From: Eriksson, Hans A
Sent: Monday, July 07, 2008 3:53 PM
To: Rak, Ihor W; O'Dowd, Liza
Subject: FW: Updated Discussion document for the 09July08 Seroquel Peds SERM

Attachments: Weight SERM 09 July 2008.doc

Ihor and Liza,

Hot off the press, additional material for SERM.

Hans

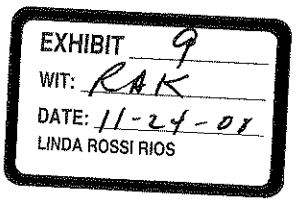
-----Original Message-----
From: Arnold, Karen
Sent: Monday, July 07, 2008 10:45 AM
To: Carey, Eileen; Dev, Vikram J; Arnold, Barry DC; Zander, Judith; Jefferies, Leigh; Leong, Ronald; Manning, Julia; Fors, Susanne (Seroquel); Boornazian, Lisa; Lee, Tara; Rolfe, Deborah; Warner, Linda (Safety); Delillio, Nina DH; Alam, Eva; Forsgren, Joachim; Spiers-Alston, Janet L; Gelman, Michele; Ni, Xiang; Eriksson, Hans A; Simpson, Brandon; Tyler, Robyn C; Åström, Mikael; Sherak, Nina; Walsh, Louisa M; Fullmer, Timothy S; Pathak, Sanjeev; Munro, Magna; Karlsson, Anders F; Patterson, Pat; Sullivan, Tim; Held, Peter; Stankowski, Jill; Nickless, Duncan M

Subject: Updated Discussion document for the 09July08 Seroquel Peds SERM

Dear all,

Additional data has been received for weight gain. An updated discussion document is attached. The new data is highlighted in yellow in the document.

Karen



AstraZeneca

Discussion Document

Drug name Quetiapine fumarate

Date *July 2008*

CONFIDENTIAL

Discussion Document

SEROQUEL/SEROQUEL XR AND WEIGHT GAIN

ALL FINDINGS PRESENTED IN THIS DOCUMENT ARE TO BE SUBJECT TO FURTHER CONSIDERATION AT SERM

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SUMMARY

Weight gain reported in pediatric patients taking SEROQUEL was identified as a subject for review by pharmacovigilance processes internal to AstraZeneca. In addition, we have reassesed the frequency of adult weight gain from the current clincial trial data. The current Core Data Sheet reference to weight gain is based on adverse evnent report data and not actual weight data.

In two acute placebo-controlled clinical trials with quetiapine in pediatric patients the incidence rate of patients with ≥ 7 % weight gain was 15.68 % respectively in the quetiapine group and 2.68 % in the placebo group. Using an increase of at least 0.5 standard deviation from baseline in BMI as a measure of clinically significant change, X% of patients on quetiapine met this criterion after 26 weeks of treatment.

In acute placebo-controlled trials of quetiapine in adult patients (≥18 years of age) the incidence rate in patients with ≥ 7 % weight gain was 9.6 % in the quetiapine group and 3.8 % in the placebo group. The relative risk estimate was 2.5 (95% CI: 2.10, 3.00). The incidence rate in patients with weight gain ≥ 7 % in all trials was 18.2 %.

The current Core Data Sheet refers to Weight Gain as common in Section 4.8 in the adult population, which is based on AE reports and not actual weight data.

Safety Evaluation and Review Meeting (SERM) is asked to consider whether the SEROQUEL CDS requires amendment with respect to the incidence of weight gain in pediatric and adult patients taking SEROQUEL.

1. INTRODUCTION

The purpose of this document is to review relevant information such as, clinical study data, received by AstraZeneca regarding the association of weight gain in pediatric patients with SEROQUEL treatment and to assess whether the Core Data Sheet for SEROQUEL requires amendment to reflect the company's current understanding of the subject.

