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

Seroquel (quetiapine)

NL/W/0004/pdWS/002

Marketing Authorisation Holder: Astra Zeneca B.V.

Rapporteur:	NL
Finalisation procedure (day 120):	17 December 2012
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(s)	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. Prior to initiating treatment, clinicians should consider the safety profile of Seroquel XR.
Pharmaco-therapeutic group (ATC Code):	Antipsychotics; diazepines, oxazepines, thiazepines and oxepines (N05AH04)
Pharmaceutical form(s) and strength(s):	Seroquel XR: Prolonged release tablets, 50/150/200/300/400 mg

I. EXECUTIVE SUMMARY

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

II. RECOMMENDATION

The paediatric study conducted with Seroquel XR in the treatment of children and adolescents (10-17) with bipolar depression failed to show significant efficacy results. Seroquel XR is currently not indicated for use in children and adolescents and the results of the trial do not change the negative benefit-risk balance in the paediatric population. It is however supported that the SmPC is updated with safety information regarding suicidality, vomiting, rhinitis and syncope, in sections 4.2, 4.4, 4.8, and 5.1, as this information is considered relevant for the prescriber (see section V of this report: 'Member states overall conclusion and recommendation.')

III. INTRODUCTION

In April 2012 the MAH submitted a completed paediatric study for Seroquel XR, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A clinical study summary has also been provided.

The MAH proposes several changes to the SmPC and patient information leaflet based on the results of this study. The MAH claims that the results of the study do not alter the overall safety and tolerability profile of Seroquel and that the benefit/risk profile remains positive.

IV. SCIENTIFIC DISCUSSION

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

Seroquel is a new generation antipsychotic containing quetiapine. The immediate-release (IR) formulation was first licensed in 1997 for the treatment of schizophrenia in adult patients.
Subsequently, quetiapine IR was licensed for the treatment of bipolar mania, bipolar depression and bipolar maintenance in adult patients.
The extended release formulation (XR) of quetiapine was subsequently developed to allow for a once-daily administration.
Seroquel XR is currently indicated for the treatment of schizophrenia, bipolar mania, bipolar depression, bipolar maintenance, major depressive disorder and generalized anxiety disorder in adult patients.

The submitted study used daily doses of quetiapine XR 150 to 300 mg/day.

IV.2 Clinical aspects

1. Introduction

The MAH submitted a final report concerning a paediatric study in with children and adolescence with bipolar depression.

2. Clinical study

Study D144AC00001
An 8-week, Multicenter, Double-blind, Randomized, Parallel-group, Placebo-controlled Study of the Efficacy and Safety of Quetiapine Fumarate (Seroquel®) Extended-release in Children and Adolescent Subjects with Bipolar Depression

➢ Description

The MAH submitted a final report for a paediatric clinical study which was carried out in 42 study centers in 7 countries (United States 29, India 3, Colombia 3, Serbia 3, Mexico 2, South Africa 1, and Taiwan 1).

➢ Methods

- Objectives

To evaluate the efficacy and safety of quetiapine XR 150 to 300 mg/day in the treatment of children and adolescents (10-17) with bipolar depression. Additional objectives included assessment of specific safety areas including: adverse events (AEs) of extrapyramidal symptoms (EPS), QTc prolongation, somnolence, suicidality, neutropenia/agranulocytosis and thyroid function.

- Study design

The study had an up to 35-day enrolment period (including a washout period lasting 7 to 28 days), 8-week double-blind treatment period with 1 of 2 treatment regimens (quetiapine XR 150 to 300 mg/day or placebo), 1-week safety follow-up period, 2- to 4-week safety follow-up period for patients with BP >95th percentile at completion/discontinuation visit, and a recall visit.

- Study population /Sample size

Eligible patients (male or female children and adolescents aged 10 to 17 years, inclusive), with a clinically established diagnosis of bipolar I or bipolar II disorder (current or most recent episode depressed) were enrolled. A Children's Depression Rating Scale-Revised (CDRS-R) total score of ≥45 and Young Mania Rating Scale (YMRS) total score ≤16 were required at both Visit 1 (screening) and Visit 2 (randomization) after washout of current medications.
Ninety-two patients were needed to provide 85% power to reject the null hypothesis of no difference assuming a true difference of 4 points on CDRS-R and a standard deviation of 9 when using a 2-sided t-test at a significance level of 5%.
There were 262 patients enrolled and 193 patients randomized from 42 study centers in 7 countries. Of the 193 patients randomized to the study, 99.5% (192/193 patients) received treatment, 74.6% (144/193 patients) completed the study, and 25.4% (49/193 patients) discontinued from the study.
Overall, the most common reason for study discontinuation was AEs (7.8%, 15/193 patients). The number and percentage of patients who discontinued due to AEs was higher in the placebo group (12.0%, 12/100 patients) than in the quetiapine group (3.2%, 3/93 patients). In general, baseline demographic data were similar in both treatment groups. Most patients enrolled in this study were white (65.1%), with a higher percentage of patients in the 13-17 year age group (72.4%). The mean weight and body mass index (BMI) at baseline were similar in both treatment groups.

