Joint Public Assessment Report for paediatric studies submitted in accordance with Article 45 and 46 of Regulation (EC) No1901/2006, as amended

Seroquel (quetiapine)

Article 45 UK/W/0004/pdWS/001

Article 46 NL/W/0004/pdWS/001

Marketing Authorisation Holder: Astra Zeneca B.V.

Rapporteur:	UK (Article 45) and NL (Article 46)
Finalisation procedure (day 120):	7 December 2009
Date of finalisation of PAR	9 September 2013

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Seroquel
INN (or common name) of the active substance(s):	quetiapine
MAH:	AstraZeneca
Currently approved indication IR formulation	Treatment of schizophrenia. 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.
Pharmaco-therapeutic group (ATC Code):	Antipsychotics; diazepines, oxazepines, thiazepines and oxepines (N05AH04)
Pharmaceutical form(s) and strength(s):	Immediate-release tablets (25 mg, 100 mg, 150 mg, 200 mg and 300 mg)

I. EXECUTIVE SUMMARY

SmPC and PL changes are proposed in sections 4.2, 4.4, 4.8 and 5.1.

Summary of outcome

☐ No change

☒ Change

☐ New study data: sections 4.4, 4.8, 5.1 and 5.2.

☒ New safety information: sections 4.4, 4.8 and 5.1

☐ Paediatric information clarified: sections 4.2, 4.4, 4.8 and 5.1

☐ New indication:

II. RECOMMENDATION

Pharmacokinetic (PK) data were provided on a small group of children (10-12 years) and adolescents, who were in steady state treatment of 400 mg quetiapine BID (IR formulation). Based on PK data alone, no dose recommendations can be made for paediatric and adolescent patients, as tolerability and efficacy might be different in these age groups, even if the plasma levels would be within the range of adults.

Autism
The data provided are limited to a small number of patients, are open-label, and did not indicate efficacy. The data submitted by the MAH do not add robust efficacy or safety data and do not merit being included in the product information.

Schizophrenia and manic episodes
Four studies with Seroquel IR in children and adolescents were assessed.
These studies show evidence for efficacy in children and adolescents with mania and adolescents with schizophrenia. However, long-term efficacy was not demonstrated for either indication. No European patients were included.
One study included patients with co-morbid ADHD, presenting difficulty in disentangling the effect on mania and ADHD. Furthermore, no dose finding studies were carried out and hence the minimal effective dose cannot be determined.

The safety results obtained in the studies mentioned above suggest that quetiapine treatment of paediatric patients is associated with some specific adverse effects that were either not encountered in adults or have higher frequency in children than in adults, or have more adverse implications for children compared to adults. Specifically these include increased appetite and increased weight with potential consequences for *e.g.* diabetes, elevation in serum prolactin with potential consequences for sexual development, and increases in blood pressure. Changes in thyroid function tests have also been observed in children and adolescents.
In addition, incidence of extrapyramidal symptoms (EPS) related symptoms was higher compared to adults. Furthermore, other AEs that were encountered in children in similar

incidence to those found in adults may have different and more far reaching consequences for children as compared to adults.

The rapporteurs concluded that the information gathered from the studies should be summarised in sections 4.2, 4.4, 4.8 and 5.1 (see section V of this report: ‘Member states overall conclusion and recommendation.’)

III. INTRODUCTION

For quetiapine (innovator product: Seroquel) data from studies in paediatric patients are available for autism, schizophrenia and manic episodes. These studies are subject to the paediatric regulation. For some of the studies an article 45 procedure applies, whereas for the others article 46 applies. The UK is Rapporteur for the article 45 procedure, and the Netherlands are Rapporteur for the article 46 procedure.

Article 45 was published by the CMD(h) on September 2008 for paediatric studies already completed by 26 January 2007. The article 46 worksharing procedure is applicable only to paediatric studies completed after 26 January 2007, which corresponds to the date of entry into force of the Paediatric Regulation.

Quetiapine is an atypical antipsychotic agent, available as immediate release formulation (25 mg, 100 mg, 150 mg, 200 mg and 300 mg tablets) and prolonged release formulation (50 mg, 150 mg, 200 mg, 300 mg and 400 mg tablets). It is licensed for the treatment of schizophrenia and the treatment of manic and major depressive episodes associated with bipolar disorders in adults. It is not licensed for use in children. The SmPC states in section 4.2 that 'The safety and efficacy of Seroquel have not been evaluated in children and adolescents'.

A previous EU-Worksharing project assessment of paediatric data (finalised 15 September 2008) with the Netherlands as Rapporteur and the UK as Co-Rapporteur assessed data from two pharmacokinetic studies in children and adolescents (D1441C00028, 5077IL/0038) and limited clinical efficacy data of one pilot, open-label study (N=15) in adolescents. A safety signal was identified and consequently two full study reports were requested and submitted as part of this EU-Worksharing project assessment of paediatric data (D1441C00112, D1441C00149).

The conclusion of the procedure was as follows:
'Pharmacokinetics
The subgroups analyses for different age groups (10-12 years old and adolescents) revealed that, compared to adults, 44-84% overexposure of the active N-desalkyl metabolite occurs in children whereas exposure to the parent drug is similar. When assessed per kg BW, these differences between adults and children disappeared. Relative overexposure of the metabolite was also observed in the adolescents, but to lesser extent. Lower levels of the parent drug were observed in adolescents compared to adults. Whether the increased exposure to N-desalkyl quetiapine in the paediatric and adolescent subjects is a result of increased formation or decreased elimination remain unclear.
Based on the PK outcomes alone, no conclusions could be drawn for the dosing; when doses are lowered for children to overcome the high exposure of the active metabolite, the parent dose levels may become too low again. Safety and efficacy conclusions could neither be extrapolated from adults based on the plasma levels only.
The company's proposal postponing the final decision about the dosing and the wording of 5.2 till the complete dataset of all on-going paediatric clinical trials is known, is agreed (submission expected last trimester of 2008).