2. BACKGROUND

2.1 SEROQUEL / 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.

It has been estimated that about 22.8 million patients worldwide have been exposed to SEROQUEL/SEROQUEL XR since launch through the end of February 2008. This estimate is based upon: (1) assumptions as to the number of prescriptions per patient, based upon 2007 United States (US) market research; and (2) projections of prescriptions since launch based upon information available in the US (dispensed prescriptions from retail, long-term care and mail order) and 12 other countries (Australia, Belgium, Canada, Egypt,Germany, Italy, Japan, Netherlands, Saudi Arabia, Spain, and United Kingdom; written prescriptions from office based physicians) in which SEROQUEL/SEROQUEL XR is marketed.

2.2 Core Data Sheet for SEROQUEL and SEROQUEL XR

The AstraZeneca CDS presents the company position on the prescribing information for SEROQUEL and provides a reference for consistency of product information documents in individual markets.

The current SEROQUEL/SEROQUEL XR Core Data Sheets contain the following information regarding weight gain in Section 4.8:

"As with other antipsychotics, weight gain, syncope, neuroleptic malignant syndrome, leucopenia, neutropenia and peripheral edema, have been associated with SEROQUEL".

Frequency	System Organ Class	Event
Common (≥ 1% - < 10%)	Investigations	Weight Gain[3]

[3] Occurs predominantly during the early weeks of treatment.

The current frequency of common is based on AE reports and not actual weight data.

3. THE LITERATURE

Not reviewed for this topic.

4. PRE-CLINICAL DATA

Not reviewed for this topic.

5. CLINICAL STUDY DATA

5.1 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 breif description of these three trials.

- D144C00112: 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

- D144C00149: 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

- D144C00150: 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

5.1.1 Acute placebo-controlled data

5.1.1.1 D144C00112

Adverse event data

Adverse events of weight increased were reported for three patients (4.12%) in the 400 mg/day mg/day quetiapine group, two patients (2.70 %) in the 800 mg/day quetiapine group, and two patients (2.66 %) in the placebo group. All adverse events of weight increased were judged related to the study medication by the investigator, and no adverse event of weight increased led to discontinuation of study treatment.

Mean increase in body weight

In study 112 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 (23.21)	10 (18.18)	3 (6.82)

5.1.1.2 D144C00149

Adverse event data

Adverse events of weight increased were reported for six patients (6.32 %) in the 400 mg/day quetiapine group, six patients (6.12 %) in the 600 mg/day quetiapine group, and none in the

placebo group. All adverse events of weight increased were judged related to study medication by the investigator and no adverse events of weight increased led to discontinuation of study treatment.

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 placebo. 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 (14.47)	8 (9.88)	0 (0)

5.1.1.3 Pooled Data (Trials 112 and 149)

Adverse events of weight increase in pediatric studies D1441C00149 and D1441C0112 (pooled data)

In the pooled data, from the two acute placebo-controlled clinical trials (study 112 and study 149) with quetiapine in pediatric patients the incidence of reports of weight increased was 5.0 % in the quetiapine group and 1.2 % in the placebo group. The relative risk estimate (quetiapine vs placebo) was 4.13 (95% confidence interval: 0.96, 17.54). When adjusted for duration of exposure the incidence density for quetiapine was 64.8 per 100 patient years and 15.6 per 100 patient years for placebo. The relative incidence density was 4.17 (95% CI: 0.96, 18.03). (See Table 5).

Table 5 Number of patients with adverse events in pediatric studies D1441C00149 and D1441C00112

MedDRA preferred term	Treatment	Patients with event	Total patients[a]	Exposure[b]	Incidence rate[c]	Relative risk QTP vs Pla	95%CI Lower	Upper	Incidence density[d]	Relative incidence density QTP vs Pla	95%CI Lower	Upper
Weight increased	QTP	17 (0)	340	26.2 (27.0)	5.0 (0.0)	4.13	0.96	17.64	64.8 (0.0)	4.17	0.96	18.03
	Pla	2 (0)	165	12.9 (13.0)	1.2 (0.0)				15.6 (0.0)			

[a] Patients must have received at least one dose of trial medication.
[b] Exposure in patient-years, cencored at first event.
[c] 100xtotal number of patients with event/total number of patients.
[d] 100xtotal number of patients with event/total patient-years of exposure.
[e] The number of patients with any of the adverse events. Since a patient can have more than one adverse ecent 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.
Studies included: D1441C00149 and D1441C00112.
Derived from: Pgm: Reg-Def\Pediatric Apr08\...\AE_pla_ctrl. Data version: V15. User: Å Hellqvist. 07MAY08 14:20.

