

ANNEX I

**LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTHS OF THE MEDICINAL
PRODUCTS, ROUTE OF ADMINISTRATION, MARKETING AUTHORISATION
HOLDER(S) IN THE MEMBER STATES**

<u>Member State</u>	<u>Marketing Authorisation Holder</u>	<u>Invented name</u>	<u>Strength</u>	<u>Pharmaceutical Form</u>	<u>Route of administration</u>
AT - Austria	AstraZeneca Österreich GmbH Schwarzenbergplatz 7 A-1037 Wien Austria	Seroquel XR 50 mg – Retardtabletten	50 mg	Prolonged-release tablet	Oral use
AT - Austria	AstraZeneca Österreich GmbH Schwarzenbergplatz 7 A-1037 Wien Austria	Seroquel XR 150 mg – Retardtabletten	150 mg	Prolonged-release tablet	Oral use
AT - Austria	AstraZeneca Österreich GmbH Schwarzenbergplatz 7 A-1037 Wien Austria	Seroquel XR 200 mg – Retardtabletten	200 mg	Prolonged-release tablet	Oral use
AT - Austria	AstraZeneca Österreich GmbH Schwarzenbergplatz 7 A-1037 Wien Austria	Seroquel XR 300 mg – Retardtabletten	300 mg	Prolonged-release tablet	Oral use
AT - Austria	AstraZeneca Österreich GmbH Schwarzenbergplatz 7 A-1037 Wien Austria	Seroquel XR 400 mg – Retardtabletten	400 mg	Prolonged-release tablet	Oral use
BE - Belgium	NV AstraZeneca SA Egide Van Ophemstraat 110 B-1180 Brussel Belgium	Seroquel XR 50 mg prolonged-release tablets	50 mg	Prolonged-release tablet	Oral use
BE - Belgium	NV AstraZeneca SA Egide Van Ophemstraat 110 B-1180 Brussel Belgium	Seroquel XR 150 mg prolonged-release tablets	150 mg	Prolonged-release tablet	Oral use
BE - Belgium	NV AstraZeneca SA Egide Van Ophemstraat 110 B-1180 Brussel Belgium	Seroquel XR 200 mg prolonged-release tablets	200 mg	Prolonged-release tablet	Oral use

<u>Member State</u>	<u>Marketing Authorisation Holder</u>	<u>Invented name</u>	<u>Strength</u>	<u>Pharmaceutical Form</u>	<u>Route of administration</u>
BE - Belgium	NV AstraZeneca SA Egide Van Ophemstraat 110 B-1180 Brussel Belgium	Seroquel XR 300 mg prolonged-release tablets	300 mg	Prolonged-release tablet	Oral use
BE - Belgium	NV AstraZeneca SA Egide Van Ophemstraat 110 B-1180 Brussel Belgium	Seroquel XR 400 mg prolonged-release tablets	400 mg	Prolonged-release tablet	Oral use
CY - Cyprus	AstraZeneca UK Limited, Silk Road Business Park, Macclesfield, Cheshire, SK10 2NA, United Kingdom	Seroquel XR 50 mg prolonged-release tablets	50 mg	Prolonged-release tablet	Oral use
CY - Cyprus	AstraZeneca UK Limited, Silk Road Business Park, Macclesfield, Cheshire, SK10 2NA, United Kingdom	Seroquel XR 200 mg prolonged-release tablets	200 mg	Prolonged-release tablet	Oral use
CY - Cyprus	AstraZeneca UK Limited, Silk Road Business Park, Macclesfield, Cheshire, SK10 2NA, United Kingdom	Seroquel XR 300 mg prolonged-release tablets	300 mg	Prolonged-release tablet	Oral use
CY - Cyprus	AstraZeneca UK Limited, Silk Road Business Park, Macclesfield, Cheshire, SK10 2NA, United Kingdom	Seroquel XR 400 mg prolonged-release tablets	400 mg	Prolonged-release tablet	Oral use
DE - Germany	AstraZeneca GmbH, Tinsdaler Weg 183, 22880 Wedel, Germany	Seroquel Prolong 50 mg Retardtabletten	50 mg	Prolonged-release tablet	Oral use

<u>Member State</u>	<u>Marketing Authorisation Holder</u>	<u>Invented name</u>	<u>Strength</u>	<u>Pharmaceutical Form</u>	<u>Route of administration</u>
DE - Germany	AstraZeneca GmbH, Tinsdaler Weg 183, 22880 Wedel, Germany	Seroquel Prolong 150 mg Retardtabletten	150 mg	Prolonged-release tablet	Oral use
DE - Germany	AstraZeneca GmbH, Tinsdaler Weg 183, 22880 Wedel, Germany	Seroquel Prolong 200 mg Retardtabletten	200 mg	Prolonged-release tablet	Oral use
DE - Germany	AstraZeneca GmbH, Tinsdaler Weg 183, 22880 Wedel, Germany	Seroquel Prolong 300 mg Retardtabletten	300 mg	Prolonged-release tablet	Oral use
DE - Germany	AstraZeneca GmbH, Tinsdaler Weg 183, 22880 Wedel, Germany	Seroquel Prolong 400 mg Retardtabletten	400 mg	Prolonged-release tablet	Oral use
DK - Denmark	AstraZeneca A/S Roskildevej 22 2620 Albertslund Denmark	Seroquel Prolong 50 mg prolonged-release tablets	50 mg	Prolonged-release tablet	Oral use
DK - Denmark	AstraZeneca A/S Roskildevej 22 2620 Albertslund Denmark	Seroquel Prolong 150 mg prolonged-release tablets	150 mg	Prolonged-release tablet	Oral use
DK - Denmark	AstraZeneca A/S Roskildevej 22 2620 Albertslund Denmark	Seroquel Prolong 200 mg prolonged-release tablets	200 mg	Prolonged-release tablet	Oral use
DK - Denmark	AstraZeneca A/S Roskildevej 22 2620 Albertslund Denmark	Seroquel Prolong 300 mg prolonged-release tablets	300 mg	Prolonged-release tablet	Oral use

<u>Member State</u>	<u>Marketing Authorisation Holder</u>	<u>Invented name</u>	<u>Strength</u>	<u>Pharmaceutical Form</u>	<u>Route of administration</u>
DK - Denmark	AstraZeneca A/S Roskildevej 22 2620 Albertslund Denmark	Seroquel Prolong 400 mg prolonged-release tablets	400 mg	Prolonged-release tablet	Oral use
EL - Greece	AstraZeneca S.A. 4 Theotokopoulou & Astronafton 151 25 Maroussi, Athens Greece	Seroquel XR 50 mg	50 mg	Prolonged-release tablet	Oral use
EL - Greece	AstraZeneca S.A. 4 Theotokopoulou & Astronafton 151 25 Maroussi, Athens Greece	Seroquel XR 150 mg	150 mg	Prolonged-release tablet	Oral use
EL - Greece	AstraZeneca S.A. 4 Theotokopoulou & Astronafton 151 25 Maroussi, Athens Greece	Seroquel XR 200 mg	200 mg	Prolonged-release tablet	Oral use
EL - Greece	AstraZeneca S.A. 4 Theotokopoulou & Astronafton 151 25 Maroussi, Athens Greece	Seroquel XR 300 mg	300 mg	Prolonged-release tablet	Oral use
EL - Greece	AstraZeneca S.A. 4 Theotokopoulou & Astronafton 151 25 Maroussi, Athens Greece	Seroquel XR 400 mg	400 mg	Prolonged-release tablet	Oral use

<u>Member State</u>	<u>Marketing Authorisation Holder</u>	<u>Invented name</u>	<u>Strength</u>	<u>Pharmaceutical Form</u>	<u>Route of administration</u>
ES- Spain	AstraZeneca Farmacéutica Spain, S.A. C/ Serrano Galvache, 56 – Edificio Roble 28033 Madrid Spain	Seroquel Prolong 50 mg comprimidos de liberación prolongada	50 mg	Prolonged-release tablet	Oral use
ES- Spain	AstraZeneca Farmacéutica Spain, S.A. C/ Serrano Galvache, 56 – Edificio Roble 28033 Madrid Spain	Seroquel Prolong 150 mg comprimidos de liberación prolongada	150 mg	Prolonged-release tablet	Oral use
ES- Spain	AstraZeneca Farmacéutica Spain, S.A. C/ Serrano Galvache, 56 – Edificio Roble 28033 Madrid Spain	Seroquel Prolong 200 mg comprimidos de liberación prolongada	200 mg	Prolonged-release tablet	Oral use
ES- Spain	AstraZeneca Farmacéutica Spain, S.A. C/ Serrano Galvache, 56 – Edificio Roble 28033 Madrid Spain	Seroquel Prolong 300 mg comprimidos de liberación prolongada	300 mg	Prolonged-release tablet	Oral use
ES- Spain	AstraZeneca Farmacéutica Spain, S.A. C/ Serrano Galvache, 56 – Edificio Roble 28033 Madrid Spain	Seroquel Prolong 400 mg comprimidos de liberación prolongada	400 mg	Prolonged-release tablet	Oral use