Clinical efficacy/safety
Until the data from the upcoming type II variation(s) are available, no revisions are recommended to the currently approved text in the SmPC which states 'The safety and efficacy of Seroquel have not been evaluated in children and adolescents.'
Because of the suicidality signal identified in the 2 'pivotal' short-term trials, the MAH is requested to specifically address the suicidality in a variation application. Should the submission

of the variation application be delayed, then the MAH should submit a paediatric suicidality review no later than 31 January 2009.'

The above mentioned variation application was submitted in the third quarter of 2008. The outcome of this variation application was that the following sections of the SmPC have been amended: 4.4 and 4.8.

SPC

Section 4.4

Suicide/suicidal thoughts or clinical worsening:

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

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

Section 4.8

Blood and lymphatic system disorders	
Uncommon:	Thrombocytopenia
Psychiatric disorders	
Common:	Abnormal dreams and nightmares
Investigations	
Uncommon:	Platelet count decreased
Rare:	Elevations in blood creatine phosphokinase

Package leaflet

Section 2

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. 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.

Section 4

Possible side effects

Common: abnormal dreams and nightmares

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the studies

Seroquel immediate-release tablets were used in the studies.

IV.2 Clinical aspects

1. Introduction

The MAH submitted final reports for:

- Study D1441C00028: an investigation of the PK profile in paediatric and adolescent patients, receiving similar doses as recommended in adults;
- Study 112: A 6 week, double-blind, placebo-controlled randomized study in 222 children and adolescents (13-17) diagnosed with schizophrenia;
- Study 149: A 3 week, double-blind, placebo-controlled randomized study in 284 children and adolescents (10-17) with mania;
- Study 150: An open label extension of studies 112 and 149 that had the primary aim to assess the safety and tolerability of quetiapine;
- Study 9025: An open label efficacy and safety study of 6 weeks duration with adolescents (15-18) with schizophrenia.

In addition, the MAH provided a Clinical Expert Opinion and two publications on treatment of children and adolescents with autistic disorder.

2. Clinical studies

Pharmacokinetics

General characteristics PK of quetiapine (in adults)
Quetiapine is rapidly absorbed from the IR formulation. Bioavailability is practically complete. As could be expected for a lipophylic drug, quetiapine is widely distributed (10 L/kg). Protein binding is approximately 85%. The major metabolic pathway is sulfoxidation to quetiapine sulfoxide, mediated by CYP3A4. Next relevant pathway is N-desalkylation, resulting in N-desalkyl quetiapine (also called norquetiapine). Oxidation to 7-hydroxy quetiapine, mediated by CYP2D6, is a minor pathway. The 7-hydroxy and N-desalkyl metabolites are biologically active. Half-life is approximately 6-7 h in adults.

STUDY D1441C0028

- **Description**

In this study, the PK profile of Seroquel IR (immediate-release) tablets was investigated in paediatric and adolescent patients, receiving similar doses as recommended in adults. The participating psychiatric patients were gradually uptitrated till maximal 400 mg BID within 11 days. Starting dose was 50 mg.
Samples were taken at Day 7, after the 200 mg morning dose, and at Day 13, when patients were at steady-state for 400 mg BID. Samples were drawn at pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 5, 8 and 12 h after the morning dose.

- Study population /Sample size

Twenty-eight patients were enrolled in this study. Data from 24 subjects (50% 10-12 years old, 50% 13-17) were available for PK analyses. One subject withdrew prior to dosing. Three additional subjects withdrew from the study while on treatment, prior to completion of the study (1 for QTc prolongation (which was in fact a misinterpretation of the ECG), 1 for substance abuse, and 1 for personal reasons). Three subjects in the 10- to 12-year age group were unable to tolerate daily doses above 600 mg and remained on 600 mg per day from Day 11 onwards.

As shown in the table below, overweight was common in this population which had been treated with other antipsychotics before.

		Age group			
		10-12 yrs		13-17 yrs	
Characteristic		n=13		n=14	
Weight (kg)	Mean (SD)	54.2	(10.2)	62.7	(11.9)
	Median	54.4		61.5	
	Min-max	36-66		45-81	
BMI (kg/m^2)	Mean (SD)	24.2	(4.7)	22.7	(2.1)
	Median	25.0		23.0	
	Min-max	16–31		20–26	

- Statistical Methods

Log-transformed paediatric PK data were compared to adolescent and historical adult data, using ANOVA.

➢ Results

- Pharmacokinetic outcomes

As shown in table S1 below, quetiapine displays dose-linear kinetics in children and adolescents. Like in adults, quetiapine was rapidly absorbed with tmax at 1-1.5 hours after dosing, and t1/2 was approximately 6 hours. Children aged 10-12 had approximately 35% higher plasma levels (and consequently a 35% lower clearance capacity) compared to the group of adolescents (See table S1 and figure 1 below). A trend was observed that Clearance was linearly and inverse related to body-weight.

Of note, the CL/F for the 3 subjects in the 10- to 12-year-old group whose daily dose was restricted to 600 mg, ranged from 42 - 218 L/hr. This was within the range of CL/F values observed for the other 21 subjects in the study (*i.e.*, 26 - 272 L/hr).

Table S1 **Selected pharmacokinetic parameters for quetiapine in subjects who received the 400-mg morning dose**

