AstraZeneca

Clinical Overview

Drug Name Quetiapine fumarate

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SEROQUEL™ (quetiapine fumarate)
Clinical Overview on Weight Gain in pediatric patients

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1. PRODUCT DEVELOPMENT RATIONALE

1.1 Introduction

The Core Data Sheets for SEROQUEL is to be amended following an internal safety evaluation and review meeting on 09 July 2008. The purpose of this document is to summarize the key information on which the decision to amend the CDS was based, to document the Core Data Sheet amendment and to support changes to local Prescribing Information.

1.1.1 SEROQUEL and SEROQUEL XR

SEROQUEL and SEROQUEL XR are atypical antipsychotic agents, presented as tablets containing quetiapine fumarate, which exhibits affinity for brain serotonin (5HT2) and dopamine D1 and D2 receptors. In addition, SEROQUEL/SEROQUEL XR also have high affinity at histaminergic and adrenergic α1 receptors, with a lower affinity at adrenergic α2 receptors, but no appreciable affinity at cholinergic, muscarinic or benzodiazepine receptors.

SEROQUEL was first approved for marketing in the United Kingdom (UK) on 31 July 1997 and was first launched in the UK on 22 September 1997. By 31 March 2008, SEROQUEL has been approved in 89 countries for schizophrenia, 86 countries for bipolar mania, (with Mexico being the first country to approve bipolar mania on 29 May 2003), 26 countries for bipolar depression, (with Czech Republic being the first country to approve bipolar depression on 27 September 2006), and in one country for bipolar maintenance (USA being the first country to approve bipolar maintenance on 14 May 2008). SEROQUEL is presented as tablets delivering a dose of 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, 300 mg, or 400 mg of quetiapine free-base. SEROQUEL is not approved for children or adolescents below 18 years of age.

SEROQUEL XR was first approved for marketing in the United States (US) for acute schizophrenia on 18 May 2007 and for maintenance of schizophrenia on 15 November 2007. By 31 March 2008, SEROQUEL XR has been approved in 30 countries for schizophrenia (including 14 countries in the Mutual Recognition Procedure), 7 countries for bipolar mania (with Slovakia being the first country to approve bipolar mania on 28 June 2007), and in one country for bipolar depression (Mexico being the first country to approve bipolar depression in October 2007). SEROQUEL XR is presented as tablets delivering a dose of 50 mg, 200 mg, 300 mg, or 400 mg of quetiapine free-base. SEROQUEL XR is not approved for children or adolescents below 18 years of age.

1.2 Proposed label change

The following text will be added to Section 4.8 *Undesirable effects* of the SEROQUEL CDS under a subheading of *Children and adolescents.*

Children and adolescents

The same ADRs described above for adults apply to children and adolescents. The following table summarizes 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.

Weight gain in children and adolescents

In one 6-week, placebo-controlled trial in adolescent patients (13-17 years of age) with schizophrenia, the mean increase in body weight, was 2.0 kg in the quetiapine group and -0.4 kg in the placebo group. Twenty one percent of quetiapine-treated patients and 7% of placebo-treated patients gained ≥ 7 % of their body weight.

In one 3-week, placebo-controlled trial in children and adolescent patients (10-17 years of age) with bipolar mania, the mean increase in body weight was 1.7 kg in the quetiapine group and 0.4 kg in the placebo group. Twelve percent of quetiapine-treated patients and 0% of placebo-treated patients gained ≥ 7 % of their body weight.

In the open-label study that enrolled patients from the above two trials, 63% of patients (241/380) completed 26 weeks of therapy with quetiapine. After 26 weeks of treatment, the mean increase in body weight was 4.4 kg. Forty five percent of the patients gained ≥ 7% of their body weight, not adjusted for normal growth. In order to adjust for normal growth over 26 weeks an increase of at least 0.5 standard deviation from baseline in BMI was used as a measure of a clinically significant change; 18.3% of patients on quetiapine met this criterion after 26 weeks of treatment.

Since clinical trials in pediatric patients have been conducted with SEROQUEL and not SEROQUEL XR this change applies only to the SEROQUEL CDS.

2. OVERVIEW OF BIOPHARMACEUTICS

This section is not relevant to this document.

3. OVERVIEW OF CLINICAL PHARMACOLOGY

This section is not relevant to this document.

4. OVERVIEW OF EFFICACY

This section is not relevant to this document.

5. OVERVIEW OF SAFETY

5.1 Data summary and discussion

5.1.1 Pediatric clinical trial data

The data presented below is taken from two acute placebo-controlled studies with SEROQUEL in pediatric patients with schizophrenia or bipolar mania and one longer-term open-label study with SEROQUEL. The patients in the longer-term trial were originally enrolled in one of the two acute placebo-controlled trials. The following is a brief description of these three trials.