- Treatments

Quetiapine XR was studied at doses ranging from 150 to 300 mg/day. Study medication (quetiapine or placebo) was administered orally, once daily in the evening. Study medication was titrated up in 50 mg increments to reach the expected therapeutic dose of 150 mg over 3 days. The dose was to be increased to 300 mg in a step-wise manner if there was deterioration.

- Outcomes/endpoints

- Primary: Change from baseline in the CDRS-R total score to final assessment (day 57).
- Secondary:
    - Efficacy:
        - Proportion of remission, defined as CDRS-R total score ≤28 at final assessment (Day 57)
        - Proportion of response, defined as >=50% reduction in CDRS-R total score from baseline to final assessment
    - Safety:
        - AEs, discontinuation due to AEs, SAEs, death
        - AEs of EPS and other specific safety areas, including QTc prolongation, somnolence, suicidality, neutropenia/agranulocytosis, and thyroid function

- Statistical Methods

All statistical comparisons were based on a 2-sided significance level of 5%, unless otherwise specified. Secondary analyses reported nominal 5% levels of significance. No other correction to the reported p-values was made for the analysis of secondary measures.

➢ Results

- Patients' dispositions

The disposition of patients in this study is summarized in Table 6.

There were 262 patients enrolled and 193 patients randomized from 42 study centers in 7 countries. Of the 193 patients randomized to the study, 192 (99.5%) received treatment, 74.6% (144/193 patients) completed the study. Approximately an equal proportion of patients discontinued the study in the active and placebo group (24.7% and 26% respectively).

Table 6 Patient disposition (All patients)

	Number (%) of patients		
	Quetiapine XR 150 to 300 mg/day (N=93)	**Placebo (N=100)**	**Total (N=193)**
Patients enrolled[a]	NA	NA	262
Patients randomized	93 (100)	100 (100)	193 (100)
Patients who were not randomized	NA	NA	69
Incorrect enrollment[b]	NA	NA	56 (81.2)
AE[b]	NA	NA	1 (1.4)
Voluntary discontinuation by patient or parent/guardian[b]	NA	NA	11 (15.9)
Patient lost to follow-up[b]	NA	NA	1 (1.4)
Patients who received treatment	92 (98.9)	100 (100)	192 (99.5)
Patients who did not receive treatment[c]	1 (1.1)	0	1 (0.5)
Patients who completed study	70 (75.3)	74 (74.0)	144 (74.6)
Patients who discontinued study[c]	23 (24.7)	26 (26.0)	49 (25.4)
AE	3 (3.2)	12 (12.0)	15 (7.8)
Patient lost to follow-up	5 (5.4)	1 (1.0)	6 (3.1)
Voluntary discontinuation by patient or parent/guardian	2 (2.2)	4 (4.0)	6 (3.1)
Severe non-compliance to protocol	2 (2.2)	4 (4.0)	6 (3.1)
Lack of therapeutic response	4 (4.3)	1 (1.0)	5 (2.6)
Other	4 (4.3)	1 (1.0)	5 (2.6)
Condition under investigation worsened	1 (1.1)	3 (3.0)	4 (2.1)
Incorrect enrollment	1 (1.1)	0	1 (0.5)
Safety reasons	1 (1.1)	0	1 (0.5)

AE adverse event; NA not applicable.
[a] Informed consent received.
[b] The percentages are based on the total number of patients who were not randomized.
[c] Excluding patients who were not randomized.
Note: The percentages are based on the total number of patients randomized within each treatment group.
Note: The data presented in this table are for all patients who completed the study as scheduled at Visit 10 or early discontinuation (ie, before the recall visit).
Derived from Table 11.1.1.1

- Baseline data

In general, baseline demographic data were similar in both treatment groups. Most patients enrolled in this study were white (65.1%), with a higher percentage of patients in the 13-17 year age group (72.4%). The mean weight and body mass index (BMI) at baseline were similar in both treatment groups.