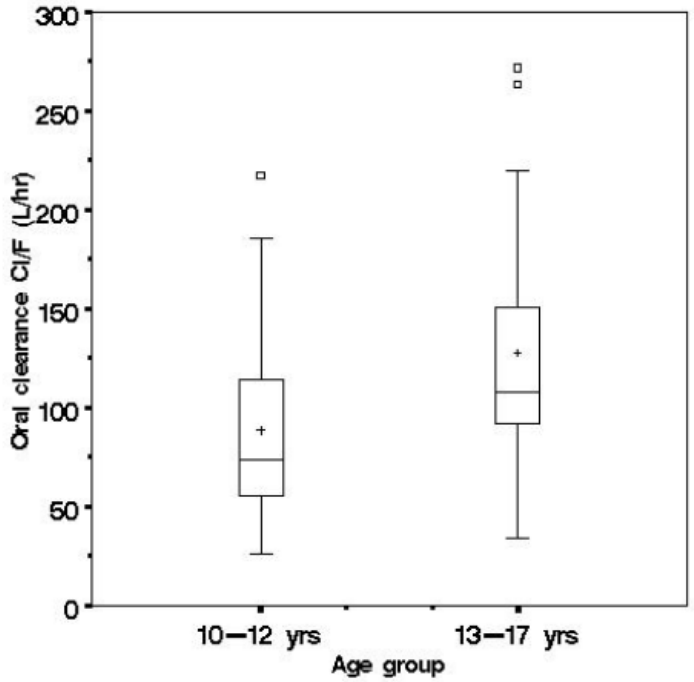
		Age group					
		10-12 yrs (n=9)[a]		13-17 yrs (n=12)		Total (n=21)[a]	
PK parameter	Statistic	Day 7 (200 mg)	Day 13 (400 mg)	Day 7 (200 mg)	Day 13 (400 mg)	Day 7 (200 mg)	Day 13 (400 mg)
AUC_{ss} (ng*hr/mL)	Geometric Mean	2560.0	5145.0	1651.4	3784.8	1992.8	4317.1
	CV (%)	56.8	29.1	64.5	46.6	65.0	42.4
$C_{ss,max}$ (ng/mL)	Geometric Mean	707.0	1426.3	414.3	924.7	520.9	1113.4
	CV (%)	37.5	33.9	69.4	51.6	63.9	49.8
t_{max} (hr)	Median	1.08	1.50	1.57	1.50	1.50	1.50
	Minimum	1.00	1.00	0.52	0.55	0.52	0.55
	Maximum	2.00	2.00	3.00	2.00	3.00	2.00
$t_{1/2}$ (hr)	Mean	3.17	5.52	2.77[b]	5.52[b]	2.96[c]	5.52[c]
	SD	0.99	1.38	0.56	0.77	0.80	1.07

[a] Number of subjects who received 400-mg morning dose on Day 13.
[b] Excludes 2 of 12 subjects for whom $t_{1/2}$ could not be calculated.
[c] Excludes 2 of 21 subjects for whom $t_{1/2}$ could not be calculated.
AUC_{ss} area under the curve at steady-state. $C_{ss,max}$ the maximum plasma concentration at steady-state. $t_{1/2}$ terminal elimination half-life.

Table 11.2.1.1.1 Summary statistics for quetiapine pharmacokinetic parameter estimates - PK evaluable subjects who received 400 mg morning dose on Day 13

		Age Group					
		10-12 (N=9)		13-17 (N=12)		All (N=21)	
Pharmacokinetic Parameter		Day 7	Day 13	Day 7	Day 13	Day 7	Day 13
AUC (ng*hr/mL)	N	9	9	12	12	21	21
	Mean	2944.446	5324.121	1962.911	4143.432	2383.569	4649.442
	SD	1911.482	1406.690	1383.731	1956.123	1662.026	1804.024
	Minimum	1302.25	3024.48	735.90	1517.21	735.90	1517.21
	Median	2443.15	5404.50	1806.18	3860.78	1860.32	4267.48
	Maximum	7603.48	7371.14	5821.13	9273.16	7603.48	9273.16
	Geometric Mean	2560.018	5144.961	1651.433	3784.823	1992.752	4317.077
	CV(%)	56.825	29.120	64.538	46.617	65.048	42.348
Cmax (ng/mL)	N	9	9	12	12	21	21
	Mean	755.667	1496.667	498.583	1016.083	608.762	1222.048
	SD	338.116	498.322	338.859	422.324	354.793	506.771
	Minimum	449.00	810.00	150.00	288.00	150.00	288.00
	Median	658.00	1400.00	396.00	989.00	570.00	1190.00
	Maximum	1590.00	2300.00	1260.00	1880.00	1590.00	2300.00
	Geometric Mean	707.001	1426.254	414.267	924.704	520.917	1113.416
	CV(%)	37.455	33.860	69.351	51.606	63.852	49.802
tmax (hr)	N	9	9	12	12	21	21
	Minimum	1.00	1.00	0.52	0.55	0.52	0.55
	Median	1.08	1.50	1.57	1.50	1.50	1.50

Fig 1. Whisker box plots of oral clearance (CL/F) of quetiapine on Day 7 and Day 13 by age group

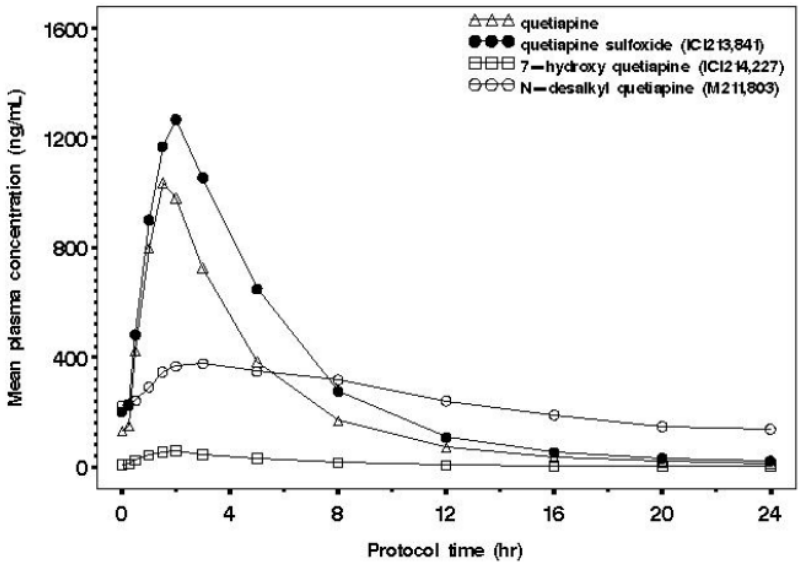


- Metabolites

Except for the parent drug, samples were analysed for 3 metabolites. In terms of in vivo exposure, the rank order of exposure with respect to both AUCss and Css,max was:

Quetiapine sulfoxide>quetiapine>N-desalkyl quetiapine>7-hydroxy quetiapine (see also fig 4 below).

Fig 2. Mean plasma concentrations of quetiapine and 3 metabolites over time on Day 13 for subjects who received the 400-mg morning dose



Exposure to active metabolite N-desalkyl quetiapine in terms of AUCss and Css,max appeared to be ± 30% higher in 10- to 12-year old subjects than in 13- to 17-year-old subjects.