- D1441C00112: a 6-week, International, Multicenter, Randomized, Double-blind, Parallel group, Placebo-controlled, Phase IIIb Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL™) Immediate-release Tablets in Daily Doses of 400 mg and 800 mg Compared with Placebo in the Treatment of Adolescents with Schizophrenia

- D1441C00149: a 3-week, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled, Phase IIIb Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL™) Immediate-release Tablets in Daily Doses of 400 mg and 600 mg Compared with Placebo in the Treatment of Children and Adolescents with Bipolar I Mania

- D1441C00150: a 26-week, International, Multicenter, Open-label Phase IIIb Study of the Safety and Tolerability of Quetiapine Fumarate (SEROQUEL™) Immediate-release Tablets in Daily Doses of 400 mg to 800 mg in Children and Adolescents with Bipolar I Disorder and Adolescents with Schizophrenia

5.1.2 Acute placebo-controlled data

5.1.2.1 D144C00112

Mean increase in body weight

In study D144C00112, mean weights were similar at baseline for the three treatment groups. Mean changes in weight from baseline were higher for quetiapine-treated patients at each time point compared to placebo. At Day 42, the mean changes from baseline were 2.2 kg in the 400 mg/day quetiapine group, 1.8 kg in the 800 mg/day quetiapine group, and –0.4 kg in the placebo group (see Table 1).

Table 1 D144C00112: Mean increase in weight from baseline

Change from Baseline	QTP 400 mg	QTP 800 mg	PLACEBO
Day 42	2.2 kg	1.8 kg	-0.4 kg

Patients with ≥7% weight gain

A higher percentage of quetiapine-treated patients (23.21% in the 400 mg/day and 18.18% in the 800 mg/day) had ≥7% weight gain at Day 42 compared to the placebo-treated patients (6.82%) (see Table 2).

Table 2 **D144C00112: Patients with ≥ 7% weight gain (Summary safety population)**

Visit	QTP 400 mg N=56 n (%)	QTP 800 mg N = 55 n (%)	PLA N = 44 n (%)
Day 42	13 (23.2)	10 (18.2)	3 (6.8)

5.1.2.2 D144C00149

Mean increase in weight

Mean increases in weight from baseline to Day 21 were higher for quetiapine-treated patients at each time point compared to placebo. These increases from baseline were 1.7 kg in the 400 mg quetiapine-treated group, 1.7 kg in the 600 mg quetiapine-treated group and 0.4 kg in the placebo group. Quetiapine-treated patients experienced higher mean increases in weight compared to placebo at Day 21 (see Table 3).

Table 3 **D144C00149: Mean increase in weight from baseline**

Change from baseline	QTP 400 mg	QTP 600 mg	PLA
Day 21	1.7 kg	1.7 kg	0.4 kg

Patients with ≥7% weight gain

A higher percentage of quetiapine-treated patients (14.47% in the 400 mg/day and 9.88% in the 600 mg/day) had ≥7% weight gain at Day 21 compared to placebo-treated patients (0%) (see Table 4).

Table 4 **D144C00149: Patients with ≥7% weight gain (Summary safety population)**

Visit	QTP 400 mg N = 76 n (%)	QTP 600 mg N = 81 n (%)	PLACEBO N = 68 n (%)
Day 21	11 (14.5)	8 (9.9)	0 (0)

5.1.3 Longer-term open-label pediatric data

5.1.3.1 D1441C00150

Study D1441C00150 was an open-label extension study designed to assess the safety and tolerability of quetiapine (flexibly dosed at 400 mg/day to 800 mg/day) in adolescents with schizophrenia (continuing from Study D144C00112) and in children and adolescents with bipolar I disorder (continuing from Study D144C00149). There were a total of 380 patients in the safety analysis set, including 175 with schizophrenia and 205 with mania. Sixty-three percent of patients (241) completed 26 weeks of therapy with quetiapine.

All patients treated with quetiapine 50 mg/day on Day 1 then escalated to 400 mg on Day 5. From Day 5, the target dose of 400 mg/day was maintained or increased by no more than 100 mg/day, up to 800 mg/day or adjusted down to 200 mg/day. Patients were treated for up to 26 weeks.

Mean increase in weight

The mean change in weight for schizophrenia and bipolar I patients (who enrolled) from OL baseline as well as DB baseline to final visit are provided in Table 5.