Table 9 Demographic characteristics (Safety analysis set)

Demographic characteristic	Quetiapine XR 150 to 300 mg/day (N=92)	Placebo (N=100)	Total (N=192)
Age (years)			
n	92	100	192
Mean (SD)	13.9 (2.18)	14.0 (2.05)	14.0 (2.11)
Median	14.0	14.0	14.0
Min	10	10	10
Max	17	17	17
Age group (years), n (%)			
10-12 years old	25 (27.2)	28 (28.0)	53 (27.6)
13-17 years old	67 (72.8)	72 (72.0)	139 (72.4)
Sex, n (%)			
Male	45 (48.9)	52 (52.0)	97 (50.5)
Female	47 (51.1)	48 (48.0)	95 (49.5)
Race, n (%)			
White	65 (70.7)	60 (60.0)	125 (65.1)
Black or African American	14 (15.2)	21 (21.0)	35 (18.2)
Other	6 (6.5)	9 (9.0)	15 (7.8)
Asian	4 (4.3)	6 (6.0)	10 (5.2)
American Indian or Alaska Native	3 (3.3)	4 (4.0)	7 (3.6)
Ethnic group, n (%)			
Not applicable	43 (46.7)	38 (38.0)	81 (42.2)
African-American	14 (15.2)	21 (21.0)	35 (18.2)
Other	14 (15.2)	18 (18.0)	32 (16.7)
Hispanic or Latino	13 (14.1)	14 (14.0)	27 (14.1)
Native American	4 (4.3)	3 (3.0)	7 (3.6)
Asian (other than Chinese or Japanese)	3 (3.3)	3 (3.0)	6 (3.1)
Chinese	1 (1.1)	3 (3.0)	4 (2.1)
Weight (kg)			
n	92	100	192
Mean (SD)	65.4 (24.60)	63.6 (23.23)	64.5 (23.85)

Demographic characteristic	Quetiapine XR 150 to 300 mg/day (N=92)	Placebo (N=100)	Total (N=192)
Median	59.5	59.0	59.0
Min	28	27	27
Max	177	151	177
BMI (kg/m^2)			
n	92	100	192
Mean (SD)	24.5 (7.4)	24.2 (7.2)	24.4 (7.3)
Median	21.994	22.893	22.688
Min	15	13	13
Max	55	50	55

BMI body mass index; Max maximum; Min minimum; SD standard deviation.
Note: The percentages were based on the total number of safety patients within each treatment group.
Derived from Table 11.1.4.1

Psychiatric diagnosis at baseline was similar in the 2 treatment groups as indicated in table 11.1.4.5

Table 11.1.4.5 Psychiatric diagnosis (Safety analysis set)

	Quetiapine XR 150 to 300 mg/day (N=92) n (%)	Placebo (N=100) n (%)	Total (N=192) n (%)
Psychiatric disorder as confirmed by the K-SADS-PL scale			
Bipolar I disorder, most recent episode depressed (codes 296.5 to 296.54)	75 (81.5%)	79 (79.0%)	154 (80.2%)
Bipolar II disorder (code 296.89)	17 (18.5%)	21 (21.0%)	38 (19.8%)
If Bipolar I disorder,			
Most recent episode depressed, unspecified (code 296.5)	6 (8.0%)	2 (2.5%)	8 (5.2%)
Most recent episode depressed, mild (code 296.51)	5 (6.7%)	3 (3.8%)	8 (5.2%)
Most recent episode depressed, moderate (code 296.52)	55 (73.3%)	62 (78.5%)	117 (76.0%)
Most recent episode depressed, severe without psychotic features (code 296.53)	7 (9.3%)	11 (13.9%)	18 (11.7%)
Most recent episode depressed, severe with psychotic features (code 296.54)	2 (2.7%)	1 (1.3%)	3 (1.9%)
Number of patients with a DSM-IV secondary diagnosis of ADHD			
No	54 (58.7%)	54 (54.0%)	108 (56.3%)
Yes, without concomitant used of psychostimulant medications	38 (41.3%)	46 (46.0%)	84 (43.8%)
Yes, with concomitant used of psychostimulant medications	0	0	0
If yes (whether concomitant used of psychostimulant medications or not), ADHD Type			
Predominantly inattentive type (code 314)	9 (23.7%)	12 (26.1%)	21 (25.0%)
Combined type (code 314.01)	25 (65.8%)	33 (71.7%)	58 (69.0%)
Predominately hyperactive-impulsive type (code 314.01)	3 (7.9%)	1 (2.2%)	4 (4.8%)
NOS (code 314.9)	1 (2.6%)	0	1 (1.2%)
Number of rapid/non-rapid cycler patients			
Rapid cycler	22 (23.9%)	23 (23.0%)	45 (23.4%)
Non rapid cycler	70 (76.1%)	77 (77.0%)	147 (76.6%)

Note: The percentages are based on the total number of safety patients with available data within each treatment group.

- Efficacy results

Primary endpoint – Change from baseline in the CDRS-R total score at day 57

Table 11 indicates that the mean reduction in CDRS-R total scores was -29.6 for quetiapine XR and -27.3 for placebo. The difference between the treatment groups was not statistically significant (p=0.252).