- Comparison to adult data

The MAH compared data of children and adolescents of Study D1441C00028 to adult reference values. In children, quetiapine levels were similar to adults, although in adolescents lower levels were observed. In contrast, the plasma levels of the active metabolite N-desalkyl quetiapine were considerable higher in both children and adolescents compared to adults.

Table 1 **Comparison of dose-normalized AUC and Cmax of quetiapine and N-desalkyl quetiapine from children (10-12 years old) and adolescents (13-17 years old) compared to adults (adult data from Study D1441C00130)**

	Comparison: Children[a] (10-12 years old) / Adults		Comparison: Adolescents[b] (13-17 years old) / Adults		Comparison: Pooled[c] paediatric patients (10-17 years old) / Adults	
	GLS Mean Ratio	90% CI	GLS Mean Ratio	90% CI	GLS Mean Ratio	90% CI
AUC (quetiapine)	1.06	0.86, 1.26	0.73	061, 0.88	0.88	0.76, 1.03
C_{max} (quetiapine)	1.16	0.99, 1.35	0.72	0.60, 0.86	0.92	0.79, 1.06
AUC (N-desalkyl quetiapine)	1.62	1.44, 1.84	1.28	1.12, 1.47	1.45	1.30, 1.61
C_{max} (N-desalkyl quetiapine)	1.49	1.27, 1.75	1.14	0.96, 1.35	1.31	1.15, 1.49

When corrected for body weight, complete different ratio's between adult and children/adolescent data were observed: After correction per kg BW, quetiapine levels were relatively low in children/adolescents, whereas N-desalkyl quetiapine levels were comparable.

Table 2 **Comparison of dose- and weight-normalized AUC and Cmax of quetiapine and N-desalkyl quetiapine from children (10-12 years old) and adolescents (13-17 years old) compared to adults (adult data from Study D1441C00130)**

	Comparison: Children[a] (10-12 years old) / Adults		Comparison: Adolescents[b] (13-17 years old) / Adults		Comparison: Pooled[c] paediatric patients (10-17 years old) / Adults	
	GLS Mean Ratio	90% CI	GLS Mean Ratio	90% CI	GLS Mean Ratio	90% CI
AUC (quetiapine)	0.65	0.53, 0.80	0.53	0.43, 0.65	0.59	0.50, 0.70
C_{max} (quetiapine)	0.72	0.60, 0.85	0.52	0.43, 0.63	0.61	0.53, 0.71
AUC (N-desalkyl quetiapine)	1.00	0.87, 1.15	0.92	0.79, 1.06	0.96	0.86, 1.07
C_{max} (N-desalkyl quetiapine)	0.92	0.78, 1.09	0.82	0.69, 0.98	0.87	0.76, 1.00

The MAH concluded that no clear conclusions could be drawn based on the paediatric/adolescent data, because of observed large variability in PK values and small group sizes.

However, inter-individual variability was 20-33% for N-dealkyl metabolite data in children and adolescents, and this relatively moderate level of variability does not indicate that comparisons between different age groups would be invalid.
Correcting the AUC and Cmax levels by both dose and body weight (BW) obscures the relationship between adult and paediatric data. AUC and Cmax data reflect the observed plasma concentrations, and it is not meaningful to report them by kg BW. In the SmPC, uncorrected values will be reported.

Clinical efficacy

Autism

The supporting data include a Clinical Expert Opinion and two publications:

1. Findling RL et al, Quetiapine in nine youths with autistic disorder, J Child Adolesc Psychopharmacol. 2004 Summer;14(2):287-94
2. Martin A et al, Open-label quetiapine in the treatment of children and adolescents with autistic disorder, J Child Adolesc Psychopharmacol. 1999;9(2):99-107

Findling RL et al, Quetiapine in nine youths with autistic disorder, J Child Adolesc Psychopharmacol. 2004 Summer;14(2): 287-94
This was a 12-week, open-label study, in medically healthy patients with autistic disorder aged 10 to 17 years. Quetiapine treatment was gradually increased over the first 6 weeks of the study to a total daily dose of 300 mg/day. Doses could then be increased to a maximum daily dose of 750 mg/day. Outcome measures included the Children's Psychiatric Rating Scale (CPRS) and the Clinical Global Impressions (CGI) scale. RESULTS: Nine boys were enrolled. Although improvements in several symptom domains were observed on quetiapine, only 2 patients met a priori criteria for response ("much" or "very much improved" on the Clinical Global Impressions-Improvement Scale). In addition, only these same 2 patients' parents/guardians chose to continue quetiapine pharmacotherapy after study participation. The authors conclude that quetiapine may not be a particularly effective agent in the treatment of adolescent patients with autistic disorder.

Martin A et al, Open-label quetiapine in the treatment of children and adolescents with autistic disorder, J Child Adolesc Psychopharmacol. 1999;9(2): 99-107
This was a 16-week, open-label trial that was prematurely terminated. It included 6 boys (mean age 10.9 +/- 3.3 years) meeting DSM-IV criteria for autistic disorder and mentally retarded (mild, n = 2; moderate, n = 3; severe, n = 1). Behavioural ratings were obtained at baseline and every four weeks thereafter. There was no statistically significant improvement between baseline and endpoint. Only two subjects completed 16 weeks of treatment and were considered "responders" by the global improvement item of the Clinical Global Impression Scale (CGIS). Dosages ranged from 100 to 350 mg/day (1.6-5.2 mg/kg/day). Subjects dropped out prematurely because of lack of response and sedation, limiting further dose increases (n = 3), and because of a possible seizure during the fourth week of treatment (n = 1). Other significant side effects included behavioural activation, increased appetite and weight gain (range, 0.9 to 8.2 kg). The authors conclude that quetiapine was poorly tolerated and associated with serious side effects in this clinical population.

In conclusion, the publications show that the available data are limited to a small number of patients, are open-label, and did not indicate efficacy. The reported adverse events are contained in the product information. The data submitted by the MAH do not add robust efficacy or safety data and do not merit being included in the product information.