<u>Member State</u>	<u>Marketing Authorisation Holder</u>	<u>Invented name</u>	<u>Strength</u>	<u>Pharmaceutical Form</u>	<u>Route of administration</u>
FI - Finland	AstraZeneca Oy Luomanportti 3 FI-02200 Espoo Finland	Seroquel Prolong 50 mg depottabletti	50 mg	Prolonged-release tablet	Oral use
FI - Finland	AstraZeneca Oy Luomanportti 3 FI-02200 Espoo Finland	Seroquel Prolong 150 mg depottabletti	150 mg	Prolonged-release tablet	Oral use
FI - Finland	AstraZeneca Oy Luomanportti 3 FI-02200 Espoo Finland	Seroquel Prolong 200 mg depottabletti	200 mg	Prolonged-release tablet	Oral use
FI - Finland	AstraZeneca Oy Luomanportti 3 FI-02200 Espoo Finland	Seroquel Prolong 300 mg depottabletti	300 mg	Prolonged-release tablet	Oral use
FI - Finland	AstraZeneca Oy Luomanportti 3 FI-02200 Espoo Finland	Seroquel Prolong 400 mg depottabletti	400 mg	Prolonged-release tablet	Oral use
IS - Iceland	AstraZeneca A/S Roskildevej 22 2620 Albertslund Denmark	Seroquel Prolong	50 mg	Prolonged-release tablet	Oral use
IS - Iceland	AstraZeneca A/S Roskildevej 22 2620 Albertslund Denmark	Seroquel Prolong	150 mg	Prolonged-release tablet	Oral use
IS - Iceland	AstraZeneca A/S Roskildevej 22 2620 Albertslund Denmark	Seroquel Prolong	200 mg	Prolonged-release tablet	Oral use

<u>Member State</u>	<u>Marketing Authorisation Holder</u>	<u>Invented name</u>	<u>Strength</u>	<u>Pharmaceutical Form</u>	<u>Route of administration</u>
IS - Iceland	AstraZeneca A/S Roskildevej 22 2620 Albertslund Denmark	Seroquel Prolong	300 mg	Prolonged-release tablet	Oral use
IS - Iceland	AstraZeneca A/S Roskildevej 22 2620 Albertslund Denmark	Seroquel Prolong	400 mg	Prolonged-release tablet	Oral use
IE - Ireland	AstraZeneca UK Ltd 600 Capability Green Luton LU1 3LU United Kingdom	Seroquel XR 50 mg prolonged-release tablets	50 mg	Prolonged-release tablet	Oral use
IE - Ireland	AstraZeneca UK Ltd 600 Capability Green Luton LU1 3LU United Kingdom	Seroquel XR 150 mg prolonged-release tablets	150 mg	Prolonged-release tablet	Oral use
IE - Ireland	AstraZeneca UK Ltd 600 Capability Green Luton LU1 3LU United Kingdom	Seroquel XR 200 mg prolonged-release tablets	200 mg	Prolonged-release tablet	Oral use
IE - Ireland	AstraZeneca UK Ltd 600 Capability Green Luton LU1 3LU United Kingdom	Seroquel XR 300 mg prolonged-release tablets	300 mg	Prolonged-release tablet	Oral use
IE - Ireland	AstraZeneca UK Ltd 600 Capability Green Luton LU1 3LU United Kingdom	Seroquel XR 400 mg prolonged-release tablets	400 mg	Prolonged-release tablet	Oral use
LU - Luxembourg	NV AstraZeneca SA Egide Van Ophemstraat 110 B-1180 Brussel	Seroquel XR 50 mg prolonged-release tablets	50 mg	Prolonged-release tablet	Oral use

<u>Member State</u>	<u>Marketing Authorisation Holder</u>	<u>Invented name</u>	<u>Strength</u>	<u>Pharmaceutical Form</u>	<u>Route of administration</u>
	Belgium				
LU - Luxembourg	NV AstraZeneca SA Egide Van Ophemstraat 110 B-1180 Brussel Belgium	Seroquel XR 150 mg prolonged-release tablets	150 mg	Prolonged-release tablet	Oral use
LU - Luxembourg	NV AstraZeneca SA Egide Van Ophemstraat 110 B-1180 Brussel Belgium	Seroquel XR 200 mg prolonged-release tablets	200 mg	Prolonged-release tablet	Oral use
LU - Luxembourg	NV AstraZeneca SA Egide Van Ophemstraat 110 B-1180 Brussel Belgium	Seroquel XR 300 mg prolonged-release tablets	300 mg	Prolonged-release tablet	Oral use
LU - Luxembourg	NV AstraZeneca SA Egide Van Ophemstraat 110 B-1180 Brussel Belgium	Seroquel XR 400 mg prolonged-release tablets	400 mg	Prolonged-release tablet	Oral use
MT - Malta	AstraZeneca UK Ltd Silk Road Business Park Macclesfield Cheshire SK10 2NA United Kingdom	Seroquel XR 50 mg prolonged-release tablets	50 mg	Prolonged-release tablet	Oral use
MT - Malta	AstraZeneca UK Ltd Silk Road Business Park Macclesfield Cheshire SK10 2NA United Kingdom	Seroquel XR 150 mg prolonged-release tablets	150 mg	Prolonged-release tablet	Oral use

<u>Member State</u>	<u>Marketing Authorisation Holder</u>	<u>Invented name</u>	<u>Strength</u>	<u>Pharmaceutical Form</u>	<u>Route of administration</u>
MT - Malta	AstraZeneca UK Ltd Silk Road Business Park Macclesfield Cheshire SK10 2NA United Kingdom	Seroquel XR 200 mg prolonged-release tablets	200 mg	Prolonged-release tablet	Oral use
MT - Malta	AstraZeneca UK Ltd Silk Road Business Park Macclesfield Cheshire SK10 2NA United Kingdom	Seroquel XR 300 mg prolonged-release tablets	300 mg	Prolonged-release tablet	Oral use
MT - Malta	AstraZeneca UK Ltd Silk Road Business Park Macclesfield Cheshire SK10 2NA United Kingdom	Seroquel XR 400 mg prolonged-release tablets	400 mg	Prolonged-release tablet	Oral use
NL - Netherlands	AstraZeneca BV Louis Pasteurlaan 5 2719 EE Zoetermeer The Netherlands	Seroquel XR 50 mg prolonged-release tablets	50 mg	Prolonged-release tablet	Oral use
NL - Netherlands	AstraZeneca BV Louis Pasteurlaan 5 2719 EE Zoetermeer The Netherlands	Seroquel XR 150 mg prolonged-release tablets	150 mg	Prolonged-release tablet	Oral use
NL - Netherlands	AstraZeneca BV Louis Pasteurlaan 5 2719 EE Zoetermeer The Netherlands	Seroquel XR 200 mg prolonged-release tablets	200 mg	Prolonged-release tablet	Oral use
NL - Netherlands	AstraZeneca BV Louis Pasteurlaan 5 2719 EE Zoetermeer The Netherlands	Seroquel XR 300 mg prolonged-release tablets	300 mg	Prolonged-release tablet	Oral use

<u>Member State</u>	<u>Marketing Authorisation Holder</u>	<u>Invented name</u>	<u>Strength</u>	<u>Pharmaceutical Form</u>	<u>Route of administration</u>
NL - Netherlands	AstraZeneca BV Louis Pasteurlaan 5 2719 EE Zoetermeer The Netherlands	Seroquel XR 400 mg prolonged-release tablets	400 mg	Prolonged-release tablet	Oral use
NO- Norway	AstraZeneca AS, Hoffsveien 70B, (PO Box 200), 0319 Oslo, Norway	Seroquel Depot 50 mg depottabletter	50 mg	Prolonged-release tablet	Oral use
NO- Norway	AstraZeneca AS, Hoffsveien 70B, (PO Box 200), 0319 Oslo, Norway	Seroquel Depot 150 mg depottabletter	150 mg	Prolonged-release tablet	Oral use
NO- Norway	AstraZeneca AS, Hoffsveien 70B, (PO Box 200), 0319 Oslo, Norway	Seroquel Depot 200 mg depottabletter	200 mg	Prolonged-release tablet	Oral use
NO- Norway	AstraZeneca AS, Hoffsveien 70B, (PO Box 200), 0319 Oslo, Norway	Seroquel Depot 300 mg depottabletter	300 mg	Prolonged-release tablet	Oral use
NO- Norway	AstraZeneca AS, Hoffsveien 70B, (PO Box 200), 0319 Oslo, Norway	Seroquel Depot 400 mg depottabletter	400 mg	Prolonged-release tablet	Oral use
PL - Poland	AstraZeneca UK Limited, 15 Stanhope Gate, London W1K 1LN, UK	Seroquel XR	50 mg	Prolonged-release tablet	Oral use

<u>Member State</u>	<u>Marketing Authorisation Holder</u>	<u>Invented name</u>	<u>Strength</u>	<u>Pharmaceutical Form</u>	<u>Route of administration</u>
PL - Poland	AstraZeneca UK Limited, 15 Stanhope Gate, London W1K 1LN, UK	Seroquel XR	150 mg	Prolonged-release tablet	Oral use
PL - Poland	AstraZeneca UK Limited, 15 Stanhope Gate, London W1K 1LN, UK	Seroquel XR	200 mg	Prolonged-release tablet	Oral use
PL - Poland	AstraZeneca UK Limited, 15 Stanhope Gate, London W1K 1LN, UK	Seroquel XR	300 mg	Prolonged-release tablet	Oral use
PL - Poland	AstraZeneca UK Limited, 15 Stanhope Gate, London W1K 1LN, UK	Seroquel XR	400 mg	Prolonged-release tablet	Oral use
PT - Portugal	AstraZeneca Produtos Farmacêuticos, Lda. Rua Humberto Madeira, 7 Valejas 2745-663 Barcarena Portugal	Seroquel SR	50 mg	Prolonged-release tablet	Oral use
PT - Portugal	AstraZeneca Produtos Farmacêuticos, Lda. Rua Humberto Madeira, 7 Valejas 2745-663 Barcarena Portugal	Seroquel SR	150 mg	Prolonged-release tablet	Oral use