Table 11 Change from baseline to Day 57 for CDRS-R total score - OC (mITT analysis set)

Variable	Statistic	Quetiapine XR 150 to 300 mg/day (N=92)	Placebo (N=100)
Baseline score	Mean (SD)	61.6 (9.93)	60.1 (9.01)
Change from baseline	Mean (SD)	-31.9 (14.86)	-28.8 (14.76)
	LS mean (SE)	-29.6 (1.65)	-27.3 (1.60)
Difference between quetiapine XR and placebo	LS mean (SE)	-2.29 (1.99)	
	95% CI	(-6.22, 1.65)	
	p-value	0.252	

CI confidence interval; LS least squares; SD standard deviation; SE standard error.
Note: Treatment comparisons were tested using a MMRM with baseline CDRS-R total score as covariate, age stratum, treatment group, time point, and treatment group-by-time point interaction as fixed effects; and center and patients within treatment group as random effects.
Derived from Tables 11.2.1.1.1 and 11.2.1.1.2

Secondary endpoints

At Day 57, the remission rate was 45.7% for quetiapine XR and 34.0% for placebo. The odds ratio (1.60) between the treatment groups was not statistically significant (p=0.156).
The proportion of patients with response (defined as ≥50% reduction from baseline in CDRSR total score) at Day 57 was 63.0% for quetiapine XR and 55.0% for placebo. The odds ratio (1.2) between the treatment groups was not statistically significant (p=0.625).

It should be noted that Seroquel XR is currently not indicated for use in children and adolescents. In this study efficacy in children and adolescents with bipolar depression was not demonstrated.

- Safety results

No deaths occurred during the study.
Five patients reported serious adverse events (SAEs) during the study (1 in the quetiapine XR group and 4 in the placebo group). The incidence of SAEs was higher in the placebo group (4.0%) than in the quetiapine XR group (1.1%).

A total of 134 patients experienced at least 1 treatment-emergent adverse event (TEAE) during the treatment period (68 patients in the quetiapine XR group and 66 patients in the placebo group). The incidence of TEAEs was higher in the quetiapine XR group (73.9%) than in the placebo group (66.0%).
Discontinuation from the study due to an AE was higher in the placebo group (12.0%) than in the quetiapine XR group (3.3%).
The most common non-serious TEAEs by system/organ class and preferred term (*i.e.* those preferred terms reported by ≥2% of patients in either treatment group) are summarized in Table 14 and sorted by decreasing incidence in the quetiapine XR group.

Table 14 **Non-serious TEAEs occurring in ≥2% of patients in either treatment group by SOC and preferred term (Safety analysis set)**

System organ class Preferred term	Number (%) of patients Quetiapine XR 150 to 300 mg/day (N=92)	 Placebo (N=100)
Patients with any TEAE	68 (73.9)	66 (66.0)
Nervous system disorders	35 (38.0)	27 (27.0)
Headache	20 (21.7)	12 (12.0)
Sedation	7 (7.6)	6 (6.0)
Dizziness	6 (6.5)	2 (2.0)
Somnolence	6 (6.5)	4 (4.0)
Infections and infestations	23 (25.0)	12 (12.0)
Influenza	4 (4.3)	1 (1.0)
Nasopharyngitis	4 (4.3)	3 (3.0)
Gastroenteritis	3 (3.3)	0
Sinusitis	3 (3.3)	0
Urinary tract infection	3 (3.3)	0
Ear infection	2 (2.2)	0
Upper respiratory tract infection	1 (1.1)	2 (2.0)
GI disorders	21 (22.8)	13 (13.0)
Diarrhoea	5 (5.4)	1 (1.0)
Nausea	5 (5.4)	1 (1.0)
Vomiting	3 (3.3)	3 (3.0)
Abdominal pain	2 (2.2)	3 (3.0)
Abdominal pain upper	2 (2.2)	1 (1.0)
Constipation	2 (2.2)	1 (1.0)
Gastrooesophageal reflux disease	2 (2.2)	0
General disorders and administration site conditions	12 (13.0)	11 (11.0)
Fatigue	5 (5.4)	2 (2.0)
Irritability	2 (2.2)	5 (5.0)
Pyrexia	2 (2.2)	1 (1.0)
Thirst	2 (2.2)	0
Influenza like illness	0	2 (2.0)

Table 14 **Non-serious TEAEs occurring in ≥2% of patients in either treatment group by SOC and preferred term (Safety analysis set)**

