR groups were similar, with no apparent dose-response relationship. There were no adverse events associated only with quetiapine XR treatment, and in general, there was no dose relationship with any common adverse events associated with drug across the dose range (300 mg/day to 800 mg/day). Well-known quetiapine adverse events are sedation, dry mouth and somnolence.

The following safety issues were measured and assessed in detail: death, serious non-fatal events, adverse events leading to discontinuation, clinical laboratory results, vital signs and ECG data, EPS, QT prolongation, diabetes mellitus, agranulocytosis and neutropenia, suicidality, weight and metabolic syndrome. With regard to all these issues no remarkable or unexpected events occurred in both the XR formulations as well as the IR formulation for all dosages. Moreover, there seems to be no difference in incidence and severity between the two formulations. At last, treatment initiation was assessed as well as safety of evening administration with no relevant differences between the XR and IR formulation.

There is a lack of long-term safety data of the XR formulation due to the termination of study 004. Only 63 patients were treated longer than 6 months. The safety in elderly was assessed in a study with patients in Alzheimer disease and psychosis and/or agitation (study 115). The study duration was 6 weeks and the dosage used varied between 50 and 300 mg Seroquel with a gradual dose escalation. Specific studies in patients with hepatic impairment have not been performed.

Risk Management Plan
A risk management plan is submitted for the prolonged release formulation of quetiapine. The MAH has considered and discussed all the important adverse events that are listed in the Seroquel SPC. As the area under the plasma concentration-time curve (AUC) for the XR formulation is comparable to the AUC achieved for the same total daily dose of the IR formulation administered twice daily, extrapolation of the safety data seems possible. However, the human safety database for the XR formulation of quetiapine is limited. The MAH summarises specifically as limited or missing information: long term data, use in elderly patients, use in paediatric patients, and use in pregnant and lactating women. Furthermore, potential risks that need further evaluation might be medication error, because of name confusion and titration errors. The introduction of this XR formulation may result in cases of confusion with the already marketed IR formulation.

Based on the list of identified and potential risks, the MAH committed to conduct a post-approval safety surveillance study using epidemiological methods over a period of 3 years, to ensure the safe introduction of prolonged release quetiapine to the market. The primary objective of this study will be to estimate the incidence of adverse events in patients with schizophrenia, who are exposed to Seroquel XR under normal prescribing conditions. The MAH should submit the study protocol after finalization of the MRP procedure for approval by the concerned member states. Besides, the MAH has a routine

pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks.

SPC
The proposed SPC for Seroquel XR has been based upon the SPC of Seroquel IR. Please note, however, that there is a major difference between the Seroquel XR and IR SPC:

- the Seroquel XR SPC does not contain the indication moderate to severe manic episodes which is present in the Seroquel IR SPC.

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The MAH has written the Seroquel XR package leaflet according to the user tested national UK Seroquel IR patient package leaflet. Therefore, most of the content and wording of the Seroquel XR package leaflet is consistent with the UK Seroquel IR package leaflet. A user test was performed that focussed specifically on the differences in the two formulations in the SPC. The testing consisted of two rounds: 1. a pilot round, 2. a final round with 20 people from the target group for this product. The results of focused user testing demonstrated that at least 90% of the participants were able to find each point of information. The readability test has been adequately performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The quality part of the dossier is of an adequate standard for authorisation. Three issues will be addressed post-authorisation (see below).

No new preclinical data have been submitted which is deemed acceptable. The current application is sufficiently supported by the non-clinical studies already presented during the application for Seroquel IR tablets.

The Seroquel XR clinical development programme is considered to have a sufficient testing strategy for registration.

Pharmacokinetic studies were performed under steady-state conditions for safety and ethical reasons, in order to prevent long-term periods of non-treatment. As the uptitration schedule is completely different than for the IR tablets, and the new dosing schedule with the XR formulation is extensively tested clinically, the lack of single-dose studies is acceptable. Pharmacokinetics of XR tablets is dose linear. As there was a significant food effect when a high fat meal was given, Seroquel XR should be taken without food.

