CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203479Orig1s000

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: 6 February 2013

FROM: Mitchell V. Mathis, M.D.
Acting Director
Division of Psychiatry Products, HFD-130

TO: File NDA 203479 [28 December 2011 submission]

SUBJECT: Approval recommendation for clozapine oral suspension (50 mg/mL) for the treatment of treatment-resistant schizophrenia and for reducing the risk of suicidal behavior in patients with schizophrenia or schizoaffective disorder

Background and Regulatory History

Clozapine was the first approved (1989) atypical antipsychotic. It is indicated for the treatment of treatment-resistant schizophrenia and it is the only drug approved (2002) to reduce suicidal behavior in patients with schizophrenia or schizoaffective disorder. Douglas Pharmaceuticals submitted this NDA under 505(b)(2) to evaluate clozapine oral suspension for the two approved indications. There is no oral clozapine suspension or oral clozapine solution approved in the U.S.

A single bioequivalence study comparing clozapine oral suspension to clozapine oral tablets was submitted for review. Clinical PK and safety data were collected from this study and there was no requirement for an efficacy study.

The currently approved products all have a "deemed" REMS in place that requires regular monitoring of white blood cell and absolute neutrophil counts, and a restricted distribution system to ensure safe use. This product also has a REMS with ETASU.

The study submitted demonstrated bioequivalence between the oral suspension and the reference listed drug (Clozaril tablets), but there were several inspection deficiencies identified during the initial 10-month review cycle. The Agency conveyed these deficiencies to the sponsor and their response required an extension of the review clock by 3 months.

Chemistry Manufacturing and Controls

Dr. Thomas Wong reviewed the application. He examined the DMF, excipients, manufacturing process, process controls, impurities, validation of the analytical procedures, the container closure system, microbial attributes and the compatibility with the oral syringe for product administration. He found the data submitted to support the drug substance and product to be acceptable, but he could not make a recommendation of approval because the Office of Compliance had yet to provide a final recommendation from their inspection of the manufacturing site. OC had a positive determination 6 February 2013 and so the application is approvable from a CMC standpoint.

Division of Good Manufacturing Practice Assessment
Dr. Linda Ng conducted the ONDQA/ GMP review. In October 2012, the District Office of Compliance conducted a pre-approval inspection of the finished product facility and noted deficiencies (problems with suspension/emulsion). She found that the master production and control records were deficient in that they did not include complete manufacturing parameters and instructions (e.g., missing (b) (4) speed, specific (b) (4) to be used, minimum holding tank fill volume required, position of (b) (4), maximum hold time to filling). Because of these deficiencies, the District Office recommended Withhold and CDER Office of Compliance (OC) concurred. These deficiencies were addressed and we obtained an acceptable recommendation from OC on 6 February 2013.

The drug substance manufacturer inspection was uneventful and the drug substance was found Acceptable upon inspection.

Microbiology
Dr. Pawar conducted the microbiology review and found all data acceptable and no microbiology deficiencies.

Nonclinical Pharmacology/Toxicology
Dr. Chalecka-Franaszek conducted the review and concluded that no additional nonclinical safety data were required for review for this NDA.

Office of Clinical Pharmacology
Dr. Jackson conducted the review. His focus was the PK data from the pivotal bioequivalence study. This study site was inspected and the clinical and analytical data generated were found to be acceptable.

Study ZPS 41-C11-005-LLB was a multicenter(3), randomized, double-blind, multiple dose, two-treatment crossover bioequivalence study conducted under fed and fasting conditions. Thirty subjects who were being treated with clozapine and who were clinically stable for at least three months were randomized to test or reference listed drug, treated for 10 days and then crossed over. Food effect was examined with a standard USFDA high-fat meal.

Dr. Jackson concluded that the PK results demonstrated that the test drug met the 90% confidence intervals for AUC and Cmax and were within the acceptable limits of 80-125% of the reference product. There was a small food effect for both products that clinical team concluded was clinically irrelevant and similar for both products. See Drs. Jackson (OCP) and Levin's (clinical) reviews for details; summary results from the study are presented below.