Schizophrenia and manic episodes

Four studies with Seroquel IR in children and adolescents were assessed: D1441C00112 (112), D1441C00149 (149), D1441C00150 (150), and IIT 5077/9025 (9025).

D1441C00112
This was a 6 week, double-blind, placebo-controlled randomized study in 222 children and adolescents (13-17) diagnosed with schizophrenia. Patients were recruited in centers located in the US, EU, Asia, and South Africa. The primary objective of study 112 was to compare the efficacy of 2 doses of quetiapine (400 mg/day and 800 mg/day) with that of placebo in the treatment of schizophrenia in adolescent patients as assessed by the change from baseline to Day 42 in the PANSS total score (primary outcome variable).

Key eligibility criteria for enrolment into this study included: male or female patients aged 13 to 17 years at randomization, either hospitalized or outpatient, DSM-IV criteria for schizophrenia (confirmed by the K-SADS-PL), PANSS score of ≥60 and a score of 4 or greater on at least 1 of the items for delusions (P1), conceptual disorganizations (P2), or hallucinations (P3).
Key exclusion criteria included: Secondary DSM-IV Axis I diagnoses of Bipolar Disorders including Cyclothymia, Schizophreniform Disorder, Schizoaffective Disorder, Psychotic Disorder Not Otherwise Specified (NOS), acute Post-traumatic Stress Disorder (PTSD), premorbid intelligence quotient (IQ) <70 or diagnosis of mental retardation, psychosis judged to be the direct physiological consequence of a medical condition or treatment or of an abused medication or substance, history of any serious suicide attempt that required medical intervention or current suicidal risk that could not be safely managed as determined by the clinical judgment of the investigator, known intolerance for or lack of response to quetiapine, as judged by the investigator, and contraindications as detailed in country-specific prescribing information for quetiapine.
Patients began study treatment on the evening of Day 1 with a single dose of quetiapine 50 mg or matching placebo. Beginning on Day 3, blinded study drug was given twice daily at 100 mg/day, with dose escalation thereafter of 100 mg/day. Patients randomized to the 400 mg/day group reached the target dose of quetiapine or matching placebo by Day 5. Patients randomized to the 800 mg/day group reached the target dose of quetiapine or matching placebo by Day 9.

The mean age of patients in the study was 15.4 years and 58.6% were male. Out of the 222 randomised patients, 164 (73.9%) completed the study.
At screening, the majority of patients (at least 67.6% in each treatment group) had a “schizophrenia, paranoid” DSM-IV diagnosis. Among the remaining patients, the most common DSM-IV diagnosis was “schizophrenia, undifferentiated” (21.8% overall with a similar distribution among treatment groups). Approximately 10% of the patients in each treatment group had a comorbid diagnosis of Attention-Deficit Hyperactivity Disorder (ADHD).
Of all randomized patients, 76.7% of 400 mg/day quetiapine-treated patients, 82.4% of 800 mg/day quetiapine-treated patients, and 62.7% of placebo-treated patients completed the study. Development of study-specific discontinuation criteria was the most common reason for discontinuation of 400 mg/day quetiapine-treated patients and placebo-treated patients, while AE was the most common reason for discontinuation of 800 mg/day quetiapine-treated patients.

The primary efficacy results of the study are presented in the table below.

Table O 3 **Summary of primary efficacy results (PANSS change from baseline) in paediatric patients with schizophrenia (MMRM analysis, ITT population, Study 112)**

Outcome Variable	Treatment group				
	Quetiapine 400 mg/day (N=73)	Quetiapine 800 mg/day (N=74)	Placebo (N=75)	Quetiapine 400 mg/day vs Placebo	Quetiapine 800 mg/day vs Placebo
PANSS total score – LS mean change from baseline					
Day 7	-8.23	-8.80	-6.65	-1.58; p=0.410	-2.16; p=0.214
Day 14	-14.24	-16.09	-10.09	-4.15; p=0.098	-6.00; p=0.012
Day 42 (primary)	-27.31	-28.44	-19.15	-8.16; p=0.043	-9.29; p=0.009

LS Least squares. ITT intent to treat. MMRM mixed model repeated measures. PANSS Positive and Negative Syndrome Scale.
Data derived from Table S3 in CSR 112, Module 5.

Results for the ITT analysis with LOCF are presented in the table below:

Outcome Variable	**Quetiapine 400mg/day (N=73)**	**Quetiapine 800mg/day (N=74)**	**Placebo (N=75)**	**Quetiapine 400 mg/day vs. Placebo (95% CI)**	**Quetiapine 800 mg/day vs. Placebo**
Improvement on YMRS total score Day 42 (primary)	-24.0	-26.1	-16.8	-7.24 (-14.02 , -0.47); p=0.036	-8.71 (-15.45 , -1.96); p=0.012
Responders (>=30% reduction from baseline on the PANSS)	38%	37%	26%		

D1441C00149
This was a 3 week, double-blind, placebo-controlled randomized study in 284 children and adolescents (aged 10-17) with mania. Patients were recruited in 34 centres in the US. This study was designed to compare the efficacy and safety of 2 fixed doses of quetiapine (400 mg/day and 600 mg/day) with placebo, in children (aged 10 to 12 years inclusive) and adolescent patients (aged 13 to 17 years inclusive) with mania. Randomization was stratified by age group (10 to 12 years or 13 to 17 years), such that within each age stratum, the ratio of patients in the 3 treatment groups was 1:1:1. The primary outcome variable was the change from baseline in YMRS (Young Mania Rating Scale) total scores at Day 21.

Key eligibility criteria for enrolment included: male or female patients aged 10 to 17 years at randomization, either hospitalized or outpatient, DSM-IV criteria for Bipolar I mania confirmed by the K-SADS-PL, patients with rapid cycling or who experienced a first manic episode, patients could also have had a secondary diagnosis of ADHD and - if judged necessary by the investigator - have continued psychostimulant treatment if the prescribed dose had been stable for ≥30 days preceding randomization. Patients must also have had a YMRS score of ≥20 both at screening and at randomization (Day 1).