System organ class Preferred term	Number (%) of patients Quetiapine XR 150 to 300 mg/day (N=92)	Placebo (N=100)
Psychiatric disorders	11 (12.0)	8 (8.0)
Insomnia	2 (2.2)	0
Nightmare	2 (2.2)	2 (2.0)
Metabolism and nutrition disorders	6 (6.5)	7 (7.0)
Increased appetite	3 (3.3)	3 (3.0)
Decreased appetite	2 (2.2)	2 (2.0)
Respiratory, thoracic and mediastinal disorders	4 (4.3)	6 (6.0)
Epistaxis	3 (3.3)	0
Cough	0	3 (3.0)
Oropharyngeal pain	0	2 (2.0)
Reproductive system and breast disorders	3 (3.3)	4 (4.0)
Dysmenorrhoea	2 (2.2)	2 (2.0)
Skin and subcutaneous tissue disorders	2 (2.2)	2 (2.0)
Dermatitis contact	2 (2.2)	1 (1.0)
Injury, poisoning and procedural complications	1 (1.1)	6 (6.0)
Orthodontic appliance complication	0	2 (2.0)
Blood and lymphatic system disorders	1 (1.1)	2 (2.0)
Neutropenia	0	2 (2.0)

GI gastrointestinal.
Note: Number (%) of patients is presented by decreasing order of frequency in the quetiapine XR group.
Note: Coding was based on MedDRA version 12.0.
Note: A patient was counted at most once within a preferred term.
Note: The number and percentage of patients with MedDRA preferred terms that occurred in <2% of patients are not presented in this table but are represented in the SOC totals.
Derived from Tables 11.3.2.3 and 11.3.2.5

Most commonly occurring AEs in both treatment groups were Nervous System Disorder events. The incidence rate for Nervous System Disorders was higher in the quetiapine XR group than in the placebo group: 38.0% (35/92) vs. 27% (27/100), respectively. Headache and sedation were the most frequently reported AEs in this category for both treatment groups.
Gastrointestinal disorders (*i.e.* diarrhoea and nausea), fatigue, Infections and Infestations (*i.e.* influenza, nasopharyngitis, gastroenteritis, sinusitis, urinary tract infection and ear infection) and psychiatric disorders were more frequent with quetiapine XR than in the placebo group.

AE of special interest

Suicidality
One patient in the quetiapine XR group experienced the TEAE of self-injurious behaviour potentially associated with suicidality; this event was reported in the 13-17 year old age group. The investigator assessed the event as not serious and not related to study medication. None were reported in the placebo group. There were no patients with TEAEs potentially related to suicidality in the 10-12 year old group.

Weight gain
The incidence of weight gain of ≥7% was higher in the quetiapine XR group than in the placebo group. Overall, 14 patients (15.2%, 14/92) in the quetiapine XR group and 10 patients (10.0%, 10/100) in the placebo group had a weight gain of ≥7% during the study period. At the end of treatment, 11 patients (12.5%, 11/88) in the quetiapine XR group and 6 patients (6.0%, 6/100) in the placebo group had a weight gain of ≥7%.

Adverse events potentially associated with EPS
One patient in the quetiapine XR group experienced the TEAE of restlessness potentially associated with EPS, while none did in the placebo group (rate is thus 1/92=1.1% in quetiapine XR and 0 in placebo).

Adverse events potentially associated with diabetes mellitus
Three patients (3.3%) in the quetiapine XR group had reports of TEAEs potentially related to symptoms of diabetes mellitus. None were reported in the placebo group. The investigator assessed 2 events, one of diabetes and one of thirst, as related to study medication and 1 event of thirst as not related to study medication.
For the 2 patients who reported the events of thirst, no increases in blood glucose (fasting or non-fasting) or insulin levels were observed upon routine testing during the study. Thus, there is no evidence to suggest that the event of thirst was a symptom of diabetes.

QTc prolongation
Treatment-emergent QT prolongation was defined as having a baseline QT evaluation of <500 ms and a post-baseline QT evaluation of ≥500 ms or an increase of ≥60 ms. Three patients (3.5%, 3/86) in the placebo group had treatment-emergent QT prolongation at Day 57. None were reported in the quetiapine XR group.

Somnolence
Adverse events potentially related to somnolence (somnolence or sedation) were higher in the quetiapine XR group (14.1%) than in the placebo group (11.0).
It is noted that this AE is a known event for adults, children and adolescents. It already appears in the SmPC of quetiapine as a warning and in the general table in section 4.8 in the category very common.

Neutropenia/agranulocitosis
Three patients (3.0%) in the placebo group experienced TEAEs potentially associated with neutropenia (2 patients) and neutrophil count decreased (1 patient). The investigator assessed all 3 events as related to the study medication (placebo). None of these events were reported in the quetiapine XR group.