<u>Member State</u>	<u>Marketing Authorisation Holder</u>	<u>Invented name</u>	<u>Strength</u>	<u>Pharmaceutical Form</u>	<u>Route of administration</u>
PT - Portugal	AstraZeneca Produtos Farmacêuticos, Lda. Rua Humberto Madeira, 7 Valejas 2745-663 Barcarena Portugal	Seroquel SR	200 mg	Prolonged-release tablet	Oral use
PT - Portugal	AstraZeneca Produtos Farmacêuticos, Lda. Rua Humberto Madeira, 7 Valejas 2745-663 Barcarena Portugal	Seroquel SR	300 mg	Prolonged-release tablet	Oral use
PT - Portugal	AstraZeneca Produtos Farmacêuticos, Lda. Rua Humberto Madeira, 7 Valejas 2745-663 Barcarena Portugal	Seroquel SR	400 mg	Prolonged-release tablet	Oral use
SE - Sweden	AstraZeneca AB AstraZeneca Sverige SE-151 85 Södertälje Sweden	Seroquel Depot 50 mg depottabletter	50 mg	Prolonged-release tablet	Oral use
SE - Sweden	AstraZeneca AB AstraZeneca Sverige SE-151 85 Södertälje Sweden	Seroquel Depot 150 mg depottabletter	150 mg	Prolonged-release tablet	Oral use
SE - Sweden	AstraZeneca AB AstraZeneca Sverige SE-151 85 Södertälje Sweden	Seroquel Depot 200 mg depottabletter	200 mg	Prolonged-release tablet	Oral use

<u>Member State</u>	<u>Marketing Authorisation Holder</u>	<u>Invented name</u>	<u>Strength</u>	<u>Pharmaceutical Form</u>	<u>Route of administration</u>
SE - Sweden	AstraZeneca AB AstraZeneca Sverige SE-151 85 Södertälje Sweden	Seroquel Depot 300 mg depottabletter	300 mg	Prolonged-release tablet	Oral use
SE - Sweden	AstraZeneca AB AstraZeneca Sverige SE-151 85 Södertälje Sweden	Seroquel Depot 400 mg depottabletter	400 mg	Prolonged-release tablet	Oral use

ANNEX II

**SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY
OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLET PRESENTED BY THE
EMA**

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF SEROQUEL XR AND ASSOCIATED NAMES (see Annex I)

Quetiapine is an atypical antipsychotic agent, which together with its active metabolite - norquetiapine interacts with several neurotransmitter receptors. As for other antipsychotic agents, the exact mechanism of action of quetiapine is unknown but the combination of receptor antagonism with a higher selectivity for serotonin 5HT₂ relative to dopamine D₂ receptors may contribute to its psychotropic activity and mood stabilizing properties.

Seroquel (quetiapine fumarate), prolonged release tablets (XR) at strength of 50 mg, 150 mg, 200 mg, 300 mg and 400 mg is authorised in the European Union via the Mutual Recognition and Decentralised procedures for the following indications:

- treatment of schizophrenia including preventing relapses in stable schizophrenic patients who have been maintained on Seroquel XR.
- treatment of moderate to severe manic episodes in bipolar disorder.
- treatment of major depressive episodes in bipolar disorder.
- prevention of recurrence in patients with bipolar disorders, in patients whose manic or depressive episode has responded to quetiapine treatment.

An application for a type II variation to the terms of the Marketing Authorisation of Seroquel XR (NL/H/156/08-011/II/058) submitted by the marketing authorisation holder (MAH), Astra Zeneca AB, via Mutual Recognition Procedure (MRP) to include treatment of recurrent episodes in patients with Major Depressive Disorders (MDD), excluding the use as initial treatment and used when patients cannot be appropriately managed on alternative antidepressant treatment was rejected by all involved Member States on 15 May 2009.

On 22 May 2009, the MAH triggered a referral under Article 6(13) of Commission Regulation (EC) No 1084/2003, requesting the CHMP to consider whether it is appropriate to introduce Seroquel XR, at 50 – 300 mg/day dosage to a population of patients with major depressive disorders, excluding the use as initial treatment and used when patients cannot be appropriately managed on alternative antidepressant treatment.

The CHMP re-evaluated the data submitted by the MAH in the Mutual Recognition type II variation, additional information submitted by the MAH in written and by oral explanations during this referral procedure.

Efficacy

Six studies in monotherapy and two add-on treatment studies were submitted by the MAH.

In five placebo controlled monotherapy studies (including a study in elderly subjects) the effects of quetiapine in an unrestricted MDD population were shown. The two adjunct (add-on) therapy studies, in patients with inadequate response to at least one initial antidepressant showed statistically and clinically relevant effects for quetiapine compared to placebo. In the relapse prevention study (monotherapy), also in unrestricted MDD population but after 14 to 26 weeks of open label treatment, responders were randomised to continuing quetiapine treatment or placebo for up to 52 weeks and showed significant and clinically relevant results in favour of active treatment.

The CHMP, based on the data available and further to consultation of the clinical neuroscience scientific advisory group (SAG-CNS), considered that efficacy in the therapeutic indication applied by the MAH, i.e., monotherapy in patients with recurrent major depression episodes that cannot be appropriately managed with alternative antidepressants, was not explicitly studied in the performed studies. The target population have not been studied in the placebo controlled monotherapy studies and the potential better safety profile of alternative antidepressants precluded a positive balance between efficacy and safety in the claimed indication.

It was nevertheless noted that supportive indirect evidence indicates that an effect can be expected after current or earlier failure (insufficient response or intolerance) with one or two antidepressants. Thus the potential benefit as add-on treatment was considered.

The short-term efficacy demonstrated in the two add-on studies in patients with inadequate response to initial antidepressant monotherapy treatment balanced positively with the already known safety profile of quetiapine. Furthermore, although lack of long-term efficacy data for add-on treatment was acknowledged, the CHMP agreed with extrapolation from the monotherapy relapse prevention study.

The CHMP concluded that there is potential benefit in the use of quetiapine as an add-on treatment of major depressive episodes in patients with MDD who have sub-optimal response to antidepressant monotherapy.

Safety

The safety profile in the MDD population was shown consistent with the already known safety profile of quetiapine in other indications.

The short-term monotherapy studies showed that patients treated with quetiapine had more adverse events and a higher dropout rate due to adverse events when compared to the active controls - Selective serotonin reuptake inhibitor - duloxetine and escitalopram. The most commonly noted adverse reactions with quetiapine were dry mouth, sedation, and somnolence while nausea and headache were more commonly noted with the active controls.

The overall safety profile in the elderly patients was similar to that in younger adult patients; however a higher frequency of somnolence, dizziness and extrapyramidal symptoms (EPS) was observed.

There are no active controlled on long-term safety data in MDD and the placebo controlled randomised withdrawal data are of limited value due to decreased numbers of patients over time. Nonetheless, the CHMP noted that the pattern of adverse events in the randomised phase of this study was similar to that seen in the short-term studies.

The CHMP concluded that the safety profile for add-on treatment in short-term studies was similar to the safety demonstrated for mono-therapy. However, the committee agreed that long-term safety on add-on treatment is needed when considering the potentially large number of possible combinations and the potential long-term safety concerns identified (i.e. metabolic changes and EPS related events). The CHMP agreed that the potential long-term safety concerns could be manageable by updated warnings in the product information and by collection of data in the already ongoing and in new post authorisation safety studies (PASSs) which will be included in the updated Risk Management Plan.

Based on the above, the benefit risk is considered positive for Seroquel XR as add-on treatment of major depressive episodes in patients with major depressive disorder, who have had suboptimal response to initial antidepressant mono-therapy subject to conditions of the marketing authorisation.

GROUNDNS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS, AND PACKAGE LEAFLET

Whereas

- The Committee considered the referral made under article 6(13) Commission Regulation (EC) No 1084/2003, for Seroquel XR and associated names initiated by the MAH (see annex I).
- The CHMP considered whether it was appropriate to introduce Seroquel XR, at 50 – 300 mg/day to a population of patients with major depressive disorders, excluding the use as initial treatment and used when patients cannot be appropriately managed on alternative antidepressant treatment.
- The Committee considered all the available data submitted on the safety and efficacy of quetiapine.
- The CHMP recognised that for add-on treatment relevant effects have been demonstrated in patients not responding to at least one antidepressant treatment. Although long-term efficacy data are lacking the committee concluded to be acceptable to extrapolate maintenance data from the monotherapy studies.
- The CHMP further concluded that, although long-term safety data are lacking, the potential long-term safety concerns (in particular metabolic changes, EPS related events) including the potentially possible combinations of quetiapine as add-on treatment to be appropriately manage by collection of data in the already ongoing and new post authorisation safety studies which will be included in the updated Risk Management Plan.
- The CHMP concluded on a positive benefit risk ratio for Seroquel XR as add-on treatment of major depressive episodes in patients with major depressive disorder, who have had suboptimal response to initial antidepressant monotherapy further to consideration of the safety profile of Seroquel.
- The CHMP concluded that the Product Information of quetiapine should reflect the current lack of long-term data of quetiapine as add-on treatment of major depressive episodes in patients with major depressive disorder, who have had suboptimal response to initial antidepressant mono-therapy and therefore recommended the amendments to the relevant sections of the Summary of Product Characteristics and Package Leaflet.

