CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-172s000

SUMMARY REVIEW

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 15, 2007

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for approval action for Seroquel XR (quetiapine) tablets for the maintenance treatment of schizophrenia

TO: File NDA 22-172
[Note: This overview should be filed with the 1-22-07 original submission of this NDA.]

1.0 BACKGROUND

Quetiapine is an atypical antipsychotic (5HT2/D2 antagonist) that is approved in an immediate release form, i.e., Seroquel, for the treatment of schizophrenia, manic episodes associated with bipolar disorder (i.e., either bipolar I or II), and bipolar depression. Seroquel IR needs to be given on a bid or tid basis. Seroquel XR is a sustained release form of quetiapine that is available in strengths of 200, 300, and 400 mg/day. Seroquel XR was approved on 5-17-07 for the acute treatment of schizophrenia, in a dose range of 400-800 mg/day. We had previously agreed with the sponsor that a maintenance study of an extended release formulation of quetiapine in schizophrenia would satisfy a phase 4 commitment to conduct a maintenance study for this compound. This NDA provides data from a maintenance study to fulfill this commitment and to obtain a maintenance claim in schizophrenia.

2.0 CHEMISTRY

This NDA has cross-referenced NDA 22-047 for Seroquel XR and, thus, the only additional CMC issues for review were a site inspection and EA. Both were found acceptable, and CMC has recommended an approval action.

3.0 PHARMACOLOGY

There were no pharm/tox issues for review in this NDA.

4.0 BIOPHARMACEUTICS

There were no biopharm issues for review in this NDA.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Study D1444C00004

Our review of this application focused on Study D1444C00004, a multicenter (Bulgaria, Poland, Russia, Ukraine, and India), double-blind, parallel group, placebo-controlled, flexible-dose randomized withdrawal study in adult patients meeting DSM-IV criteria for schizophrenia. The first part of this trial was a 16-week, open-label stabilization phase during which 327 schizophrenic patients who were already taking a stable dose of another antipsychotic agent (for at least 4 weeks) and were deemed to be stable by the investigator were crossed over to Seroquel XR (flexible dose range of 400 to 800 mg/day) to maintain a stable responder status. Cross titration was achieved by phasing out the previous antipsychotic drug over 4 days, and phasing in Seroquel XR with 300 mg on day 1, 600 mg on day 2, and then titration in the 400-800 range. The following criteria were used for establishing stability during the 16-week stabilization period: (1) CGI-S $\leq$4 and PANSS total score $\leq$60 (with no change $\geq$10 points in this score from beginning to end and during the last 8 weeks of this period); (2) received stable dose of Seroquel XR. N=197 patients who achieved this status were then randomized to receive either the same dose of Seroquel XR that was needed to maintain stability or to placebo. The planned observation period for relapse was for up to 1 year, and the primary endpoint was time to relapse. Relapse was defined as:

-Hospitalization due to worsening of schizophrenia,
-An increase of PANSS total score of 30% from baseline,
-A rating of much worse or very much worse on the CGI-I, or
-Need for other antipsychotic medication to treat the psychosis.

The primary analysis model was the Cox proportional hazard model. The SAP provided for 2 interim analyses, with use of the O'Brien-Flemming method. At the first interim analysis (at 45 relapses), the DSMB recommended stopping the study for efficacy. At this point, the maximum observation interval was 9 months. The ITT sample was n=171 (87 on placebo and 84 on Seroquel XR). The hazard ratio favoring Seroquel XR over placebo on time to relapse was 0.16 ($p<0.0001$). The relapse rates were 41% for placebo and 11% for Seroquel XR. The results were robust to explorations by gender, age, and site. All members of the review team were in agreement that this was a positive study.

5.1.3 Conclusions Regarding Efficacy Data

The sponsor has, in my view, provided sufficient evidence to support the claim of maintenance efficacy for Seroquel XR in the treatment of schizophrenia.

5.2 Safety Data

The safety data for this supplement were derived from the 327 patients enrolled in the open label phase of Study 004, a smaller number of whom were continued in the double-blind phase of that study. There were no new or unusual safety findings that emerged from this experience that would impact on an approval decision or on labeling.

5.3 Clinical Sections of Labeling

We have made a number of modifications to the sponsor's proposed labeling and reached agreement with them on final labeling. As part of this approval action, we required that the Seroquel XR labeling include a black box for suicidality as Seroquel immediate release does. The box was added to Seroquel when it gained an indication for bipolar depression. This was a fairly conservative decision given the very different pharmacology of quetiapine compared to the other drugs with antidepressant claims. However, given that quetiapine now falls within the general class of "antidepressants," we felt it was appropriate. Although Seroquel XR does not have the bipolar depression claim, we felt we needed to add the same warning language because it is the same active compound.

6.0 WORLD LITERATURE

The sponsor provided a warrant that they reviewed an update of the literature beyond what they had provided for the previous NDA, and found no relevant papers that would adversely affect conclusions about the safety of Seroquel XR in the treatment of schizophrenia.

7.0 FOREIGN REGULATORY ACTIONS

Seroquel XR is apparently approved in Hungary, Slovakia, and the Netherlands for the treatment of schizophrenia.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this application to the PDAC.

9.0 DSI INSPECTIONS

Inspections were conducted at 2 sites from this maintenance study (both in the Ukraine). The data from these sites were deemed to be acceptable.

10.0 LABELING AND APPROVAL LETTER

10.1 Labeling

As noted, we have reached agreement with the sponsor on final labeling.

10.2 Foreign Labeling

We have not reviewed foreign labeling for Seroquel XR.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that the sponsor has submitted sufficient data to support the conclusion that Seroquel XR is effective and acceptably safe in the maintenance treatment of schizophrenia. In addition, we have reached agreement with the sponsor on final labeling. Thus, we will issue an approval letter for this NDA.

cc:
Orig NDA 22-047
HFD-130
HFD-130/TLaughren/MMathis/NKhin/MChuen/KUpdegraff

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/s/

Thomas Laughren
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MEDICAL OFFICER