Patients with ≥ 7% weight gain by BMI (pooled data)

A higher percentage of quetiapine treated patients had ≥ 7 % weight gain compared to placebo in the majority of the different BMI categories (30.8 % vs. 9.5 % in the 0-<18.5; 18.6 % vs. 2.2 % in the 18.5 - <25; 5.2 % vs. 0% in the 25 - <30). A higher percentage of quetiapine treated patients had ≥ 7 % weight gain compared to placebo in the age group ≤ 12 year old in the majority of the different BMI categories. (23.8% vs. 0 % in the 0-<18.5, 16.3 % vs. 0 % in 18.5 - <25). Similarly, a higher percentage of quetiapine treated patients had ≥ 7 % weight gain compared to placebo in the age group 13-18 year old in the majority of the different BMI categories (34.1 % vs.14.3 % in the 0-<18.5, 19.4 vs. 2.8 % in 18.5 - <25). (See Table 6).

Table 6 Patients with ≥ 7% weight gain by BMI in pediatric studies D144C00149 and D144C00112 (pooled data)

Weight Cut-offs	BMI group	PLA	All QTP	PLA ≤ 12	All QTP ≤ 12	PLA 13-18	All QTP 13-18
≥ 7 % increase at any visit		N n (%)	N n (%)	N n (%)	N n (%)	N n (%)	N n (%)
	0-<18.5	21 2 (9.5)	65 20 (30.8)	7 0 (0)	21 5 (23.8)	14 2 (14.3)	44 15 (34.1)
	18.5 - < 25	89 2 (2.2)	177 33 (18.6)	17 0 (0)	43 7 (16.3)	72 2 (2.8)	134 26 (19.4)
	25-<30	36 0 (0)	58 3 (5.2)	9 0 (0)	16 0 (0)	27 0 (0)	42 3 (7.1)
	30 - < 40	14 0 (0)	27 0 (0)	2 0 (0)	4 0 (0)	12 0 (0)	23 0 (0)
	≥ 40	2 0 (0)	2 0 (0)	0 0 (0)	0 0 (0)	2 0 (0)	2 0 (0)
	Total	163 4 (2.5)	335 57 (17.0)	36 0 (0)	85 12 (14.1)	127 4 (3.1)	250 45 (18)

Change from baseline in weight and BMI by BMI category (pooled data)

The pooled data for patients with a mean increase in weight and BMI from baseline to end of treatment were higher for quetiapine treated patients compared to placebo in each of the different BMI categories. (See Table 7).

Table 7 Change from baseline in weight and BMI by BMI category in pediatric studies D144C00149 and D144C00112 (pooled data)

BMI category (kg/m^2)		QTP		PLA	
	n	65		24	
Underweight BMI < 18.5		**Weight**	**BMI**	**Weight**	**BMI**
Baseline	Mean (SD)	42.5 (7.5)	17.1 (1.2)	42.3 (10.2)	16.9 (1.2)
End of treatment	Mean (SD)	44.5 (7.9)	17.8 (1.5)	42.8 (10.0)	17.0 (1.3)
Change	Mean (SD)	2.0 (2.3)	0.7 (0.9)	0.5 (1.5)	0.2 (0.6)
Normal weight 18.5 ≤ BMI≤ 25	**n**	**181**		**90**	
		Weight	**BMI**	**Weight**	**BMI**
Baseline	Mean (SD)	57.1 (9.7)	21.5 (1.8)	58.3 (9.6)	21.6 (1.8)
End of treatment	Mean (SD)	58.9 (10.3)	22.0 (2.0)	58.6 (9.8)	21.7 (2.1)
Change	Mean (SD)	1.8 (2.4)	0.6 (0.9)	0.4 (2.5)	0.1 (0.9)
Overweight 25 ≤ BMI≤30	**n**	**60**		**33**	
		Weight	**BMI**	**Weight**	**BMI**
Baseline	Mean (SD)	72.4 (10.7)	27.4 (1.4)	69.5 (8.3)	26.8 (1.3)
End of treatment	Mean (SD)	73.5 (11.0)	27.7 (1.7)	68.8 (7.5)	26.4 (1.3)
Change	Mean (SD)	1.1 (2.6)	0.3 (1.0)	-0.8 (2.7)	-0.3 (0.9)
Obese BMI ≥ 30	**N**	**34**		**18**	
		Weight	**BMI**	**Weight**	**BMI**
Baseline	Mean (SD)	92.4 (14.5)	33.5 (3.1)	96.7 (11.3)	34.8 (3.6)
End of treatment	Mean (SD)	94.9 (16.7)	34.1 (3.4)	97.4 (12.5)	34.9 (3.9)
Change	Mean (SD)	2.5 (3.8)	0.7	0.7 (2.8)	0.1 (1.1)