Key exclusion criteria included diagnosis of a current DSM-IV Axis I disorder with the exception of those noted in the inclusion criteria. Excluded diagnoses included Tourette's Disorder,

Obsessive-Compulsive Disorder (OCD), acute (<3 months) posttraumatic stress disorder (PTSD), Panic Disorder, and Pervasive Developmental Disorders (e.g. Autistic Disorder and Asperger's Disorder). In addition, patients were excluded who had: premorbid intelligence quotient (IQ) <70 or diagnosis of mental retardation, psychosis judged to be the direct physiological consequence of a medical condition or treatment or of an abused medication or substance, current manic episode judged to be the direct physiological effect of psychostimulant or antidepressant medication, history of any serious suicide attempt that required medical intervention or current suicidal risk that cannot be safely managed as determined by the clinical judgment of the investigator, known intolerance for or lack of response to quetiapine (as judged by the investigator) substance abuse or dependence, use of haloperidol decanoate, fluphenazine decanoate or risperidone microspheres within 1 dosing interval prior to randomization, laboratory test results outside the reference range and considered by the investigator to be clinically significant, or concurrent cognitive-behavioral therapy initiated within 6 weeks prior to randomization.

Patients began study treatment on the evening of Day 1 with a single dose of quetiapine 50 mg or matching placebo. Beginning on Day 3, blinded study drug was given twice daily at 100 mg/day, with dose escalation thereafter of 100 mg/day. Patients randomized to the 400 mg/day group reached the target dose of quetiapine or matching placebo by Day 5. Patients randomized to the 600 mg/day group reached the target dose of quetiapine or matching placebo by Day 7.

Of the 393 patients recruited, 284 patients were randomized to treatment and 283 patients were analysed for safety, of which 277 were analysed for efficacy in the ITT analysis set and 215 in the PP set. The mean patient age was approximately 13 years, and there was similar distribution of the age groups (10-12 years and 13-17 years) among the 3 treatment groups. There were a slightly higher percentage of males (56%) than females, and approximately 75% of patients in all 3 treatment groups were Caucasian.
At screening, the majority of patients (approximately 77% in each treatment group) had a "most recent manic" DSM-IV diagnosis. There were similar DSM-IV diagnoses across treatment groups, and very few patients had a mixed diagnosis. Approximately 45% of the patients in each treatment group had a comorbid diagnosis of ADHD.

The primary efficacy results of the study are presented in the table below.

Table O 4 Summary of primary efficacy results (YMRS change from baseline) in paediatric patients with mania (MMRM analysis, ITT population, Study 149)

Outcome Variable	Treatment group				
	Quetiapine 400 mg (N=93)	Quetiapine 600 mg (N=95)	Placebo (N=89)	Quetiapine 400 mg vs Placebo	Quetiapine 600 mg vs Placebo
YMRS total score – LS mean change from baseline					
Day 4	-8.05	-6.84	-5.01	-3.05; p=0.015	-1.83; p=0.120
Day 7	-11.88	-11.83	-6.78	-5.10; p<0.001	-5.05; p<0.001
Day 21 (primary)	-14.25	-15.60	-9.04	-5.21; p<0.001	-6.56; p<0.001

LS Least squares. ITT intent to treat. MMRM mixed model repeated measures. YMRS Young Mania Rating Scale.
Data derived from Table S3 in CSR 149, Module 5.

Results for the ITT analysis with LOCF are presented in the table below:

Outcome Variable	**Quetiapine 400 mg/day (N=93)**	**Quetiapine 800 mg/day (N=95)**	**Placebo (N=89)**	**Quetiapine 400 mg/day vs. Placebo (95% CI)**	**Quetiapine 800 mg/day vs. Placebo**
Improvement on YMRS total score Day 21 (primary)	-13.2	-15.1	-8.6	-5.15 (-7.93 , -2.36); p=0.01	-6.90 (-9.66 , -4.13); p=0.01
Responders (>=50% reduction from baseline on the YMRS)	54%	56%	28%		

D1441C00150
This was an open label extension of studies 112 and 149 that had the primary aim to assess the safety and tolerability of quetiapine. The duration of this study was 26 weeks. A total of 381 patients were enrolled in this study of whom 380 were included in the safety population (205 patients had bipolar I disorder and 175 had schizophrenia). Altogether, 125 patients with schizophrenia (71.0% of enrolled) completed the study and 112 patients with bipolar I disorder (54.6% of enrolled).

Efficacy measures showed continued improvements during the 26 weeks of open label treatment in both schizophrenia and mania patients. The mean open label baseline PANSS score for the total schizophrenia population was 73.1. By Week 26, the mean decrease from open label baseline was -9.8 points. The mean open label baseline YMRS score for the total bipolar I disorder population was 16.3. By Week 26, the mean decrease from open label baseline was -3.5 points.

5077/9025
This was an open label efficacy and safety study of 6 weeks duration with adolescents (15-18) with schizophrenia. A total of 16 patients were included in this study; 11 remained after 6 weeks. The primary efficacy outcome was change from baseline in the PANSS positive and negative symptoms. Secondary outcome included assessment of safety.
The results showed reductions in both the negative and the positive symptoms over the 6 weeks of treatment. On the positive scale the reduction was from a mean of 28.7 to 18.2 and on the negative scale from 36.0 to 25.0. No formal statistical test was carried out due to the pilot nature of the study and the small number of patients.
The safety evaluation showed that 14 patients experienced a total of 48 different AEs. One severe AE occurred: depression followed by a suicide attempt. The most frequently reported AEs were psychiatric disorders (24), heart rate and rhythm disorders (8), general disorders (6), and central and peripheral nervous disorders (%).

Clinical safety

<u>Schizophrenia and manic episodes</u>

Extent of exposure
In the schizophrenia study (Study 112; 6 weeks duration), study completion rates were 82% for the quetiapine 800 mg/day group (out of 74 randomised), 77% for the quetiapine 400 mg/day group (out of 73 randomised), and 63% for the placebo group (out of 75 randomised). The mean duration of exposure to study medication was 40 days for the both quetiapine groups (800 mg/day or 400 mg/day), and 37 days for the placebo group.
In the mania study (Study 149; 3 weeks duration), study completion rates were 82% for the quetiapine 600 mg/day group (out of 95 randomised), 80% for the quetiapine 400 mg/day group

(out of 93) and 73% for the placebo group (out of 89). The mean duration of exposure to study medication was 20 days for the quetiapine 600 mg/day group, 21 days for the quetiapine 400 mg/day group, and 20 days for the placebo group.
In the open label 26 weeks study (Study 150), 62.4% of the 380 treated patients completed the study, including 71% of the patients with schizophrenia and 55% of the patients with bipolar disorder. The mean duration of exposure to quetiapine was 146 days (median 181 days) overall.