Thyroid function
After the scheduled study completion date it was discovered that the central laboratory (QLAB) did not conduct the prolactin and thyroid function tests at Visits 6 and 10 (or study discontinuation visit) although these were detailed in the protocol. As a result, the company issued a CSP Amendment 2 (dated 4 May 2010) to recall all randomized patients who took at least one dose of study medication to provide an additional blood sample for prolactin and

thyroid function tests. This was an unscheduled visit and was added to the procedures currently required in the protocol. The study was completed in February 2010 and the recall visits occurred from June till November 2010, hence 4-9 month after study completion.
Of the 193 randomized patients, 89 agreed to come back for the recall visit. Of these 89 patients, 46 were previously randomized to the quetiapine XR group and 43 were previously randomized to the placebo group. Of the 89 patients who agreed to come back for a recall visit, only 9 were still on Seroquel. No signal was detected in these patients with respect to either changes in prolactin or thyroid function (see table below).

Table 11.3.7.1.2.2.5 Shift table comparing baseline to recall visit for prolactin and thyroid function laboratory safety variables for patients on Seroquel at recall visit (Safety analysis set)

Laboratory safety variable (SI unit)	Group	N	n	Baseline	Recall Visit Low n (%)	Normal n (%)	High n (%)
Free T3 (pmol/L)	Quetiapine XR 150 to 300 mg/day	92	9	Low	0	0	0
				Normal	0	9 (100%)	0
				High	0	0	0
	Placebo	100	15	Low	0	0	0
				Normal	0	13 (86.7%)	0
				High	0	2 (13.3%)	0
Free T4 (pmol/L)	Quetiapine XR 150 to 300 mg/day	92	9	Low	0	0	0
				Normal	0	9 (100%)	0
				High	0	0	0
	Placebo	100	15	Low	0	0	0
				Normal	0	15 (100%)	0
				High	0	0	0
TSH (mIU/L)	Quetiapine XR 150 to 300 mg/day	92	9	Low	-	-	-
				Normal	-	9 (100%)	0
				High	-	0	0
	Placebo	100	15	Low	-	-	-
				Normal	-	14 (93.3%)	0
				High	-	1 (6.7%)	0
Prolactin (mIU/L)	Quetiapine XR 150 to 300 mg/day	92	9	Low	-	-	-
				Normal	-	9 (100%)	0
				High	-	0	0
	Placebo	100	15	Low	-	-	-
				Normal	-	14 (93.3%)	1 (6.7%)
				High	-	0	0

Note: According to Potentially Clinically Significant (PCS) laboratory values criteria, laboratory test results have been categorized as low (<lower PCS), normal (within PCS), and high (>upper PCS).
Note: The percentages are based on the number of safety patients with both a baseline and a post-baseline assessment within each treatment group.

Because of the time intervening between randomized treatment and the recall visit, the results from this recall visit are confounded and difficult to interpret.
Hyperprolactemia and hypothyroidism are already described in the SmPC of Seroquel, both in section 4.8 and in section 5.1. For children and adolescents hyperprolactemia is described in section 4.8 but there is no information regarding effects on sexual maturation. The current study does not add to the knowledge regarding these phenomena in children and adolescents.

Vomiting data

Table 8 (below) shows all-trial data pertaining to adverse events related to vomiting. Upon review of the data, the incidence rate for all patients 18-64 years is 3.45%, which corresponds to a CIOMS (Council for International Organizations of Medical Sciences) frequency category of Common (≥1%-<10); Upon review of the paediatric data, the incidence rate for vomiting in all clinical trials for all paediatric patients (<18 years) is 11.15%, a CIOMS frequency category of (≥10%) or Very common.

Table 8 Number of patients 18 to 64 years of age with adverse events related to specified terms (All trials)

	MedDRA preferred term	Treatment	Patients with event	Total patients[a]	Incidence rate[b]	Exposure[c]	Incidence density[d]
Vomiting	Any	QTP	885 (11)	25651	3.45	7506.1	11.79
	Vomiting	QTP	885 (11)	25651	3.45	7506.1	11.79

[a] Patients must have received at least one dose of trial medication.
[b] 100 x total number of patients with event/total number of patients.
[c] Exposure in patient-years, censored at first events.
[d] 100 x total number of patients with event/total patient years of censored exposure..
Note: Any row shows the number of patients with any of the adverse events in the group. Since a patient can have more than one adverse event within the adverse event group, the number does not necessarily equal the sum of the numbers below.
Note: Numbers outside brackets refer to all adverse events and numbers in brackets refer to serious adverse events.
Note: The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded.
Table ID: AE_ALL_18_64. Program: Pediatric May 11 SERM\...\Make_report_aes.sas. User: khwf452. Data created: 09MAY2011:15:19. Table created: 10MAY2011:08:49. DB version: 22

Rhinitis

Tables 10-11 (below) show all-trial data pertaining to adverse events related to rhinitis. Upon review of the data, the incidence rate for patients 18-64 years is 0.31%, which corresponds to a CIOMS frequency category of Uncommon (≥0.01%-<0.1%), as currently represented in the Seroquel/Seroquel XR Core Data Sheets (CDS).