5.1.2 Longer-term open label pediatric data

5.1.2.1 D1441C00150

Study 150 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 112) and in children and adolescents with bipolar I disorder (continuing from Study 149). There were a total of 380 patients in the safety analysis set, including 175 with schizophrenia and 205 with mania.

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.

Adverse event data

Adverse events of weight increased were reported for 51 patients (13.4%) in the safety population, including 24 patients (18.6%) who were treated with placebo during the acute feeder studies and 27 patients (10.8%) who received quetiapine during the acute feeder studies. Nearly all adverse events of weight increased were judged related to study medication by the investigator; three adverse events of weight increased led to discontinuation of study treatment.

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 8.

The mean change in weight for all schizophrenia patients who enrolled from OL baseline to final visit was 3.3 kg; the increase in weight was greater in patients who were treated with placebo (4.3 kg) compared with quetiapine (2.8 kg) during the acute feeder study. The change in mean weight from DB baseline was 4.6 kg for schizophrenia patients.

The mean change in weight for all bipolar I disorder patients who enrolled from OL baseline to final visit was 4.0 kg; the increase in weight was greater in patients who were treated with placebo (5.5 kg) compared with quetiapine (3.2 kg) during the acute feeder study. The change in mean weight from DB baseline was 5.3 kg for bipolar I disorder patients.

The mean change in weight for all patients who enrolled in trial 150 (n=380) from OL baseline to final visit was 3.7 kg; the increase in weight was greater in patients who were treated with placebo (4.9 kg) compared with quetiapine (3.0 kg) during the acute feeder studies. The change in mean weight from DB baseline was 5.0 kg for the total population. The mean change in weight for patients (from OL baseline) who completed 26 weeks of treatment with quetiapine (n= 241) was 4.4 kg.

Table 8 Study 150: 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	16.34	113	64.8	19.18	175	65.7	18.22
Change from 112 DB BSLN	62	4.1	8.46	113	4.8	10.75	175	4.6	9.98
Change from 150 OL Baseline	62	4.3	6.90	113	2.8	10.07	175	3.3	9.08
149 DB Baseline									
Final visit (150 OL BSLN)	64	68.3	21.85	136	64.5	18.43	200	65.8	19.61
Change from 149 DB BSLN	64	5.8	6.42	136	5.1	5.66	200	5.3	5.90
Change from 150 OL Baseline	64	5.5	5.81	135	3.2	4.75	199	4.0	5.21
Total 149 and 112 pooled DB Baseline									
Final visit (150 OL BSLN)	126	67.9	19.26	249	64.7	18.74	375	65.7	18.95
Change from DB BSLN	126	5.0	7.50	249	5.0	8.34	375	5.0	8.06
Change from 150 OL Baseline	126	4.9	6.38	248	3.0	7.64	374	3.7	7.28

In patients who completed 26 weeks of therapy with quetiapine (n=241) in Trial 150, the mean change in weight from baseline was 4.4 kg. In these patients, the average percentiles at baseline and 26 weeks, respectively, were 64.0% and 64.7% for weigh, 49.4% and 49.0% for height, and 66.3% and 67.7% for BMI.

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 9). The incidence of ≥7% weight gain was higher in patients who were treated with placebo (39.4%) compared with quetiapine (33.7%) during the acute feeder studies.