The CHMP has recommended the granting of the variation of the Marketing Authorisation(s) for which the Summary of Product Characteristics and package leaflet are set out in Annex III for Seroquel XR and associated names (see Annex I) and in accordance to the conditions set out in Annex IV.

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLET

1. NAME OF THE MEDICINAL PRODUCT

Seroquel XR 50 mg prolonged-release tablets
Seroquel XR 150 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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Seroquel XR 50 mg contains 50 mg quetiapine (as quetiapine fumarate)
Excipient : 119 mg lactose (anhydrous) per tablet
Seroquel XR 150 mg contains 150 mg quetiapine (as quetiapine fumarate)
Excipient : 71 mg lactose (anhydrous) per tablet
Seroquel XR 200 mg contains 200 mg quetiapine (as quetiapine fumarate)
Excipient : 50 mg lactose (anhydrous) per tablet
Seroquel XR 300 mg contains 300 mg quetiapine (as quetiapine fumarate)
Excipient : 47 mg lactose (anhydrous) per tablet
Seroquel XR 400 mg contains 400 mg quetiapine (as quetiapine fumarate)
Excipient : 15 mg lactose (anhydrous) per tablet

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet

Seroquel XR 50 mg tablets are peach-coloured and engraved with “XR 50” on one side
Seroquel XR 150 mg tablets are white and engraved with “XR 150” 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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Seroquel XR is indicated for:

- treatment of Schizophrenia, including
 - preventing relapse in stable schizophrenic patients who have been maintained on Seroquel XR.
- treatment of bipolar disorder :
 - For the treatment of moderate to severe manic episodes in bipolar disorder
 - For the treatment of major depressive episodes in bipolar disorder
 - For the prevention of recurrence in patients with bipolar disorder, in patients whose manic or depressive episode has responded to quetiapine treatment .
- add-on treatment of major depressive episodes in patients with Major Depressive Disorder (MDD) who have had sub-optimal response to antidepressant monotherapy (see Section 5.1). Prior to initiating treatment, clinicians should consider the safety profile of SEROQUEL XR (see Section 4.4).

4.2 Posology and method of administration

Different dosing schedules exist for each indication. It must therefore be ensured that patients receive clear information on the appropriate dosage for their condition.

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

Adults:

For the treatment of schizophrenia and moderate to severe manic episodes in bipolar disorder

Seroquel XR should be administered at least one hour before a meal. 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, however if clinically justified the dose may be increased to 800 mg daily. 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 depressive episodes in bipolar disorder

Seroquel XR should be administered at bedtime. The total daily dose for the first four days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). The recommended daily dose is 300 mg. In clinical trials, no additional benefit was seen in the 600 mg group compared to the 300 mg group (see section 5.1). Individual patients may benefit from a 600 mg dose. Doses greater than 300 mg should be initiated by physicians experienced in treating bipolar disorder. In individual patients, in the event of tolerance concerns, clinical trials have indicated that dose reduction to a minimum of 200 mg could be considered.

For preventing recurrence in bipolar disorder

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

For add-on treatment of major depressive episodes in MDD:

Seroquel XR should be administered prior to bedtime. The daily dose at the start of therapy is 50 mg on Day 1 and 2, and 150 mg on Day 3 and 4. Antidepressant effect was seen at 150 and 300 mg/day in short-term trials as add-on therapy (with amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline and venlafaxine - see Section 5.1) and at 50 mg/day in short-term monotherapy trials. There is an increased risk of adverse events at higher doses. Clinicians should therefore ensure that the lowest effective dose, starting with 50 mg/day, is used for treatment. The need to increase the dose from 150 to 300 mg/day should be based on individual patient evaluation.

Switching from Seroquel immediate-release tablets:

For more convenient dosing, patients who are currently being treated with divided doses of immediate release Seroquel tablets may be switched to Seroquel XR at the equivalent total daily dose taken once daily. Individual dosage adjustments may be necessary.

Elderly:

As with other antipsychotics and antidepressants, Seroquel XR should be used with caution in the elderly, especially during the initial dosing period. The rate of dose titration of Seroquel XR 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.

In elderly patients with major depressive episodes in MDD, dosing should begin with 50 mg/day on Days 1-3, increasing to 100 mg/day on Day 4 and 150 mg/day on Day 8. The lowest effective dose, starting from 50 mg/day should be used. Based on individual patient evaluation, if dose increase to 300 mg/day is required this should not be prior to Day 22 of treatment.

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

Children and Adolescents:

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

Renal impairment:

Dosage adjustment is not necessary in patients with renal impairment.

Hepatic impairment:

Quetiapine is extensively metabolized by the liver. Therefore, Seroquel XR should be used with caution in patients with known hepatic impairment, especially during the initial dosing period. Patients with hepatic impairment should be started on 50 mg/day. The dose can be increased in increments of 50 mg/day to an effective dose, depending on the clinical response and tolerability of the individual patient.

4.3 Contraindications

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

Concomitant administration of cytochrome P450 3A4 inhibitors, such as HIV-protease inhibitors, azole-antifungal agents, erythromycin, clarithromycin and nefazodone, is contraindicated. (See section 4.5).

4.4 Special warnings and precautions for use

As Seroquel XR is indicated for the treatment of schizophrenia, bipolar disorder and add-on treatment of major depressive episodes in patients with MDD, the safety profile should be considered with respect to the individual patient's diagnosis and the dose being administered.

Long-term efficacy and safety in patients with MDD has not been evaluated as add-on therapy, however long-term efficacy and safety has been evaluated in adult patients as monotherapy (see Section 5.1).

Children and adolescents (10 to 17 years of age)

Seroquel XR is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. Clinical trials with Seroquel have shown that in addition to the known safety profile identified in adults (see section 4.8), certain adverse events occurred at a higher frequency in children and adolescents compared to adults (increased appetite, elevations in serum prolactin and extrapyramidal symptoms) and one was identified that has not been previously seen in adult studies (increases in blood pressure). Changes in thyroid function tests have also been observed in children and adolescents.

Furthermore, the long-term safety implications of treatment with Seroquel on growth and maturation have not been studied beyond 26 weeks. Long-term implications for cognitive and behavioural development are not known.

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

Suicide/suicidal thoughts or clinical worsening:

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery. In addition, physicians should consider the potential risk of suicide-related events after abrupt cessation of quetiapine treatment, due to the known risk factors for the disease being treated.

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

Patients with a history of suicide related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta analysis of placebo controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present. In shorter-term placebo controlled clinical studies of patients with major depressive episodes in bipolar disorder an increased risk of suicide-related events was observed in young adults patients (younger than 25 years of age) who were treated with quetiapine as compared to those treated with placebo (3.0% vs. 0%, respectively). In clinical studies of patients with MDD the incidence of suicide-related events observed in young adult patients (younger than 25 years of age) was 2.1% (3/144) for quetiapine and 1.3% (1/75) for placebo.

Extrapyramidal symptoms:

In placebo controlled clinical trials of adult patients quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for major depressive episodes in bipolar disorder and major depressive disorder (see sections 4.8 and 5.1).

The use of quetiapine has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Tardive Dyskinesia:

If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of Seroquel XR should be considered. The symptoms of tardive dyskinesia can worsen or even arise after discontinuation of treatment (see Section 4.8).

Somnolence and dizziness:

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

Quetiapine treatment has been associated with orthostatic hypotension and related dizziness (see Section 4.8) which, like somnolence has onset usually during the initial dose-titration period. This could increase the occurrence of accidental injury (fall), especially in the elderly population. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medication.

Cardiovascular:

Seroquel XR should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension. Quetiapine may induce orthostatic hypotension especially during the initial dose-titration period and therefore dose reduction or more gradual titration should be considered if this occurs. A slower titration regimen could be considered in patients with underlying cardiovascular disease.

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).

Neuroleptic Malignant Syndrome:

Neuroleptic malignant syndrome has been associated with antipsychotic treatment, including quetiapine (see section 4.8). Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatinine phosphokinase. In such an event, Seroquel XR should be discontinued and appropriate medical treatment given.

Severe Neutropenia:

Severe neutropenia (neutrophil count $<0.5 \times 10^9/L$) has been uncommonly reported in quetiapine clinical trials. Most cases of severe neutropenia have occurred within a couple of months of starting therapy with quetiapine. There was no apparent dose relationship. During post-marketing experience, resolution of leucopenia and/or neutropenia has followed cessation of therapy with quetiapine. Possible risk factors for neutropenia include pre-existing low white cell count (WBC) and history of drug induced neutropenia. Quetiapine should be discontinued in patients with a neutrophil count $<1.0 \times 10^9/L$. Patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed $1.5 \times 10^9/L$). (See section 5.1).