The C_{max} for the XR formulation is significantly lower compared to the IR formulation: A 13-50% lower C_{max} may allow for a higher initial dose and a faster uptitration schedule with the XR formulation compared to IR formulation. AUC values of the parent drug and sum of active moieties at a 300 mg and 400 mg XR tablet QD regimen were bioequivalent to a daily dose of 150-200 mg IR tablets BID, at steady state.

The pharmacodynamic results showed that there were no relevant differences between the fast and more gradual uptitration schedules regarding the vital signs. The small-scaled dose-titration and tolerability studies indicated that a starting dose of 300 mg and an uptitration schedule till 800 mg within 3 days mighty be feasible for the XR formulation. This was further investigated in Phase-III clinical safety and efficacy studies.

The efficacy of quetiapine given as the immediate release formulation Seroquel IR, registered in 1998, is well-known. However, for the extended release formulation additional studies are necessary. Three short-term studies were performed. Two of these short-term placebo-controlled studies failed due to design failures that caused massive early withdrawals in one study, and the inclusion of an unusually high proportion of moderately ill patients in the other study. The third short-term study clearly showed short-term efficacy. Also, the switching study convincingly showed that switching from quetiapine IR to

quetiapine XR did not result in lack of efficacy. Moreover, the well-conducted long-term study was showing that active treatment (= XR quetiapine) was superior to placebo treatment with regard to time to relapse indicating the need for continuation of Seroquel XR in schizophrenic patients who had an initial response.
Therefore, efficacy (including short-term and long-term efficacy) has been shown for Seroquel XR for the indications *"schizophrenia"* and *"prevention of relapse in stable schizophrenic patients"*.

There seems to be no difference in the type, frequency and intensity of adverse events observed in the Seroquel XR and Seroquel IR groups. There were no adverse events associated only with Seroquel XR treatment, and in general, there was no dose relationship with any common adverse events associated with drug across the dose range (300 mg/day to 800 mg/day). However, the human safety database for the XR formulation of quetiapine is limited. Consequently, the MAH committed to perform a safety surveillance study post approval over 3 years.

The SPC, package leaflet and labelling are in the agreed templates. Braille conditions are met by the MAH.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

In the Board meeting of 5 April 2007 the clinical aspects of the Seroquel XR procedure were discussed. The Board approved the indications schizophrenia and prevention of relapse in stable schizophrenic patients, whereas the indication for mania was rejected due to the lack of studies for the extended release formulation.
The member states, on the basis of the data submitted, considered that Seroquel XR 50, 200, 300 and 400 mg tablets demonstrated adequate evidence of efficacy for the approved indications as well as satisfactory risk/benefit profile and therefore granted a marketing authorisation.

There was no discussion in the CMD(h). Agreement between the concerned member states was reached during a written procedure.

A European harmonised birth date has been allocated (31-07-1997) and subsequently the first data lock point for quetiapine is 31 July 2008. The first PSUR is expected in September 2008, after which a PSUR should be submitted every year. The PSURs will combine the data for Seroquel immediate release tablets and Seroquel prolonged-release tablets.

The common renewal date for Seroquel XR will be 22 September 2011. This will be aligned with the current PSUR schedule for quetiapine. The renewal application will thus be submitted end of September 2011 and include PSURs covering the period until 31 July 2011.

The following post-approval commitments were made during the procedure:

<u>Quality – Medicinal product</u>

- The first three manufacturing batches and one batch annually thereafter will be placed on long-term stability. Accelerated stability studies will be performed on the first three manufacturing batches.

<u>Risk management plan</u>

- The MAH committed to conduct a post-approval safety surveillance using epidemiological methods over a period of 3 years, to ensure the safe introduction of prolong-release quetiapine to the market. The MAH should submit the study protocol after finalization of the MRP procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BID	Twice-daily
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EPS	Extrapyramidal symptoms
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
IR	Immediate release
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PSUR	Periodic Safety Update Report
RH	Relative Humidity
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States
XR	Prolonged release

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached

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