In the schizophrenia population, 29.1% of patients experienced ≥7% weight gain. The incidence of ≥7% weight gain was similar in patients on quetiapine in the Study 150 who were treated with placebo (30.6%) compared with quetiapine (28.3%) during the acute feeder studies.

In the bipolar I disorder population, 41.3% of patients experienced ≥7% weight gain. The incidence of ≥7% weight gain was higher in patients on quetiapine in the Study 150 who were treated with placebo (47.7%) compared with quetiapine (38.2%) during the acute feeder studies.

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

Table 9 Study 150: 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

5.1.3 Additional analysis of Pediatric data

5.1.3.1 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 in 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 with 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 150) 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 10).

The mean BMI Z-scores (for patients who enrolled in study 150) from the DB baseline for bipolar-I patients to the final visit and end of treatment are similar for the prior placebo group compared to the prior quetiapine group. (See Table 10).

The mean BMI Z-scores (for patients who enrolled in study 150) from the total DB baseline to the end of treatment and final visit were higher in the prior placebo group compared to the prior quetiapine group. (See Table 10).

The mean BMI Z-scores for each visit are plotted over time for the treatment of placebo, quetiapine and total for study 150 (See Appendix A).

Table 10 Study 150: 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**	1.20	113	**-0.1**	1.40	175	**0.0**	1.34
Week 26	41	0.4	1.05	86	0.1	1.22	127	0.2	1.17
Final Visit	62	**0.5**	1.03	113	**0.2**	1.25	175	**0.3**	1.19
149 DB Baseline	67	**1.0**[a]	1.01	138	**0.9**[a]	1.06	205	**0.9**[a]	1.04
Week 26	37	1.2	0.97	77	1.2	0.96	114	1.2	0.96
Final Visit	63	**1.2**	0.95	135	**1.0**	1.03	198	**1.1**	1.00
DB Total Baseline	129	**0.6**	1.15	251	**0.4**	1.32	380	**0.5**	1.27
Week 26	78	0.8	1.08	163	0.6	1.22	241	0.7	1.18
Final Visit	125	**0.9**	1.04	248	**0.7**	1.21	373	**0.7**	1.16

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

Schizophrenia patients with ≥ 0.5 shift in standardized BMI Z score

A higher percentage of quetiapine treated patients (15 % at the end of treatment) had ≥ 0.5 shift in standardized BMI Z score compared to placebo treated patients (3 % at the end of treatment). (See Table 11).

A higher percentage of prior placebo treated patients, who enrolled in study 150, (27.4 % at the end of treatment) had ≥ 0.5 shift in standardized BMI Z score compared to prior quetiapine treated patients (21 % at the end of treatment). (See Table 11).

A higher percentage of prior placebo treated patients, who enrolled in study 150, (24.2 % at EOT) vs. prior quetiapine treated patients (14.2 % at EOT) from the OL baseline for schizophrenia had ≥ 0.5 shift in standardized BMI Z score. (See Table 11).

Table 11 Patients with ≥ 0.5 shift in standardized BMI Z score in Study 112 and patients from study 112 extending into Study 150

Occurrence	Double blind Study 112		Study 112 to OL Study 150		
Time/baseline	All Quetiapine	Placebo	DB All Quetiapine	DB Placebo	OL All - Quetiapine
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
End of Treatment /DB	22/147 (15)	2/75 (3)	24/113 (21)[a]	17/62 (27.4)[a]	41/175 (23.4)[a]
End of Treatment /OL			16/113 (14.2)[b]	15/62 (24.2)[b]	31/175 (18)[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

Patients with ≥ 0.5 shift in standardized BMI Z score in Study 150 by indication

A higher percentage of schizophrenia patients, (who enrolled in study 150) treated with prior placebo (27.4 % at EOT) had ≥ 0.5 shift in standardized BMI Z-score compared to prior quetiapine treated patients (21.2 % at EOT) from the DB baseline of study 112. (See Table 12).