Since the adverse event profile in paediatric patients with schizophrenia was similar to that to paediatric patients with mania, the results of these two studies are combined in table O5.
Table O 5 presents the most common AEs occurring in all paediatric patients in placebo-controlled studies (Studies 112 and 149), and table O6 presents the most common AEs in the open-label, uncontrolled extension study (Study 150).

Table O 5 **Number (%) of patients in Studies 112 (schizophrenia) and 149 (mania) with the most commonly reported adverse events (pooled safety analysis set)**

	Quetiapine 400 mg/day to 800 mg/day (N=340)		Placebo (N=165)	
Preferred term	**n**	**%**	**n**	**%**
Somnolence	100	29.4	14	8.5
Sedation	55	16.2	7	4.2
Dizziness	52	15.3	6	3.6
Headache	50	14.7	28	17.0
Fatigue	30	8.8	7	4.2
Increased appetite	26	7.6	4	2.4
Dry mouth	24	7.1	1	0.6
Insomnia	23	6.8	24	14.5
Nausea	23	6.8	17	10.3
Tachycardia	23	6.8	0	
Vomiting	22	6.5	9	5.5
Agitation	19	5.6	16	9.7
Weight increased	17	5.0	2	1.2

NOTE: This table uses a cutoff of 5% within the quetiapine treatment group. Data are ordered by descending incidence in the quetiapine group.
Derived from Table SA 01.

Table O 6 **Number (%) of patients in Study 150 with the most commonly reported adverse events (safety population)**

	Quetiapine 400 mg/day to 800 mg/day (N=380)	
Preferred term	**n**	**%**
Somnolence	87	22.9
Headache	71	18.7
Sedation	54	14.2
Weight increased	51	13.4
Vomiting	41	10.8
Nausea	36	9.5
Dizziness	33	8.7
Fatigue	31	8.2
Insomnia	31	8.2
Increased appetite	27	7.1
Upper respiratory tract infection	26	6.8
Agitation	20	5.3
Irritability	19	5.0
Tachycardia	19	5.0

NOTE: This table uses a cutoff of 5% for the total safety population. Data are ordered by descending incidence in the total safety population.
Derived from Table 39, CSR 150, Module 5.3.5.2.

The AEs occurring with an incidence of ≥5% and at least twice the placebo incidence in the placebo-controlled studies (studies 112 and 149) were: somnolence, sedation, dizziness, fatigue, increased appetite, dry mouth, tachycardia, and weight increased. These observations are generally consistent with the adverse event profile of quetiapine in adults described in the current adult labelling, except for the higher rate of “increased appetite”. The increased rate of this AE was especially pronounced in patients 10-12 years old (quetiapine = 14% vs. placebo = 0). In the combined safety population that included studies 112, 149, 150 and PK study 38, the rate of “increased appetite” was 10.5%.

In the open-label extension Study 150, the profile of most commonly reported adverse events was similar to that seen in the acute placebo-controlled studies, though the frequency of some of these events is higher in the long-term study. This may be due to the longer duration of exposure (i.e. increased appetite is reflected in weight gain in the long-term study). Similar to the acute studies, “increased appetite” occurred more frequently in paediatric patients compared to the current adult label.

Death and serious adverse events (SAEs)
There were no deaths in any of the 3 studies.

The incidence of serious adverse events in the quetiapine treated groups was similar to that observed in the placebo groups.

Adverse events leading to discontinuation
In both placebo controlled studies there were more AEs leading to discontinuation in the active arms compared to placebo. In study 112 this was 8% in the quetiapine group compared to 3% in placebo and in study 149 this was 11% vs. 4%. Psychiatric disorders, nervous system disorders, sedation, fatigue, irritability, syncope, and somnolence were the most common types of AE leading to discontinuation.
In the long-term study there were more discontinuations due to AEs among the bipolar disorder patients (12.7%) than among the schizophrenia patients (6.3%). Irritability was the most frequently reported AE that led to discontinuation (6 patients, 1.6%), followed by psychiatric disorder, sedation, tachycardia and weight increase, each of which were experienced by 3 patients (0.8%).

Clinical laboratory, vital sign, and ECG data
Increases in serum prolactin and blood pressure were observed at a higher frequency in the quetiapine treated patients than in placebo. These increases had not been observed in the adult's trials (blood pressure) or were observed in higher frequency in children and adolescents.
For prolactin, the rate of shifts from a normal prolactin level at baseline to an elevated value at any time in males was 13.4% in the quetiapine group vs. 4.0% the placebo. In females, the rate was 8.7% in the quetiapine group vs. 0.0% in placebo. In Study 150, 6.3% of patients shifted from a normal prolactin level at open label baseline to an elevated value at any time. And the rate of such shift in the total safety population was 11%.

For blood pressure, clinically important increases in systolic blood pressure were observed in 15% of the quetiapine treated patients vs. 6% in placebo. For diastolic blood pressure, this was 17% vs. 7%.

In addition, changes in leukocytes, lipids, heart rate and weight gain were observed that are similar to the adult profile of quetiapine safety.

In addition, safety issues specific for quetiapine were focused on: EPS, suicidality, QTc prolongation, neutropenia, syncope, and diabetes.

In study 150 hypertension has been reported 4 times.

EPS. The results of this examination indicated that the incidence of adverse events potentially related to extrapyramidal symptoms (EPS) was higher in quetiapine-treated patients compared to placebo in both adolescents and children and in both schizophrenia and bipolar mania studies. EPS related symptoms included: akathisia, tremor, extrapyramidal disorder, hypokinesia, restlessness, psychomotor hyperactivity, muscle rigidity, and dyskinesia. Such increase in EPS symptoms was not observed in the adult's trials. Specifically, the incident of EPS related symptoms in the study 112 was: 13.5% in the 800 mg group and, 12.3% in the 400 mg group compared to 5.3% in placebo. In study 149, the incident was 3.1% in the 600 mg group; 4.2% in the 400 mg group compared to 1.1% in placebo. In study 150, the incident was 10% (38 patients), including 20 (11.4%) patients with schizophrenia, and 18 (8.8%) with bipolar disorder. Three of these AEs were judged to be severe in intensity by the investigator, and 1 patient discontinued due to severe akathisia.