Interactions:

See also section 4.5.

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 XR treatment should only occur if the physician considers that the benefits of Seroquel XR 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).

Weight:

Weight gain has been reported in patients who have been treated with quetiapine, and should be monitored and managed as clinically appropriate as in accordance with utilised antipsychotic guidelines (see Sections 4.8 and 5.1).

Hyperglycaemia:

Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported rarely, including some fatal cases (see section 4.8). In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. Patients treated with any antipsychotic agent including quetiapine, should be observed for signs and symptoms of hyperglycaemia, (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly.

Lipids:

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

Metabolic Risk

Given the observed changes in weight, blood glucose (see hyperglycemia) and lipids seen in clinical studies, there may be possible worsening of the metabolic risk profile in individual patients, which should be managed as clinically appropriate (see also section 4.8).

QT Prolongation:

In clinical trials and use in accordance with the SPC, quetiapine was not associated with a persistent increase in absolute QT intervals. In post marketing, QT prolongation was reported with quetiapine at the therapeutic doses (see Section 4.8) and in overdose (see Section 4.9). As with other antipsychotics, caution should be exercised when quetiapine is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also caution should be exercised when quetiapine is prescribed either with medicines known to increase QT interval, or with concomitant neuroleptics, especially 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 insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability have been described after abrupt cessation of quetiapine. Gradual withdrawal over a period of at least one to two weeks is advisable.(see section 4.8)

Elderly patients with dementia-related psychosis:

Seroquel XR 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 XR should be used with caution in patients with risk factors for stroke.

In a meta-analysis of atypical antipsychotics, 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.

Dysphagia:

Dysphagia (See section 4.8 Undesirable effects) has been reported with quetiapine. Quetiapine should be used with caution in patients at risk for aspiration pneumonia.

Venous Thromboembolism (VTE):

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

Additional information:

Quetiapine data in combination with divalproex or lithium in acute 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.

Lactose:

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

4.5 Interaction with other medicinal products and other forms of interaction

Given the primary central nervous system effects of quetiapine, Seroquel XR should be used with caution in combination with other centrally acting medicinal products 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 consume grapefruit juice while on quetiapine therapy.

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 XR 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 XR treatment should only occur if the physician considers that the benefits of Seroquel XR 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).

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 medicinal products have not been performed.

Caution should be exercised when quetiapine is used concomitantly with medicinal products known to cause electrolyte imbalance or to increase QT 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 XR 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 XR.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

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

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

<i>Blood and lymphatic system disorders</i>	
<i>Common:</i>	Leucopenia ¹
<i>Uncommon:</i>	Eosinophilia, Thrombocytopenia
<i>Unknown:</i>	Neutropenia ¹
<hr/>	
<i>Immune system disorders</i>	
<i>Uncommon:</i>	Hypersensitivity
<i>Very rare:</i>	Anaphylactic reaction ⁶
<hr/>	
<i>Endocrine disorders</i>	

<i>Common:</i>	<i>Hyperprolactinemia</i> ¹⁶
<i>Metabolism and nutritional disorders</i>	
<i>Common:</i>	Increased appetite
<i>Very rare:</i>	Diabetes Mellitus ^{1,5,6,}
<i>Psychiatric disorders</i>	
<i>Common:</i>	Abnormal dreams and nightmares Suicidal ideation and suicidal behaviour ²⁰
<i>Nervous system disorders</i>	
<i>Very common:</i>	Dizziness ^{4,17} , somnolence ^{2,17} , headache
<i>Common:</i>	Syncope ^{4,17} Extrapyramidal symptoms ^{1,21} , Dysarthria
<i>Uncommon:</i>	Seizure ¹ , Restless legs syndrome, Tardive dyskinesia ^{1,6}
<i>Cardiac disorders</i>	
<i>Common:</i>	Tachycardia ⁴
<i>Eye Disorders</i>	
<i>Common:</i>	Vision blurred
<i>Vascular disorders</i>	
<i>Common:</i>	Orthostatic hypotension ^{4,17}
<i>Rare:</i>	Venous thromboembolism ¹
<i>Respiratory, thoracic and mediastinal disorder</i>	
<i>Common:</i>	Rhinitis
<i>Gastrointestinal disorders</i>	
<i>Very common:</i>	Dry mouth
<i>Common:</i>	Constipation, dyspepsia
<i>Uncommon:</i>	Dysphagia ⁸
<i>Hepato-biliary disorders</i>	
<i>Rare:</i>	Jaundice ⁶
<i>Very rare:</i>	Hepatitis ⁶
<i>Skin and subcutaneous tissue disorders</i>	
<i>Very rare:</i>	Angioedema ⁶ , Stevens-Johnson syndrome ⁶
<i>Reproductive system and breast disorders</i>	
<i>Rare:</i>	Priapism, Galactorrhoea
<i>General disorders and administration site conditions</i>	
<i>Very common</i>	Withdrawal (discontinuation) symptoms ^{1,10}
<i>Common:</i>	Mild asthenia, peripheral oedema, irritability

Rare: Neuroleptic malignant syndrome ¹

Investigations

Very common Elevations in serum triglyceride levels ¹¹
Elevations in total cholesterol (predominantly LDL cholesterol) ¹²,
Decreases in HDL cholesterol ¹⁸, Weight gain ⁹

Common: Elevations in serum transaminases (ALT, AST) ³, decreased neutrophil count, blood glucose increased to hyperglycaemic levels ⁷

Uncommon: Elevations in gamma-GT levels ³, Platelet count decreased ¹⁴,
QT prolongation ^{1,13, 19}

Rare Elevations in blood creatine phosphokinase ¹⁵

- (1) See Section 4.4.
- (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).
- (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) Fasting blood glucose ≥ 126 mg/dL (≥ 7.0 mmol/L) or a non fasting blood glucose ≥ 200 mg/dL (≥ 11.1 mmol/L) on at least one occasion
- (8) An increase in the rate of dysphagia with quetiapine vs. placebo was only observed in the clinical trials in bipolar depression
- (9) Based on $>7\%$ increase in body weight from baseline. Occurs predominantly during the early weeks of treatment
- (10) The following withdrawal symptoms have been observed most frequently in acute placebo-controlled, monotherapy clinical trials, which evaluated discontinuation symptoms: insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability. The incidence of these reactions had decreased significantly after 1 week post-discontinuation.
- (11) Triglycerides ≥ 200 mg/dL (≥ 2.258 mmol/L) (patients ≥ 18 years of age) or ≥ 150 mg/dL (≥ 1.694 mmol/L) (patients < 18 years of age) on at least one occasion
- (12) Cholesterol ≥ 240 mg/dL (≥ 6.2064 mmol/L) (patients ≥ 18 years of age) or ≥ 200 mg/dL (≥ 5.172 mmol/L) (patients < 18 years of age) on at least one occasion. An increase in LDL cholesterol of ≥ 30 mg/dL ($\square 0.769$ mmol/L) has been very commonly observed. Mean change among patients who had this increase was 41.7 mg/dL ($\square 1.07$ mmol/L).
- (13) See text below
- (14) Platelets $\leq 100 \times 10^9/L$ on at least one occasion
- (15) Based on clinical trial adverse event reports of blood creatine phosphokinase increase not associated with neuroleptic malignant syndrome
- (16) Prolactin levels (patients > 18 years of age): > 20 $\mu\text{g/L}$ (> 869.56 pmol/L) males; > 30 $\mu\text{g/L}$ (> 1304.34 pmol/L) females at any time.
- (17) May lead to falls.
- (18) HDL cholesterol: < 40 mg/dL (1.025 mmol/L) males; < 50 mg/dL (1.282 mmol/L) females at any time.
- (19) Incidence of patients who have a QTc shift from < 450 msec to ≥ 450 msec with a ≥ 30 msec increase. In placebo-controlled trials with quetiapine the mean change and the

incidence of patients who have a shift to a clinically significant level is similar between quetiapine and placebo.

(20) Cases of suicidal ideation and suicidal behaviours have been reported during Seroquel XR therapy or early after treatment discontinuation (see Sections 4.4 and 5.1).

(21) See Section 5.1

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

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.

Children and adolescents (10 to 17 years of age)

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

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).

Metabolism and nutritional disorders

Very common: Increased appetite

Investigations

Very common: Elevations in prolactin¹, increases in blood pressure²

Nervous system disorders

Very common: Extrapyramidal symptoms³

General disorders and administration site conditions

Common: Irritability⁴

1. Prolactin levels (patients < 18 years of age): >20 ug/L (>869.56 pmol/L) males; >26 ug/L (>1130.428 pmol/L) females at any time. Less than 1% of patients had an increase to a prolactin level >100 ug/L.
2. Based on shifts above clinically significant thresholds (adapted from the National Institutes of Health criteria) or increases >20mmHg for systolic or >10 mmHg for diastolic blood pressure at any time in two acute (3-6 weeks) placebo-controlled trials in children and adolescents.
3. See .5.1.
4. Note: The frequency is consistent to that observed in adults, but irritability might be associated with different clinical implications in children and adolescents as compared to adults.

