AstraZeneca

Clinical Overview

Drug Name Quetiapine fumarate

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SEROQUEL™ and SEROQUEL XR ™ (quetiapine fumarate)

Clinical Overview on Weight Gain

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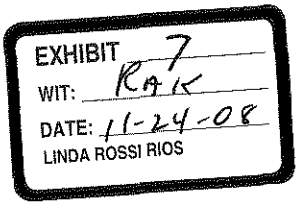

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1. PRODUCT DEVELOPMENT RATIONALE

1.1 Introduction

The Core Data Sheets for SEROQUEL and SEROQUEL XR are 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.

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.

1.2 Proposed label change

The event of weight gain is to be changed from common to very common in the table in Section 4.8 *Undesirable effects* of the SEROQUEL and SEROQUEL XR Core Data Sheets. In addition, footnote three will be updated as follows (new text: double underline):

Undesirable effects

Frequency	System organ class	Event
Very common (≥10 %)	Investigations	Weight Gain[3]

[3] Based on >7% increase in body weight from baseline. Occurs predominantly during the early weeks of treatment in adults.

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

The frequency of weight gain previously categorized as uncommon was based on adverse event (AE) data from AstraZeneca clinical trials. Beginning in approximately 2001, according to AstraZeneca standard operating procedure (SOP 110-G), abnormal laboratory/vital signs values are not reported as AEs unless the abnormal value fulfils any criterion for a serious AE (SAE), the abnormal value results in the subject's discontinuing from the study (DAE) or the investigator insists that the abnormal value be reported as an AE. Symptoms associated with the abnormal laboratory value are reported as AEs. Thus, since this percentage includes AE reports both before and after the institution of this SOP, the percentage is difficult to interpret.

5.1.1 Acute placebo-controlled trials

The data below are taken from the cumulative clinical trial database (v15 [through 18 June 2008]) 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 1).

Table 1 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

5.1.2 All Trials

In all adult quetiapine clinical trials, the incidence of patients who had an increase of ≥7% of their body weight from baseline at any time was 18.2% (see Table 2).

Table 2 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.
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5.1.3 Overall summary of adult clinical trial data

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. In all adult quetiapine clinical trials, the incidence of patients who had an

increase of ≥7% of their body weight from baseline at any time was 18.2%. Therefore, the incidence of weight gain is to be changed from common to very common in the SEROQUEL and SEROQUEL XR Core Data Sheet, which represents the frequency in patients ≥18 years of age. In addition, the frequency will be changed from representing AE reports to actual weight gain data.

6. BENEFITS AND RISKS CONCLUSIONS

The purpose of this application is to update the SEROQUEL and SEROQUEL XR Core Data Sheets 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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Correll CU, Carlson HE. Endocrine and metabolic adverse effects of psychotropic medications in children and adolescents. J. Am. Acad. Child. Adolesc. Psychiatry. 2006; 45 (7):771-791.

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

CLINICAL:

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Date:

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.