Suicidality. No patient committed suicide during any of the quetiapine paediatric studies. Columbia-type suicidality analysis in the pooled short-term safety population identified 11 patients (3.2%) in the quetiapine group compared to 2 (1.2%) in the placebo group with events that were possibly related to suicidality. These rates are similar to the rates found by the FDA analysis of the pooled data from short-term placebo controlled studies of antidepressant drugs in

children and adolescents, where the rate was 4% in the antidepressants treated groups compared to 2% in placebo.

The findings with respect to the other safety issues: although there were 5 patients with QT prolongations in the long-term study, none of these patients met the predefined criteria for clinically important QTc prolongation. With respect to neutropenia, there were 5 cases with AEs that were potentially associated with neutropenia of whom 2 were judged to be severe in intensity and 1 was listed as a serious AE. In addition, there were higher rates of AEs related to syncope and to diabetes in the quetiapine treated group compared to placebo. Altogether, the rates of these safety issues specific to quetiapine (QTc prolongation, neutropenia, syncope, and diabetes) were similar to what is already known regarding the safety profile of quetiapine in adults.

3. Discussion on clinical aspects

Although the studies show evidence for efficacy in children and adolescents with mania and adolescents with schizophrenia, long-term efficacy has not been shown and no dose finding studies were conducted. Moreover, certain adverse events (increased appetite, elevations in serum prolactin, and extrapyramidal symptoms) occurred at a higher frequency in children and adolescents compared to adults.
In conclusion, based on the results of pharmacokinetic, efficacy and safety studies, use in paediatric or adolescent patients cannot be recommended.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

Pharmacokinetic (PK) data were provided on a small group of children (aged 10-12 years) and adolescents, who were in steady state treatment of 400 mg quetiapine BID (IR formulation). In children, C_{max} of the parent drug was in the high ranges as reported in adults (with normal liver/renal function), and the active metabolite norquetiapine levels were approximately 50% higher compared to adults. The PK profile in adolescents was similar to adults, except for the fact that metabolite levels were slightly increased. No dose recommendations can be made for paediatric and adolescent patients based on PK data alone, as tolerability and efficacy might be different in these age groups, even if the plasma levels would be within the range of adults.

Autism
The data provided are limited to a small number of patients, are open-label, and did not indicate efficacy. The reported adverse events (AEs) are contained in the product information.
The data submitted by the MAH do not add robust efficacy or safety data and do not merit being included in the product information.

Schizophrenia and manic episodes
Four studies with Seroquel IR in children and adolescents were assessed: D1441C00112, D1441C00149, and D1441C00150, and IIT 5077/9025.

These studies show evidence for efficacy in children and adolescents with mania and adolescents with schizophrenia. However, there are several weaknesses regarding clinical efficacy. These include:
- The fact that long-term efficacy was not demonstrated for either indication

- Study 149 (mania) included only patients in the US and no European patients were included.
- Study 149 included patients with co-morbid ADHD, presenting difficulty in disentangling the effect on the 2 disorders (mania and ADHD) in this study.
- No dose finding studies were carried out and hence the minimal effective dose cannot be determined.

The safety results obtained in the studies mentioned above suggest that quetiapine treatment of paediatric patients is associated with some specific adverse effects that were not encountered in adults. Specifically these include increased appetite and increased weight with potential consequences for e.g. diabetes, elevation in serum prolactin with potential consequences for sexual development, 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.

In addition, incidence of extrapyramidal symptoms (EPS) related symptoms was higher compared to adults. Furthermore, other AEs that were encountered in children in similar incidence to those found in adults (i.e. somnolence, sedation, dizziness, fatigue, increased appetite, weight gain, dry mouth, tachycardia, changes in leukocytes, lipids, and increased heart rate) may have different and more far reaching consequences for children as compared to adults.

Based on the study results assessed, Seroquel is not recommended for use in paediatric or adolescent patients.

➢ Recommendation

The rapporteurs concluded that the information gathered from the studies should be summarised in sections 4.2, 4.4, 4.8, 5.1 and 5.2 as indicated below.

4.2 Posology and method of administration

Children and Adolescents:
{Product name} 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 is presented in sections 4.4, 4.8, 5.1 and 5.2.

4.4 Special warnings and precautions for use
Children and adolescents (10 to 17 years of age)
{Product name} 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 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 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, 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).

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

4.8 Undesirable effects

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]

11. Triglycerides ≥200mg/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 ≥240mg/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 (≥0.769 mmol/L) has been very commonly observed. Mean change among patients who had this increase was 41.7 mg/dL (≥1.07 mmol/L).

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 prolactin[1], increases in blood pressure[2]
Nervous system disorders	
Very common:	Extrapyramidal symptoms[3]
General disorders and administration site conditions	
Common:	Irritability[4]

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.

5.1 Pharmacodynamic properties

Children and adolescents (10 to 17 years of age)
The efficacy and safety of quetiapine 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 quetiapine were excluded. Treatment with quetiapine 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 Quetiapine 400 mg/day and –6.56 for Quetiapine 600 mg/day. Responder rates (YMRS improvement ≥50%) were 64% for Quetiapine 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 Quetiapine 400 mg/day and –9.29 for Quetiapine 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 ≥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 Quetiapine 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 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 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 of schizophrenia and bipolar mania, the aggregated incidence of treatment-emergent EPS was 10%.

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

Suicide/Suicidal thoughts or Clinical worsening
In short-term placebo-controlled clinical trials 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 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

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

The PL has been revised as follows:

Section 3
Children and adolescents under 18 years
Seroquel should not be used by children and adolescents aged under 18 years.

Section 4
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 patient in 10):
- Increase in blood pressure.

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

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

- 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.