4.9 Overdose

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

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

In general, reported signs and symptoms were those resulting from an exaggeration of the active substance'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 can be indicated in severe poisonings and if possible to perform within one hour of ingestion. The administration of activated charcoal 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; Diazepines, oxazepines and thiazepines
ATC code: N05A H04

Mechanism of action:

Quetiapine is an atypical antipsychotic agent. Quetiapine and the active human plasma metabolite, norquetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and norquetiapine exhibit affinity for brain serotonin (5HT₂) and dopamine D₁- and D₂- receptors. It is this combination of receptor antagonism with a higher selectivity for 5HT₂ relative to D₂- receptors, which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal undesirable effect (EPS) liability of Seroquel compared to typical antipsychotics. Additionally, norequetiapine has high affinity for the norepinephrine transporter (NET). Quetiapine and norquetiapine also have high affinity at histaminergic and adrenergic α_1 receptors, with a lower affinity at adrenergic α_2 - and serotonin 5HT_{1A} receptors. Quetiapine has no appreciable affinity at muscarinic or benzodiazepine receptors.

Pharmacodynamic effects:

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.

In pre-clinical tests predictive of EPS, quetiapine is unlike typical antipsychotics and has an atypical profile. Quetiapine does not produce dopamine D₂-receptor supersensitivity after chronic administration. Quetiapine produces only weak catalepsy at effective dopamine D₂-receptor blocking doses. Quetiapine demonstrates selectivity for the limbic system by producing depolarisation blockade of the mesolimbic but not the nigrostriatal dopamine-containing neurones following chronic administration. Quetiapine exhibits minimal dystonic liability in haloperidol-sensitised or drug-naive Cebus monkeys after acute and chronic administration. (See Section 4.8)

Clinical efficacy:

Schizophrenia

The efficacy of Seroquel XR in the treatment of schizophrenia was demonstrated in one 6-week placebo-controlled trial in patients who met DSM-IV criteria for schizophrenia, and one active-controlled Seroquel immediate release-to-Seroquel XR switching study in clinically stable outpatients with schizophrenia.

The primary outcome variable in the placebo-controlled trial was change from baseline to final assessment in the PANSS total score. Seroquel XR 400 mg/day, 600 mg/day and 800 mg/day were

associated with statistically significant improvements in psychotic symptoms compared to placebo. The effect size of the 600 mg and 800 mg doses 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 immediate release 400 mg to 800 mg, efficacy was maintained when patients were switched to an equivalent daily dose of Seroquel XR given once daily.

In a long-term study in stable schizophrenic patients who had been maintained on Seroquel XR for 16 weeks, Seroquel XR was more effective than placebo in preventing relapse. The estimated risks of relapse after 6 months treatments was 14.3% for the Seroquel XR 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 XR 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 XR.

Bipolar Disorder

In the treatment of moderate to severe manic episodes, Seroquel demonstrated superior efficacy to placebo in reduction of manic symptoms at 3 and 12 weeks, in two monotherapy trials. The efficacy of Seroquel XR was further demonstrated with significance versus placebo in an additional 3 week study. Seroquel XR was dosed in the range of 400 to 800 mg/day and the mean dose was approximately 600 mg/day. Seroquel data in combination with divalproex or lithium in acute 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.

In a clinical trial, in patients with depressive episodes in bipolar I or bipolar II disorder, 300 mg/day Seroquel XR showed superior efficacy to placebo in reduction of MADRS total score.

In 4 additional clinical trials with quetiapine, with a duration of 8 weeks in patients with moderate to severe depressive episodes in bipolar I or bipolar II disorder, Seroquel IR 300 mg and 600 mg was significantly superior to placebo treated patients for the relevant outcome measures: mean improvement on the MADRS and for response defined as at least a 50% improvement in MADRS total score from baseline. There was no difference in magnitude of effect between the patients who received 300 mg Seroquel IR and those who received 600 mg dose.

In the continuation phase in two of these studies, it was demonstrated that long-term treatment, of patients who responded on Seroquel IR 300 or 600 mg, was efficacious compared to placebo treatment with respect to depressive symptoms, but not with regard to manic symptoms.

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

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

Major depressive episodes in MDD

Two short-term (6 week) studies enrolled patients who had shown an inadequate response to at least one antidepressant. Seroquel XR 150 mg and 300 mg/day, given as add-on treatment to ongoing antidepressant therapy (amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline or venlafaxine) demonstrated superiority over antidepressant therapy alone in reducing depressive symptoms as measured by improvement in MADRS total score (LS mean change vs. placebo of 2-3.3 points).

Long-term efficacy and safety in patients with MDD has not been evaluated as add-on therapy, however long-term efficacy and safety has been evaluated in adult patients as monotherapy (see below).

The following studies were conducted with Seroquel XR as monotherapy treatment, however Seroquel XR is only indicated for use as add-on thereapy:

In three out of four short term (up to 8 weeks) monotherapy studies, in patients with major depressive disorder, Seroquel XR 50 mg, 150 mg and 300 mg/day demonstrated superior efficacy to placebo in reducing depressive symptoms as measured by improvement in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score (LS mean change vs. placebo of 2-4 points).

In a monotherapy relapse prevention study, patients with depressive episodes stabilised on open-label Seroquel XR treatment for at least 12 weeks were randomised to either Seroquel XR once daily or placebo for up to 52 weeks. The mean dose of Seroquel XR during the randomised phase was 177 mg/day. The incidence of relapse was 14.2% for Seroquel XR treated patients and 34.4% for placebo-treated patients.

In a short-term (9 week) study non-demented elderly patients (aged 66 to 89 years) with major depressive disorder, Seroquel XR dosed flexibly in the range of 50 mg to 300 mg/day demonstrated superior efficacy to placebo in reducing depressive symptoms as measured by improvement in MADRS total score (LS mean change vs placebo -7.54). In this study patients randomised to Seroquel XR received 50 mg/day on Days 1-3, the dose could be increased to 100 mg/day on Day 4, 150 mg/day on Day 8 and up to 300 mg/day depending on clinical response and tolerability. The mean dose of Seroquel XR was 160 mg/day. Other than the incidence of extrapyramidal symptoms (see section 4.8 and 'Clinical Safety' below) the tolerability of Seroquel XR once daily in elderly patients was comparable to that seen in adults (aged 18-65 years). The proportion of randomized patients over 75 years of age was 19%.

Clinical safety

In short-term, placebo-controlled clinical trials in schizophrenia and bipolar mania the aggregated incidence of extrapyramidal symptoms was similar to placebo (schizophrenia: 7.8% for quetiapine and 8.0% for placebo; bipolar mania: 11.2% for quetiapine and 11.4% for placebo). Higher rates of extrapyramidal symptoms were seen in quetiapine treated patients compared to those treated with placebo in short-term, placebo-controlled clinical trials in MDD and bipolar depression. In short-term, placebo-controlled bipolar depression trials the aggregated incidence of extrapyramidal symptoms was 8.9% for quetiapine compared to 3.8% for placebo. In short-term, placebo-controlled monotherapy clinical trials in major depressive disorder the aggregated incidence of extrapyramidal symptoms was 5.4% for Seroquel XR and 3.2% for placebo. In a short-term placebo-controlled monotherapy trial in elderly patients with major depressive disorder, the aggregated incidence of extrapyramidal symptoms was 9.0% for Seroquel XR and 2.3% for placebo. In both bipolar depression and MDD, the incidence of the individual adverse events (eg, akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, muscle contractions involuntary, psychomotor hyperactivity and muscle rigidity) did not exceed 4% in any treatment group.

In short term, fixed dose (50mg/d to 800 mg/d), placebo-controlled studies (ranging from 3 to 8 weeks), the mean weight gain for quetiapine-treated patients ranged from 0.8 kg for the 50 mg daily dose to 1.4 kg for the 600 mg daily dose (with lower gain for the 800 mg daily dose), compared to 0.2 kg for the placebo treated patients. The percentage of quetiapine treated patients who gained $\geq 7\%$ of

body weight ranged from 5.3% for the 50 mg daily dose to 15.5% for the 400 mg daily dose (with lower gain for the 600 and 800 mg daily doses), compared to 3.7% for placebo treated patients.

Longer term relapse prevention trials had an open label period (ranging from 4 to 36 weeks) during which patients were treated with quetiapine, followed by a randomized withdrawal period during which patients were randomized to quetiapine or placebo. For patients who were randomized to quetiapine, the mean weight gain during the open label period was 2.56 kg, and by week 48 of the randomized period, the mean weight gain was 3.22 kg, compared to open label baseline. For patients who were randomized to placebo, the mean weight gain during the open label period was 2.39 kg, and by week 48 of the randomized period the mean weight gain was 0.89 kg, compared to open label baseline.

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.

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.

Children and adolescents (10 to 17 years of age)

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

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

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

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

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

Extrapyramidal Symptoms

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

Weight Gain

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

Suicide/Suicidal thoughts or Clinical worsening

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

5.2 Pharmacokinetic properties

Absorption:

Quetiapine is well absorbed following oral administration. Seroquel XR achieves peak quetiapine and norquetiapine plasma concentrations at approximately 6 hours after administration (T_{max}). Steady-state peak molar concentrations of the active metabolite norquetiapine are 35% of that observed for quetiapine.