A higher percentage of schizophrenia patients (who enrolled in study 150) treated with prior placebo (24 % at EOT) had ≥ 0.5 shift in standardized BMI Z-score compared to prior quetiapine treated patients (14.2 % at EOT) from the OL baseline. (See Table 12).

A similar percentage of bipolar patients (who enrolled in study 150) treated with prior placebo (19 % at EOT) had ≥ 0.5 shift in standardized BMI Z-score compared to prior quetiapine treated patients (21.5 % at EOT) form the DB baseline of study 149 (See Table 12).

A higher percentage of bipolar patients (who enrolled in study 150) treated with prior placebo (19 % at EOT) had ≥ 0.5 shift in standardized BMI Z score compared to prior quetiapine treated patients (8.3 % at EOT) form the OL baseline (See Table 12).

Table 12 Patients with ≥ 0.5 shift in BMI Z score in Study 150 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

Of all patients who completed 26 weeks of treatment with quetiapine, 18.3% (44/241) had a shift of ≥ 0.5 BMI Z-score.

Patients with ≥ 0.5 shift in standardized BMI z score in Study 150 by age group

A similar percentage of ≤ 12 years old patients (who enrolled in study 150) treated with prior placebo (28 % at EOT) had ≥ 0.5 shift in standardized BMI Z score compared to prior quetiapine treated patients (25 % at EOT) from the DB baseline (See Table 13).

A higher percentage of ≤ 12 year old patients (who enrolled in study 150) treated with prior placebo (24 % at EOT) had ≥ 0.5 shift in standardized BMI Z-score compared to prior quetiapine treated patients (8.6 % at EOT) from the OL baseline (See Table 13).

A similar percentage of 13-18 year old pediatric patients (who enrolled in study 150) 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 13).

A higher percentage of 13-18 year old pediatric patients (who enrolled in study 150) 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 13).

Table 13 Patients with ≥ 0.5 shift in BMI Z score in Study 150 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)

5.2 Adult clinical trial data

An analysis of SEROQUEL and long-term weight gain was performed. This retrospective study assessed the magnitude and pattern of weight change during long-term treatment with SEROQUEL. Analysis of data collected from patients with schizophrenia, who were treated with SEROQUEL in AstraZeneca clinical trials from July 1993 to May 1999, was performed.

Weight changes were analyzed in patients treated for 12 weeks (± 4 days), 52 weeks (±30 days), and 104 week (±45 days). To be eligible for inclusion in the analyses patients had to have weight measurements recorded at baseline, and at the relevant time points (12, 52, 104 weeks). The primary cohort was the 52-week group.

All concomitant medications were stopped before entry into the trials, but in some concomitant antipsychotic medication was permitted during the open-label extension phases. Data were analyzed for all patients receiving quetiapine, and for the subgroup of patients who received quetiapine monotherapy.

In total, 378 patients with schizophrenia had weight data available after treatment with quetiapine for 12 weeks; of these 340 received quetiapine Monotherapy. Mean (95% CI) weight gain was 1.46 (0.98, 1.95) kg for all patients and 1.48 (0.98, 1.99) kg for the monotherapy group. Median weight gain was 1.15 kg for all patients and 1.36 kg for the monotherapy group.

In total, 352 patients with schizophrenia had weight data available after treatment with quetiapine for 52 weeks; of these 297 received quetiapine Monotherapy. Mean (95% CI) weight gain was 3.19 (2.27, 4.11) kg for all patients and 3.59 (2.57, 4.61) kg for the Monotherapy group.

In total, 166 patients with schizophrenia had weight data available after treatment with quetiapine for 104 weeks; of these, 143 received quetiapine Monotherapy. Mean (95% CI) weight gain was 5.16 (3.62, 6.70) kg for all patients and 5.59 (3.98, 7.20) kg for the Monotherapy group. Median weight gain was 4.1 kg for all patients and 4.5 kg for the Monotherapy group.

Ninety-seven patients with schizophrenia had bodyweight data available at Weeks 12, 26, and 52. These data indicate that during one year of treatment with quetiapine, 69% of the total mean weight gain occurred within the first 12 weeks and 96% in the first 26 weeks. Similarly, data from the 12, 52, 104 week cohort (n = 5) indicated that 62% of the total weight gain occurred in the first 12 weeks of treatment. Furthermore, 99% of weight gain occurred in the first year, with negligible weight change between one and two years.