Table 5 **Study D1441C00150: mean changes from baseline to the final visit (safety population)**

	Acute feeder study treatment								
	Prior Placebo (N=129)			All prior QTP (N=251)			Total (N=380)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
112 DB Baseline									
Final visit (150 OL BSLN)	62	67.4	16.3	113	64.8	19.2	175	65.7	18.2
Change from 112 DB BSLN	62	4.1	8.5	113	4.8	10.8	175	4.6	10.0
Change from 150 OL Baseline	62	4.3	6.9	113	2.8	10.1	175	3.3	9.1
149 DB Baseline									
Final visit (150 OL BSLN)	64	68.3	21.9	136	64.5	18.4	200	65.8	19.6
Change from 149 DB BSLN	64	5.8	6.4	136	5.1	5.7	200	5.3	5.9
Change from 150 OL Baseline	64	5.5	5.8	135	3.2	4.8	199	4.0	5.2
Total 149 and 112 pooled DB Baseline									
Final visit (150 OL BSLN)	126	67.9	19.3	249	64.7	18.7	375	65.7	19.0
Change from DB BSLN	126	5.0	7.50	249	5.0	8.3	375	5.0	8.1
Change from 150 OL Baseline	126	4.9	6.4	248	3.0	7.6	374	3.7	7.3

In patients who completed 26 weeks of therapy with quetiapine (n=241) in Trial D1441C00150, the mean change in weight from OL baseline was 4.4 kg.

Patients with ≥7% weight gain

In the safety population, 134 patients (35.6%) experienced ≥7% weight gain from OL baseline to final visit (see Table 6).

Table 6 **Study D1441C00150: Patients with ≥ 7% weight gain (Summary safety population)**

	Acute feeder study treatment								
	Prior Placebo (N=129)			Prior All QTP (N=251)			Total (N=380)		
	N	n	(%)	N	n	(%)	N	n	(%)
Pooled data 149 and 112									
From DB Baseline	127	58	45.7	249	119	47.8	376	177	47.1
From 150 OL Baseline	127	50	39.4	249	84	33.7	376	134	35.6
Study 112 (schizophrenia)									
From DB Baseline	62	24	38.7	113	43	38.1	175	67	38.3
From 150 OL Baseline	62	19	30.6	113	32	28.3	175	51	29.1
Study 149 (BP I)									
From DB Baseline	65	34	52.3	136	76	55.9	201	110	54.7
From 150 OL Baseline	65	31	47.7	136	52	38.2	201	83	41.3

Of the patients who completed 26 weeks of treatment with quetiapine, 44.8% (108/241) had a ≥7% increase in weight from OL baseline.

5.1.4 Additional analysis of Pediatric data

5.1.4.1 Z-scores

Since body weight and height should increase in children, data showing an increase in weight with time sometimes may not indicate a problem. One convenient way to express body weight is in terms of body mass index (BMI), since with BMI, the weight is adjusted for height (Correll et al 2006).

A better measure of weight change in children and adolescents is to convert the mean weight and BMI to a Z-score taking into consideration the age and gender of the subject. Z-scores are able to show how different a child's weight or BMI is from the average children of the same height (Reyes et al 2006).

One of the criteria proposed to show significant weight gain in children and adolescents is a greater than or equal to an increase in BMI Z-score of 0.5 over any duration of time (Correll et al 2006). This increase represents a change of 0.5 standard deviation from baseline.

BMI Z-scores

The mean BMI Z-scores (for patients who enrolled in study D1441C00150) from the DB baseline for schizophrenia to the final visit and end of treatment are higher for the prior placebo group compared to the prior quetiapine group (see Table 7).

Table 7 **Study D1441C00150: Mean values of BMI Z score at baseline, end of treatment and final visit (safety population)**

	Acute feeder study treatment								
	Prior Placebo (N=129)			All prior QTP (N=251)			Total (N=380)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
112 DB Baseline	62	**0.3**	1.2	113	**-0.1**	1.4	175	**0.0**	1.3
Week 26	41	0.4	1.1	86	0.1	1.22	127	0.2	1.2
Final Visit	62	**0.5**	1.0	113	**0.2**	1.3	175	**0.3**	1.2
149 DB Baseline	67	**1.0**[a]	1.0	138	**0.9**[a]	1.1	205	**0.9**[a]	1.0
Week 26	37	1.2	1.0	77	1.2	1.0	114	1.2	1.0
Final Visit	63	**1.2**	1.0	135	**1.0**	1.0	198	**1.1**	1.0
DB Total Baseline	129	**0.6**	1.2	251	**0.4**	1.3	380	**0.5**	1.3
Week 26	78	0.8	1.1	163	0.6	1.2	241	0.7	1.2
Final Visit	125	**0.9**	1.0	248	**0.7**	1.2	373	**0.7**	1.2

[a] The mean BMI Z score at baseline is much higher for the 149 population

Table 8 below shows patients who had a ≥ 0.5 shift in BMI Z-score during trial D1441C00150 from both DB baseline and OL baseline and by indication. Of all patients who completed 26 weeks of treatment with quetiapine, 18.3% (44/241) had a shift of ≥ 0.5 BMI Z-score.