The pharmacokinetics of quetiapine and norquetiapine are linear and dose-proportional for doses up to 800 mg administered once daily. When Seroquel XR administered once daily is compared to the same total daily dose of immediate-release quetiapine fumarate (Seroquel immediate release) administered twice daily, the area under the plasma concentration-time curve (AUC) is equivalent, but the maximum plasma concentration (C_{max}) is 13% lower at steady state. When Seroquel XR is compared to Seroquel immediate release, the norquetiapine metabolite AUC is 18% lower.

In a study examining the effects of food on the bioavailability of quetiapine, a high-fat meal was found to produce statistically significant increases in the Seroquel XR C_{max} and AUC of approximately 50% and 20% respectively. It cannot be excluded that the effect of a high fat meal on the formulation may be larger. In comparison, a light meal had no significant effect on the C_{max} or AUC of quetiapine. It is recommended that Seroquel XR is taken once daily without food.

Distribution:

Quetiapine is approximately 83% bound to plasma proteins.

Metabolism:

Quetiapine is extensively metabolised by the liver, with parent compound accounting for less than 5% of unchanged drug-related material in the urine or faeces, following the administration of radiolabelled quetiapine.

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

Quetiapine and several of its metabolites (including norquetiapine) were found to be weak inhibitors of human cytochrome P450 1A2, 2C9, 2C19, 2D6 and 3A4 activities *in vitro*. *In vitro* CYP inhibition is observed only at concentrations approximately 5 to 50 fold higher than those observed at a dose range of 300 to 800 mg/day in humans. Based on these *in vitro* results, it is unlikely that co-administration of quetiapine with other drugs will result in clinically significant drug inhibition of cytochrome P450 mediated metabolism of the other drug. From animal studies it appears that quetiapine can induce cytochrome P450 enzymes. In a specific interaction study in psychotic patients, however, no increase in the cytochrome P450 activity was found after administration of quetiapine.

Elimination:

The elimination half lives of quetiapine and norquetiapine are approximately 7 and 12 hours, respectively. Approximately 73% of a radiolabelled drug was excreted in the urine and 21% in the faeces with less than 5% of the total radioactivity representing unchanged drug-related material. The average molar dose fraction of free quetiapine and the active human plasma metabolite norquetiapine is <5% excreted in the urine.

Special populations

Gender:

The pharmacokinetics of quetiapine does not differ between men and women.

Elderly:

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

Renal impairment:

The mean plasma clearance of quetiapine was reduced by approximately 25% in subjects with severe renal impairment (creatinine clearance less than 30 ml/min/1.73 m²), but the individual clearance values are within the range for normal subjects.

Hepatic impairment:

The mean quetiapine plasma clearance decreases with approximately 25% in persons with known hepatic impairment (stable alcoholcirrhosis). 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).

Children and adolescents (10 to 17 years of age)

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

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

5.3 Preclinical safety data

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core

Cellulose, microcrystalline
Sodium citrate
Lactose monohydrate
Magnesium stearate
Hypromellose

Coating

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Polychlorotrifluoroethylene and polyvinylchloride with aluminium blister

Tablet Strength	Carton (pack) contents	Blisters
50 mg, 150 mg 200 mg, 300 mg and 400 mg tablets	<i>10 tablets</i>	<i>1 blister of 10 tablets</i>
	<i>30 tablets</i>	<i>3 blisters of 10 tablets</i>
	<i>50 tablets</i>	<i>10 blisters of 5 tablets</i>
	<i>50 tablets</i>	<i>5 blisters of 10 tablets</i>
	<i>60 tablets</i>	<i>6 blisters of 10 tablets</i>
	<i>100 tablets</i>	<i>10 blisters of 10 tablets</i>
	<i>100 tablets</i>	<i>100 blisters of 1 tablet</i>

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

- 8. MARKETING AUTHORISATION NUMBER(S)**

- 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

- 10. DATE OF REVISION OF THE TEXT**

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Seroquel XR 50 mg prolonged-release tablets
quetiapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 50 mg quetiapine (as fumarate)

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 prolonged-release tablets
30 prolonged-release tablets
50 prolonged-release tablets
60 prolonged-release tablets
100 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not split, chew or crush the tablets.
Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

{Name and Address}
<{tel}>

<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

16. INFORMATION IN BRAILLE

Seroquel XR 50 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL

1. NAME OF THE MEDICINAL PRODUCT

Seroquel XR 50 mg prolonged-release tablets
quetiapine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Seroquel XR 150 mg prolonged-release tablets
quetiapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 150 mg quetiapine (as fumarate)

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 prolonged-release tablets
30 prolonged-release tablets
50 prolonged-release tablets
60 prolonged-release tablets
100 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not split, chew or crush the tablets.
Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>

<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

16. INFORMATION IN BRAILLE

Seroquel XR 150 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL

1. NAME OF THE MEDICINAL PRODUCT

Seroquel XR 150 mg prolonged-release tablets
quetiapine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Seroquel XR 200 mg prolonged-release tablets
quetiapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200 mg quetiapine (as fumarate)

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 prolonged-release tablets
30 prolonged-release tablets
50 prolonged-release tablets
60 prolonged-release tablets
100 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not split, chew or crush the tablets.
Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

{Name and Address}
<{tel}>

<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

16. INFORMATION IN BRAILLE

Seroquel XR 200 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL

1. NAME OF THE MEDICINAL PRODUCT

Seroquel XR 200 mg prolonged-release tablets
quetiapine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Seroquel XR 300 mg prolonged-release tablets
quetiapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg quetiapine (as fumarate)

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 prolonged-release tablets
30 prolonged-release tablets
50 prolonged-release tablets
60 prolonged-release tablets
100 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not split, chew or crush the tablets.
Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

{Name and Address}
<{tel}>

<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

16. INFORMATION IN BRAILLE

Seroquel XR 300 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL

1. NAME OF THE MEDICINAL PRODUCT

Seroquel XR 300 mg prolonged-release tablets
quetiapine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Seroquel XR 400 mg prolonged-release tablets
quetiapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 400 mg quetiapine (as fumarate)

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 prolonged-release tablets
30 prolonged-release tablets
50 prolonged-release tablets
60 prolonged-release tablets
100 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not split, chew or crush the tablets.
Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

{Name and Address}
<{tel}>

<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

16. INFORMATION IN BRAILLE

Seroquel XR 400 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL

1. NAME OF THE MEDICINAL PRODUCT

Seroquel XR 400 mg prolonged-release tablets
quetiapine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

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

quetiapine

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 XR is and what it is used for
2. Before you take Seroquel XR
3. How to take Seroquel XR
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1. WHAT SEROQUEL XR IS AND WHAT IT IS USED FOR

Seroquel XR contains a substance called quetiapine. This belongs to a group of medicines called antipsychotics. Seroquel XR can be used to treat several illnesses, such as:

- Schizophrenia: where you may hear or feel things that are not there, believe things that are not true or feel unusually suspicious, anxious, confused, guilty, tense or depressed
- Mania: where you may feel very excited, elated, agitated, enthusiastic or hyperactive or have poor judgment including being aggressive or disruptive.
- Bipolar depression and major depressive episodes in major depressive disorder: where you may feel sad or you may find that you feel depressed, feel guilty, lack energy, lose your appetite or can't sleep.

When Seroquel XR is being taken to treat major depressive episodes in major depressive disorder, it will be taken in addition to another drug being used to treat this illness.

Your doctor may continue to prescribe Seroquel XR even when you are feeling better.

2. BEFORE YOU TAKE SEROQUEL XR

Do not take Seroquel XR if:

- you are allergic (hypersensitive) to quetiapine or any of the other ingredients of Seroquel XR (see section 6: Further information)
- you are taking any of the following medicines:
 - some medicines for HIV
 - azole medicines (for fungal infections)
 - erythromycin or clarithromycin (for infections)
 - nefazodone (for depression).

Do not take Seroquel XR if the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking Seroquel XR.

Take special care with Seroquel XR

Before you take your medicine, tell your doctor if:

- You, or someone in your family, have or have had any heart problems, for example heart rhythm problems or if you are taking any medicines that may have an impact on the way your heart beats.
- You have low blood pressure.
- You have had a stroke, especially if you are elderly.
- You have problems with your liver.
- You have ever had a fit (seizure).
- 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 XR.
- 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 are an elderly person with dementia (loss of brain function). If you are, Seroquel XR should not be taken because the group of medicines that Seroquel XR belongs to may increase the risk of stroke, or in some cases the risk of death, in elderly people with dementia.
- You or someone else in your family has a history of blood clots, as medicines like these have been associated with formation of blood clots.

Tell your doctor immediately if you experience:

- Fever, severe muscle stiffness, sweating or a lowered level of consciousness (a disorder called “neuroleptic malignant syndrome”). Immediate medical treatment may be needed.
- Uncontrollable movements, mainly of your face or tongue.
- Dizziness or a severe sense of feeling sleepy. This could increase the risk of accidental injury (fall) in elderly patients.

These conditions can be caused by this type of medicine.

Thoughts of suicide and worsening of your depression

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

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

Weight gain has been seen in patients taking Seroquel XR. You and your doctor should check your weight regularly.

Taking other medicines

Please tell your doctor if you are taking or have recently taken any other medicines because it may affect the way the medicines work. This includes medicines that you buy without a prescription and herbal medicines.

Do not take Seroquel XR if you are taking any of the following medicines:

- Some medicines for HIV.
- Azole medicines (for fungal infections).
- Erythromycin or clarithromycin (for infections).
- Nefazodone (for depression).