Upon review of the paediatric data, the incidence rate in all clinical trials for all paediatric patients (<18 years) for rhinitis is 1.33%, a CIOMS frequency category of (≥1% and <10%) or Common.

Table 10 Number of patients < 18 years of age with adverse events related to specified terms (All trials)

	MedDRA preferred term	Treatment	Patients with event	Total patients[a]	Incidence rate[b]	Exposure[c]	Incidence density[d]
Rhinitis	Any	QTP	8 (0)	601	1.33	202.3	3.95
	Rhinitis	QTP	8 (0)	601	1.33	202.3	3.95

[a] Patients must have received at least one dose of trial medication.
[b] 100 x total number of patients with event/total number of patients.
[c] Exposure in patient-years, censored at first events.
[d] 100 x total number of patients with event/total patient years of censored exposure..
Note: Any row shows the number of patients with any of the adverse events in the group. Since a patient can have more than one adverse event within the adverse event group, the number does not necessarily equal the sum of the numbers below.
Note: Numbers outside brackets refer to all adverse events and numbers in brackets refer to serious adverse events.
Note: The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded.
Table ID: AE_ALL_U18. Program: Pediatric May 11 SERM\...\Make_report_aes.sas. User: khwf452. Data created: 09MAY2011:15:23. Table created: 10MAY2011:08:49. DB version: 22

Table 11 Number of patients 18 to 64 years of age with adverse events related to specified terms (All trials)

	MedDRA preferred term	Treatment	Patients with event	Total patients[a]	Incidence rate[b]	Exposure[c]	Incidence density[d]
	Rhinitis	QTP	80 (0)	25651	0.31	7722.3	1.04

[a] Patients must have received at least one dose of trial medication.
[b] 100 x total number of patients with event/total number of patients.
[c] Exposure in patient-years, censored at first events.
[d] 100 x total number of patients with event/total patient years of censored exposure..
Note: Any row shows the number of patients with any of the adverse events in the group. Since a patient can have more than one adverse event within the adverse event group, the number does not necessarily equal the sum of the numbers below.
Note: Numbers outside brackets refer to all adverse events and numbers in brackets refer to serious adverse events.
Note: The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded.
Table ID: AE_ALL_18_64. Program: Pediatric May 11 SERM\...\Make_report_aes.sas. User: khwf452. Data created: 09MAY2011:15:19. Table created: 10MAY2011:08:49. DB version: 22

Syncope

Tables 13-14 (below) show all-trial data pertaining to adverse events related to syncope. Upon review of the data, the incidence rate for patients 18-64 years is 0.80%, both of which have a CIOMS frequency category of Uncommon (≥0.01%-<0.1%), as currently represented in the Seroquel CDSs.

Upon review of the paediatric data, the incidence rate in all clinical trials for all paediatric patients (< 18 years) for syncope is 1.83%, a CIOMS frequency category of (≥1% and < 10%) or Common.

Table 13 Number of patients 18 to 64 years of age with adverse events related to specified terms (All trials)

	MedDRA preferred term	Treatment	Patients with event	Total patients[a]	Incidence rate[b]	Exposure[c]	Incidence density[d]
Syncope	Any	QTP	206 (15)	25651	0.80	7694.0	2.68
	Presyncope	QTP	55 (4)	25651	0.21	7742.1	0.71
	Syncope	QTP	153 (11)	25651	0.60	7699.9	1.99

[a] Patients must have received at least one dose of trial medication.
[b] 100 x total number of patients with event/total number of patients.
[c] Exposure in patient-years, censored at first events.
[d] 100 x total number of patients with event/total patient years of censored exposure..
Note: Any row shows the number of patients with any of the adverse events in the group. Since a patient can have more than one adverse event within the adverse event group, the number does not necessarily equal the sum of the numbers below.
Note: Numbers outside brackets refer to all adverse events and numbers in brackets refer to serious adverse events.
Note: The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded.
Table ID: AE_ALL_18_64. Program: Pediatric May 11 SERM\...\Make_report_aes.sas. User: khwf452. Data created: 09MAY2011:15:19. Table created: 10MAY2011:08:49. DB version: 22

Table 14 **Number of patients < 18 years of age with adverse events related to specified terms (All trials)**

	MedDRA preferred term	Treatment	Patients with event	Total patients[a]	Incidence rate[b]	Exposure[c]	Incidence density[d]
Syncope	Any	QTP	11 (2)	601	1.83	203.5	5.41
	Presyncope	QTP	3 (0)	601	0.50	204.2	1.47
	Syncope	QTP	8 (2)	601	1.33	203.9	3.92

[a] Patients must have received at least one dose of trial medication.
[b] 100 x total number of patients with event/total number of patients.
[c] Exposure in patient-years, censored at first events.
[d] 100 x total number of patients with event/total patient years of censored exposure..
Note: Any row shows the number of patients with any of the adverse events in the group. Since a patient can have more than one adverse event within the adverse event group, the number does not necessarily equal the sum of the numbers below.
Note: Numbers outside brackets refer to all adverse events and numbers in brackets refer to serious adverse events.
Note: The placebo run-in periods in trials D1441L00016 and D144AL00002 are excluded.