The results of the analysis show that long-term treatment with quetiapine monotherapy was associated with moderate weight gain in patients with schizophrenia. Most weight gain occurs within the first 12 weeks of treatment and has no clear dose relationship. (Brecher et al 2007)

5.2.1 Acute placebo-controlled trials

The data below is taken from the cumulative clinical trial database (v15) for quetiapine. In acute placebo-controlled trials of quetiapine in adult patients (≥18 years of age) the incidence rate in patients with ≥ 7 % weight gain was 9.6 % in the quetiapine group and 3.8 % in the placebo group. The relative risk estimate was 2.5 (95% CI: 3.00, 2.10). (see Table 14).

The incidence rate in adult patients with weight gain ≥ 7 % in all trials was 18.2 % (see Table 15).

Table 14 Incidence and relative incidence for weight gain risk, adult subjects – all Placebo-controlled trials

Risk	QTP incidence rate N=7481	Pla incidence rate N=3501	Relative incidence compared to Pla	Relative incidence 95% CIs	
	n (%)	n (%)	Ratio	Lower	Upper
Weight gain (> 7% increase)	721 (9.6)	134 (3.8)	2.5	2.1	3.0

CI Confidence interval. Pla Placebo. QTP Quetiapine.
Numbers in heading are patients with weight values at baseline and at least one value post baseline.
Note: Patients with multiple adverse events are counted only once.
Note: Percentages are calculated as (n/N)*100.
Note: Trial D1448C00005, D1444C00004, D1447C00126, D1447C00144, D1448C00012 and D1447C00127 are excluded due to their initial uncontrolled open label phase prior to the randomised phase. Only the acute phase is included for trial D1447C00001and D1447C00134.
Program: Reg-Def\Prolactin May 08 MHRA\...\weigth_inc_pla_ctr.SAS. Programmer: F Strömberg. 2008-06-18 15:23. DB version: 15

Table 15 Incidence weight gain, adult subjects – all trials

Risk	QTP incidence rate N=22382
	n (%)
Weight gain (> 7% increase)	4070 (18.2)

Number in heading are patients with weight values at baseline and at least one value post baseline.
Note: Patients with multiple adverse events are counted only once.
Note: Percentages are calculated as (n/N)*100.
Program: Reg-Def\Prolactin May 08 MHRA\...\weigth_inc_all.SAS. Programmer: F Strömberg. 2008-06-26 9:14. DB version: 15

6. HOUSE SAFETY DATABASE OR POST-MARKETED USE

The post-marketing data was not reviewed for this topic.

7. DISCUSSION

Weight gain reported in pediatric patients taking SEROQUEL was identified as a subject for review by pharmacovigilance processes internal to AstraZeneca. In addition, we have reassesed the frequency of adult weight gain from the clincial trial data. The current Core Data Sheet reference to weight gain is based on adverse evnent report data and not acutal weight data.

In two acute placebo-controlled clinical trials with quetiapine in pediatric patients the incidence rate of patients with ≥ 7 % weight gain was 15.68 % respectively in the quetiapine group and 2.68 % in the placebo group. Using an increase of at least 0.5 standard deviation from baseline in BMI as a measure of clinically significant change, X% of patients on quetiapine met this criterion after 26 weeks of treatment.

In acute placebo-controlled trials of quetiapine in adult patients (≥18 years of age) the incidence rate in patients with ≥ 7 % weight gain was 9.6 % in the quetiapine group and 3.8 % in the placebo group. The relative risk estimate was 2.5 (95% CI: 3.00, 2.10). The incidence rate in adult patients with weight gain ≥ 7 % in all trials was 18.2 %.

The current Core Data Sheet refers to Weight Gain as common in Section 4.8 in the adult population, which is based on AE reports and not actual weight data.

Safety Evaluation and Review Meeting (SERM) is asked to consider whether the SEROQUEL CDS requires amendment with respect to the incidence of weight gain in pediatric and adult patients taking SEROQUEL.

8. REFERENCES

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