Tell your doctor if you are taking any of the following medicines:

- Epilepsy medicines (like phenytoin or carbamazepine).
- High blood pressure medicines.
- Barbiturates (for difficulty sleeping).
- Thioridazine (another anti-psychotic medicine).
- Medicines that have an impact on the way your heart beats, for example, drugs that can cause an imbalance in electrolytes (low levels of potassium or magnesium) such as diuretics (water pills) or certain antibiotics (drugs to treat infections).

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

Taking Seroquel XR with food and drink

- Seroquel XR can be affected by food and you should therefore take your tablets at least one hour before a meal or prior to bedtime.
- Be careful how much alcohol you drink. This is because the combined effect of Seroquel XR and alcohol can make you sleepy.
- Do not drink grapefruit juice while you are taking Seroquel XR. 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 before taking Seroquel XR. You should not take Seroquel XR during pregnancy unless this has been discussed with your doctor. Seroquel XR should not be taken if you are breast-feeding.

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.

Important information about some of the ingredients of Seroquel XR

Seroquel XR contains lactose which is a type of sugar. If you have been told by your doctor that you have an intolerance to some sugars, talk to your doctor before taking this medicine.

3. HOW TO TAKE SEROQUEL XR

Always take Seroquel XR 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. The maintenance dose (daily dose) will depend on your illness and needs but will usually be between 150 mg and 800 mg.

- You will take your tablets once a day.
- Do not split, chew or crush the tablets.
- Swallow your tablets whole with a drink of water.
- Take your tablets without food (at least one hour before a meal or at bedtime, your doctor will tell you when).
- Do not drink grapefruit juice while you are taking Seroquel XR . It can affect the way the medicine works.
- Do not stop taking your tablets even if you feel better, unless your doctor tells you.

Liver problems

If you have liver problems your doctor may change your dose.

Elderly people

If you are elderly your doctor may change your dose.

Children and adolescents under 18 years

Seroquel XR should not be used by children and adolescents aged under 18 years.

If you take more Seroquel XR than you should

If you take more Seroquel XR than prescribed by your doctor, you may feel sleepy, feel dizzy and experience abnormal heart beats. Contact your doctor or nearest hospital straight away. Keep the Seroquel XR tablets with you.

If you forget to take a dose of Seroquel XR

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 XR

If you suddenly stop taking Seroquel XR, you may be unable to sleep (insomnia), you may feel sick (nausea), or you may experience headache, diarrhoea, being sick (vomiting), dizziness or irritability. 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 XR can cause side effects, although not everybody gets them. If any of the following side effects get serious, or if you notice side effects not listed in this leaflet, please tell your doctor or pharmacist.

Very common (affects more than 1 in 10 people):

- Dizziness (may lead to falls), headache, dry mouth.
- Feeling sleepy (this may go away with time, as you keep taking Seroquel XR) (may lead to falls).
- Discontinuation symptoms (symptoms which occur when you stop taking Seroquel XR) include not being able to sleep (insomnia), feeling sick (nausea), headache, diarrhoea, being sick (vomiting), dizziness, and irritability. Gradual withdrawal over a period of at least 1 to 2 weeks is advisable.
- Putting on weight.

Common (affects less than 1 in 10 people):

- Rapid heartbeat.
- Stuffy nose.
- Constipation, upset stomach (indigestion).
- Feeling weak, fainting (may lead to falls).
- Swelling of arms or legs.
- Low blood pressure when standing up. This may make you feel dizzy or faint (may lead to falls).
- Increased levels of sugar in the blood.
- Blurred vision
- Abnormal muscle movements. These include difficulty starting muscle movements, shaking, feeling restless or muscle stiffness without pain.
- Abnormal dreams and nightmares
- Feeling more hungry Increased appetite
- Feeling irritated

- Disturbance in speech and language
- Thoughts of suicide and worsening of your depression

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.
- Unpleasant sensations in the legs (also called restless legs syndrome).
- Difficulty swallowing
- Uncontrollable movements, mainly of your face or tongue.

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.
- Yellowing of the skin and eyes (jaundice).
- A long-lasting and painful erection (priapism).
- Swelling of breasts and unexpected production of breast milk (galactorrhoea).
- Blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing. If you notice any of these symptoms seek medical advice immediately.

Very rare (affects less than in 10,000 people):

- Worsening of pre-existing diabetes.
- Inflammation of the liver (hepatitis)
- Severe rash, blisters, or red patches on the skin.
- A severe allergic reaction (called anaphylaxis) which may cause difficulty in breathing or shock.
- Rapid swelling of the skin, usually around the eyes, lips and throat (angioedema).

The class of medicines to which Seroquel XR belongs can cause heart rhythm problems, which can be serious and in severe cases may be fatal.

Some side effects are only seen when a blood test is taken. These include changes in the amount of certain fats (triglycerides and total cholesterol) or sugar in the blood, decreases in the number of certain types of blood cells and increases in the amount of the hormone prolactin in the blood. Increases in the hormone prolactin could in rare cases lead to the following:

- Men and women to have swelling of breasts and unexpectedly produce breast milk.
- Women to have no monthly period or irregular periods.

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

Children and adolescents

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

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

Very Common (affects more than 1 in 10 people):

- Increase in blood pressure.

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

Very Common (affects more than 1 in 10 people):

- Increase in the amount of a hormone called prolactin, in the blood. Increases in the hormone prolactin could in rare cases lead to the following:
 - Boys and girls to have swelling of breasts and unexpectedly produce breast milk
 - Girls to have no monthly period or irregular periods
 - Increased appetite
 - Abnormal muscle movements. These include difficulty starting muscle movements, shaking, feeling restless or muscle stiffness without pain.

5. HOW TO STORE SEROQUEL XR

- Keep out of the reach and sight of children.
- Do not use Seroquel XR after the expiry date which is stated on the container after EXP. The expiry date refers to the last day of that month.
- Seroquel XR does not require any special storage conditions.
- 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 XR contains

- The active substance is quetiapine. Seroquel XR tablets contain 50 mg, 150 mg, 200 mg, 300 mg or 400 mg of quetiapine (as quetiapine fumarate).
- The other ingredients are:
 Tablet core: microcrystalline cellulose, sodium citrate, lactose monohydrate, magnesium stearate, hypromellose.
 Tablet coating: hypromellose, macrogol, titanium dioxide (E171). The 50 mg, 200 mg and 300 mg tablets also contain iron oxide yellow (E172) and the 50 mg tablets contain iron oxide red (E172).

What Seroquel XR looks like and contents of the pack

All prolonged-release tablets are capsule shaped and marked with XR and the strength. 50 mg tablets are peach coloured; 150 mg tablets are white coloured, 200 mg tablets are yellow coloured; 300 mg tablets are pale yellow coloured and 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 available.

Marketing Authorisation Holder and Manufacturer

<[To be completed nationally]>

{Name and address}

<{tel}>

<{fax}>

<{e-mail}>

This medicinal product is authorised in the Member States of the EEA under the following names:

COUNTRY	TRADE NAME
Austria	Seroquel XR
Belgium	Seroquel XR
Bulgaria	Seroquel XR
Cyprus	Seroquel XR
Czech Republic	Seroquel Prolong
Denmark	Seroquel Prolong
Estonia	Seroquel XR
Finland	Seroquel Prolong
Germany	Seroquel Prolong
Greece	Seroquel XR
Hungary	Seroquel XR
Iceland	Seroquel Prolong
Ireland	Seroquel XR
Italy	Seroquel compresse a rilascio prolungato
Latvia	Seroquel XR
Lithuania	Seroquel XR
Luxembourg	Seroquel XR
Malta	Seroquel XR
Netherlands	Seroquel XR
Norway	Seroquel Depot
Poland	Seroquel XR
Portugal	Seroquel SR
Romania	Seroquel XR
Slovakia	Seroquel XR
Slovenia	Seroquel SR
Spain	Seroquel Prolong
Sweden	Seroquel Depot
United Kingdom	Seroquel XL

This leaflet was last approved in {MM/YYYY}.

ANNEX IV
CONDITIONS OF THE MARKETING AUTHORISATION

National Competent Authorities, coordinated by the Reference Member State, shall ensure that the following conditions are fulfilled by the Marketing Authorisation Holders:

- Update the protocols for the following ongoing Post Authorisation Safety Studies (PASSs) to collect long-term safety data of quetiapine XR in MDD patients:
 - Modified Prescription Event Monitoring (M-PEM) Study;
 - General Practice Research Database (GPRD) Study;

The amended protocols should be submitted to the Reference Member State within two months of the CHMP Opinion on this referral procedure.

- Perform the following new PASS studies in MDD patients to further characterise the long-term safety and use of quetiapine XR, including the specialist care setting:
 - Swedish Record Linkage Study (SE-RLS) in accordance with an agreed protocol. The protocol should be submitted to the Reference Member State within two months of the CHMP Opinion on this referral procedure.
 - Perform new EU Multi-Country Drug Utilisation Study (EU DUS) in accordance with an agreed protocol. The protocol should be submitted to the Reference Member State within two months of the CHMP Opinion on this referral procedure.
- An updated version of the Risk Management Plan should be submitted by 30th September 2010 in line with the annual submission of the Period Safety Update Report for Seroquel XR and reflecting the above conditions.