CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022047Orig1s000

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: May 17, 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 short-term treatment of schizophrenia

TO: File NDA 22-047
[Note: This overview should be filed with the 7-17-06 original submission of this NDA.]

1.0 BACKGROUND

Seroquel (quetiapine) is an atypical antipsychotic (5HT2/D2 antagonist) that is approved in the immediate release form 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 would be available in strengths of 50, 200, 300, and 400 mg/day. This NDA includes data in support of Seroquel XR for the acute treatment of schizophrenia, in a dose range of 400-800 mg/day. During development we let the sponsor know that one positive study would be sufficient to support this claim, given the positive data for the IR form.

2.0 CHEMISTRY

All the CMC issues have been resolved and this application can be approved from a CMC standpoint.

3.0 PHARMACOLOGY

There were no pharm/tox data requested or submitted, so the only pharm/tox issue was a review of labeling in the new PLR format. The pharm/tox group has found the new labeling to be acceptable from their standpoint.

4.0 BIOPHARMACEUTICS

Seroquel XR is a sustained release formulation of quetiapine. Tmax occurs at about 6 hours and this has a lower Cmax than seen with Seroquel. Steady state is reached after several days. AUCs for the same mg dose of the IR and XR formulations are equivalent. There are no biopharmaceutic issues that would preclude an approval action for this NDA.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Our review of this application focused on 3 randomized, double-blind, placebo-controlled, fixed-dose, parallel group, short-term (6-week) multicenter studies in adult patients meeting DSM-IV criteria for schizophrenia (132, 041, and 133). Only one of these studies, 132, a non-US study, was positive. The primary endpoint for all 3 studies was change from baseline to endpoint in PANSS total score.

Study 132: This non-US study included Seroquel XR doses of 400, 600, and 800 mg/day and a Seroquel IR dose of 400 mg/day. All 3 XR doses and the IR dose were statistically superior to placebo, with a numerical advantage for the higher 2 XR doses (31 point improvement from baseline for both 600 and 800 mg) compared to a 25 point improvement for the 400 mg XR dose and a 19 point improvement for placebo (for the LOCF analysis). The pharmacometrics group was able to demonstrate a clear dose response relationship for this study (this relationship was much clearer for the MMRM analysis, a much better analytical approach for these data than LOCF). The robust treatment effect for placebo was somewhat unusual. Also unusual was the relatively low dropout rate across all treatment groups (roughly 25% across the groups, including only a 28% rate for placebo). LOCF was the primary analysis, but OC and MMRM sensitivity analyses were also positive. Despite some unusual features to this study (relatively robust placebo response and relatively low dropout rates across all treatment groups), I agree with Drs. Chuen, Dinh, and Khin that this is a positive study.

Study 041: This US and Canadian study included Seroquel XR doses of 300, 600, and 800 mg/day and Seroquel IR doses of 300 and 600 mg/day. The dropout rate was higher for this study than for study 132, roughly 60% and again fairly uniform across all treatment groups. The efficacy results were not impressive in this trial, with only the 600 mg XR dose showing statistical superiority over placebo, with all other drug groups failing to distinguish from placebo.

Study 133: This US study included Seroquel XR doses of 400, 600, and 800 mg/day and a Seroquel IR dose of 800 mg/day. There was little indication of positive effects for any of the dose groups in this trial.

5.1.2 Comment on Other Important Clinical Issues Regarding Efficacy

Evidence Bearing on the Question of Dose/Response for Efficacy

As noted, there was a clear demonstration of dose response in study 132, the only consistently positive study.

Clinical Predictors of Response

Exploratory analyses were done to detect subgroup interactions on the basis age and gender, however, there were not sufficient data to explore racial differences in efficacy. There was no indication of any difference in effectiveness based on these analyses.

Size of Treatment Effect

The effect sizes as measured by the difference between drug and placebo in change from baseline on the PANSS was reasonably consistent with other trials in this indication.

Duration of Treatment

There is no information from this program pertinent to the question of longer-term efficacy for schizophrenia for Seroquel XR. However, the sponsor has now submitted data from a maintenance trial with Seroquel XR in schizophrenia and this application is currently under review.

5.1.3 Conclusions Regarding Efficacy Data

The sponsor has, in my view, provided sufficient evidence to support the claim of short-term efficacy for Seroquel XR in the treatment of schizophrenia, if considered in the context of multiple positive schizophrenia studies with the IR formulation.

5.2 Safety Data

The safety data for this supplement were derived from a total of over 1500 patients exposed to Seroquel XR at doses ranging from 300 to 800 mg/day across 21 studies. Overall, the observed safety profile of Seroquel in this population, including adverse events, labs, vital signs, and ECGs was the same as that observed in the other populations exposed to this drug. Thus, I agree with Drs. Khin and Dubitsky that the sponsor has adequately assessed the safety of Seroquel XR in schizophrenia.

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 of 5-17-07). I would note that the Seroquel XR labeling does not include the 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 very conservative decision given the very different pharmacology of quetiapine compared to the other drugs with antidepressant claims. We considered adding this to Seroquel XR as well, but decided not to, in part because it does not have the bipolar depression claim but also because there is not a hint from the actual data for quetiapine that there is any induction of suicidality. We will continue to consider this issue, however, as the maintenance NDA for Seroquel XR is actively under review.

6.0 WORLD LITERATURE

The sponsor provided a warrant that they reviewed the literature 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

To my knowledge, Seroquel XR is not approved anywhere at this time 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 one positive study (both in the Philippines). 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

Seroquel XR is not approved anywhere at this time for the treatment of schizophrenia.

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 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/GDubitsky/KUpdegraff

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/s/

Thomas Laughren
5/17/2007 09:40:27 AM
MEDICAL OFFICER