Table 8 **Patients with ≥ 0.5 shift in BMI Z score in Study D1441C00150 by indication**

Occurrence	Schizophrenia to OL 150		BP to OL 150		OL 150
Time/baseline	DB All Quetiapine	DB Placebo	DB All Quetiapine	DB Placebo	OL All - Quetiapine
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	N/N (%)
End of Treatment/DB	24/113 (21.2)[a]	17/62 (27.4)[a]	29/135 (21.5)[c]	12/63 (19)[c]	82/373 (22)
End of Treatment/OL	16/113 (14.2)[b]	15/62 (24)[b]	11/133 (8.3)[b]	12/63 (19)[b]	54/371 (14.6)[b]

[a] From double blind baseline of study 112 to end of study 150; [b] From OL baseline of study 150 to end of study 150; [c] From double blind baseline of study 149 to end of study 150

Patients with ≥0.5 shift in standardized BMI Z-score in Study D1441C00150 by age group

A similar percentage of patients ≤12 years of age (who enrolled in study D1441C00150) treated with prior placebo (28% at EOT) had ≥0.5 shift in standardized BMI Z-score compared with prior quetiapine-treated patients (25% at EOT) from the DB baseline (see Table 9).

A higher percentage of patients ≤12 years of age (who enrolled in study D1441C00150) treated with prior placebo (24% at EOT) had ≥0.5 shift in standardized BMI Z-score compared with prior quetiapine-treated patients (8.6% at EOT) from the OL baseline (see Table 9).

A similar percentage of pediatric patients 13-18 years of age (who enrolled in study D1441C00150) treated with prior placebo (22% at EOT) had ≥0.5 shift in standardized BMI Z-score compared to prior quetiapine-treated patients (20.1% at EOT) from the DB baseline (see Table 9).

A higher percentage of pediatric patients 13-18 years of age (who enrolled in study D1441C00150) treated with prior placebo (21% at EOT) had ≥0.5 shift in standardized BMI Z-score compared to prior quetiapine-treated patients (11.7% at EOT) from the OL baseline (see Table 9).

Table 9 **Patients with ≥0.5 shift in BMI Z score in Study D1441C00150 by age group***

Occurrence	≤ 12 years OL 150		13 to 17 years OL 150		OL 150
Time/baseline	DB All Quetiapine	DB Placebo	DB All Quetiapine	DB Placebo	OL All - Quetiapine
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
End of Treatment/DB	15/59 (25)	7/25 (28)	38/189 (20.1)	22/100 (22)	82/373 (22)
End of Treatment/OL	5/58 (8.6)	6/25 (24)	22/188 (11.7)	21/100 (21)	54/371 (14.6)

* Study 112 was a six week placebo controlled trial in adolescent patients (13-17 years) and study 149 was a three week trial in children and adolescent patients (10-17 years)

5.1.4.2 Overall summary of pediatric clinical trial data

In trial D1441C00112, the mean increase in body weight was 2 kg in the quetiapine group and -0.4 kg in the placebo group. Twenty-one percent of quetiapine patients and 7% of placebo patients had gained ≥7% of their body weight.

In trial D144C00149, the mean increase in body weight was 1.7 kg in the quetiapine group and 0.4 kg in the placebo group. Twelve percent of quetiapine patients and 0% of placebo patients had gained ≥7% of their body weight.

In trial D1441C00150, where 63% of patients (241/380) completed 26 weeks of therapy with quetiapine, the mean increase in body weight was 4.4 kg. Forty-five percent of the patients had ≥7% increase in body weight, not adjusted for normal growth. In order to adjust for normal growth over 26 weeks, an increase of at least 0.5 standard deviation from baseline in BMI was used as a measure of a clinically significant change; 18.3% of patients on quetiapine met this criterion after 26 weeks of treatment.

6. BENEFITS AND RISKS CONCLUSIONS

The purpose of this application is to update the SEROQUEL Core Data Sheet and local Prescribing information with current findings in relation to weight gain in patients treated with quetiapine. AstraZeneca believes that these data do not alter the overall safety and tolerability profile of SEROQUEL and SEROQUEL XR and that the benefit/risk profile of SEROQUEL and SEROQUEL XR remains positive.

7. REFERENCES

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Reyes et al 2006
Reyes M, Croonenberghs J, Augustyns I, Eerdekens M. Long-term use of risperidone in children with disruptive behavior disorders and subaverage intelligence: efficacy, safety and tolerability. J. Child. Adolescent. Psychopharmacol. 2006; 16(3): 260-272.

According to his/her respective qualification the undersigned expert declares hereby to have performed the duties set out in the Article 12 and in accordance with Annex I Part I 1.4 of Directive 2001/83/EC, as amended

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According to the Annex I of Directive 2001/83/EC as amended, brief information (curriculum vitae) on the educational, training and occupational experience of the expert is attached.