Although the data should be interpreted with care, as no confidence intervals are available, the data appear to indicate that the incidence of syncope, vomiting and rhinitis is higher for children/adolescent than adults. Inclusion of these adverse events in the SmPC is therefore considered appropriate.

3. Discussion on clinical aspects

Seroquel XR is currently indicated for the treatment of schizophrenia, bipolar mania, bipolar depression, bipolar maintenance, major depressive disorder and generalized anxiety disorder in adult patients. It is not indicated for use in children and adolescents. In this study efficacy in children and adolescents with bipolar depression was not demonstrated; this is included in section 5.1 of the SmPC. In the context of this worksharing procedure inclusion of the adverse events vomiting, rhinitis and syncope in the SmPC is justified, as well as further information regarding suicide related events in section 5.1.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

➢ Overall conclusion

The paediatric study with Seroquel XR in the treatment of children and adolescents (10-17) with bipolar depression failed to show significant efficacy results. Seroquel XR is currently not indicated for use in children and adolescents and the results of the trial do not change the negative benefit-risk balance in the paediatric population. It is however supported that the SmPC is updated with safety information regarding suicidality, vomiting, rhinitis and syncope, as this information is considered relevant for the prescriber.

➢ Recommendation

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

4.2 Posology and method of administration

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.~~.~~

4.4 Special warnings and precautions for use

Children and adolescents (10 to 17 years of age)
Quetiapine 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 quetiapine ~~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, vomiting, rhinitis and syncope ~~and extrapyramidal symptoms~~) or may have different implications for children and adolescents (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.

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

4.8 Undesirable effects

Children and adolescents (10 to 17 years of age)

Nervous system disorders	
~~Very common~~:	~~Extrapyramidal symptoms~~[1]
Common:	Syncope
Respiratory, thoracic and mediastinal disorders	
Common:	Rhinitis
Gastrointenstinal disorders	
Very common:	Vomiting

[1] appears as 'very common' for all patients (Table 1).

5.1 Pharmacodynamic properties

Children and adolescents (10 to 17 years of age)

Clinical efficacy
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 ≥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 ≥30% reduction from baseline in PANSS total score. Both in mania and schizophrenia higher doses resulted in numerically lower response rates.

In a third short-term placebo-controlled monotherapy trial with Seroquel XR in children and adolescent patients (10-17 years of age) with bipolar depression, efficacy was not demonstrated.

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

~~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 placebocontrolled 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 treatmentemergent EPS was 10%.~~

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

~~Suicide/Suicidal thoughts or Clinical worsening~~
~~In short-term placebo-controlled clinical trials with Seroquel in paediatric patients with schizophrenia, the incidence of suicide related events was 1.4% (2/147) for quetiapine and 1.3% (1/75) for placebo in patients <18 years of age. In short-term placebocontrolled 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.~~

Clinical safety
In the short-term pediatric trials with quetiapine described above, the rates of EPS in the active arm vs. placebo were 12.9% vs. 5.3% in the schizophrenia trial, 3.6% vs. 1.1% in the bipolar mania trial, and 1.1% vs. 0% in the bipolar depression trial. The rates of weight gain ≥7% of baseline body weight in the active arm vs. placebo were 17% vs. 2.5% in the schizophrenia and bipolar mania trials, and 12.5% vs. 6% in the bipolar depression trial. The rates of suicide related events in the active arm vs. placebo were 1.4% vs. 1.3% in the schizophrenia trial, 1.0% vs. 0% in the bipolar mania trial, and 1.1% vs. 0% in the bipolar depression trial. During an extended posttreatment follow-up phase of the bipolar depression trial, there were two additional suicide related events in two patients; one of these patients was on quetiapine at the time of the event.

Long-term safety
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).
With respect to weight gain, when adjusting for normal growth over the 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.

The PL has been revised as follows:

Section 4. Possible side effects

Very common (**may affect 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.
- Abnormal muscle movements. These include difficulty starting muscle movements, shaking, feeling restless or muscle stiffness without pain.

Common (**may affect up to 1 in 10 people**):
- Rapid heartbeat.
- Feeling like your heart is pounding, racing or has skipped beats.
- 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

- Feeling irritated
- Disturbance in speech and language
- Thoughts of suicide and worsening of your depression
- Shortness of breath
- Vomiting (mainly in the elderly)
- Fever

Children and adolescents

Very Common (may affect 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.~~