Summary Results:

Fasting Pharmacokinetic Results:

Pharmacokinetic Parameters	Clozapine 50 mg/ml suspension (II) Batch: 7805.005A, Douglas, America (n=30) (mean ± S.D) (Range)	Clozaril® 100 mg tablets (I) Batch: F0133, Novartis, USA (n=30) (mean ± S.D) (Range)
AUC_{0-t} (ng.hr/ml)	3223.09±1452.61 (721.51-8329.98)	3284.70±1355.04 (978.22-7602.87)
Cmax (ng/ml)	275.01±104.90 (104.59-722.84)	275.09±98.69 (127.92-654.14)
Cmin (ng/ml)	74.70±38.73 (10.73-197.73)	74.64±40.79 (9.10-210.56)
DF (%)	163.01±51.22 (85.70-312.22)	157.73±45.98 (92.68-291.50)
Tmax (hr)	2.18±0.85 (1.00-3.52)	2.53±1.25 (1.00-6.00)

	Clozapine 50 mg/ml suspension (II) vs Clozaril® 100 mg tablet (I)			
	Anova	Mean ratio %	Geometric mean ratio %	90% confidence interval
$Log_{10}(AUC_{0-t})$	0.161	99.55	-	(0.924,1.007)*
Log_{10}(Cmax)	0.870	99.91	-	(0.946,1.047)*
Log_{10}(Cmin)	0.559	100.29	-	(0.978,1.047)
AUC_{0-t}	0.429	98.12	96.44	(0.942,1.021)
Cmax	0.993	99.97	99.51	(0.947,1.052)
Cmin	0.968	100.09	101.20	(0.964,1.037)
DF	0.300	103.35	-	(0.980,1.087)
Tmax	0.139	86.23	-	(0.709,1.016)
Tmax[a]	-	-	-	(0.764,1.002)

* Criteria used to assess Bioequivalence i.e. 90% CI between 0.80 and 1.25 for AUC_{0-t} and Cmax

[a] Nonparametric Analysis

Clinical
Dr. Ritter reviewed the safety data from the trial. There were no new or unexpected safety findings compared to the known safety and tolerability profile of clozapine, and there were no clinically significant laboratory or ECG findings.

Division of Risk Management and Product REMS
Dr. Lehrfeld reviewed the sponsor's proposed REMS and recommended revisions to clarify the compliance and monitoring schedule for white blood cell and absolute neutrophil count monitoring prior to dispensing the product. The sponsor accepted the revisions and the REMS has been finalized.

Clozapine labels (including this one) have a boxed warning for severe neutropenia and agranulocytosis. The innovator product was approved with a risk management program that requires the sponsor to maintain a registry of all prescribers, pharmacists, and patients in the clozapine program. The program is designed to ensure that clozapine is only dispensed to enrolled patients with normal total leukocyte and absolute neutrophil counts as defined in labeling.

Clozapine was included among the products required to have an approved REMS ("deemed" REMS) under section 505-1 of the FDAAA of 2007; all sponsors submitted REMS and those are currently under review, but in the meantime, clozapine products are marketed with risk minimization action plans (RiskMAPs). This product will be approved with a formal REMS to meet the current regulatory standard. The goal of the REMS is to reduce the risk of severe neutropenia and includes elements to assure safe use (ETASU), a communication plan, and implementation plan, and a timetable for submission of assessments. See Dr. Lehrfeld's review for details about the REMS.

Division of Medication Error Prevention and Analysis (DMEPA)
Dr. Holmes conducted the DMEPA labeling review. She also reviewed the sponsor's proposed product packaging, container and carton labeling, and instructions for use. The product kit contains bottles and oral syringes (2 different sizes for different doses) and there is a risk for medication errors (primarily inaccurate dosing). Several labeling deficiencies (error-prone symbols, unclear patient instructions, and use of potentially ambiguous abbreviations) were identified during the review, and this information was conveyed to the sponsor. The sponsor responded to DMEPA's requests and corrected these problems to the satisfaction of DMEPA. Dr. Holmes proposed and the sponsor agreed to conduct a human factors (usability) study post-approval to assess how kit packaging and labeling is performing to limit medication errors.

Revised Labeling
This label is formed to the Physician Labeling Rule (PLR) guidelines for labeling. The labeling was negotiated with sponsor and we have agreed on a final version.

Pediatric Plan
The sponsor asked for, the division agreed with, and the Pediatric Review Committee (PeRC) granted a full waiver to study adolescents and children. There are a very limited number of young patients with treatment-resistant schizophrenia, and all agree a study in pediatric patients would be impractical.

Conclusions and Recommendations

The sponsor has conducted an adequate bioequivalence study to support approval of this product; there were no new or unexpected clinical safety findings compared to what is known about the reference product. The review team has recommended approval of this product and I agree with the team. The manufacturing issues have been resolved to the CMC team's and the Office of Compliance's satisfaction. Labeling has been negotiated and finalized.

The sponsor has agreed to labeling, the REMS, and they have agreed to conduct a usability study postmarketing as described above.

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/s/

MITCHELL V Mathis
02/06/2013