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APPLICATION NUMBER:

203479Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

NDA 203479 Cross-Discipline Team Leader Review Memorandum

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| Date of Review | February 06 2013 |
| From | Robert L. Levin, M.D. |
| Subject | Cross-Discipline Team Leader Review |
| NDA | 203479 |
| Related IND | 108466 |
| Sponsor | Douglas Pharmaceuticals America LTD |
| Submission Date | January 7, 2012 |
| Proprietary / Established name | Versacloz Clozapine Oral Suspension |
| Dosage forms / strength: | Oral Suspension Concentration: 50 mg clozapine per 1 mL |
| Proposed Indications: | 1. Treatment Resistant Schizophrenia 2. Recurrent Suicidal Behavior in Schizophrenia or Schizoaffective Disorder |
| Recommended Action: | Approval |

1. Introduction

Clozapine is the first atypical antipsychotic. On September 26, 1989 Clozaril (clozapine tablets) was approved for treatment-resistant schizophrenia; it is the only drug approved for this indication. On December 18, 2002 Clozaril was approved for reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder; it is the only drug approved for this indication.

On 07 January 2012, Douglas Pharmaceuticals submitted NDA 203479: clozapine oral suspension (Versacloz) for the two indications above. This is a 505(b)(2) application for a new dosage formulation of clozapine, referencing Clozaril Tablets. Currently, there is no oral suspension or oral solution formulation of clozapine in the US. The application is based on a single clinical bioequivalence study comparing oral clozapine suspension to clozapine oral tablets. The sponsor has submitted clinical PK and safety data from the bioequivalence study. There was no requirement to conduct an efficacy and safety study. The submission also includes CMC, microbiological, and biopharmaceutics data. The sponsor has also submitted a Risk Evaluation and Mitigation Strategy (REMS) with elements to assure safe use (ETASU).

The bioequivalence study demonstrated bioequivalence between clozapine oral suspension (Versacloz) and the reference list drug, Clozaril tablets. However, the Office of Compliance observed a number of critical CMC deficiencies upon inspection of the finished product manufacturing site. During the initial 10-month review cycle, the Agency conveyed to the sponsor. The Division granted a 3-month extension of the review period for the sponsor to address the CMC problems. The sponsor has provided acceptable data regarding the CMC deficiencies, and there are no unresolved CMC issues.

Reviewers from all disciplines have concluded that there are no unresolved issues, and they support approval of the application. I agree with the conclusions and recommendations of all reviewers, and I recommend approval of the application.

2. Background and Regulatory History

On 29 June 2010, the Division held a Type B Pre-IND meeting with Douglas Pharmaceuticals America to discuss the requirements for a 505(b)(2) NDA for Clozapine Oral Suspension (50 mg per mL). The reference listed product is Clozaril Tablets. The sponsor had previously (from 2003 to 2006) developed and marketed a formulation of clozapine oral suspension that is bioequivalent to the EU innovator product. The product is marketed in New Zealand and Australia (Clopine); it is marketed in the UK, Ireland, and Germany (under various trade names). The sponsor has reformulated the US oral suspension for the NDA, because there were concerns about differences in performance between the US formulation of the Clozaril tablet and the European/Australasian formulation of the Clozaril tablet. During development of the US formulation, the sponsor focused on the following: 1) matching the dissolution profile of the US Clozaril® RLD using the FDA-recommended media and conditions (pH 4, 100rpm, acetate buffer), 2) establishing appropriate re-suspension characteristics, 3) preventing crystallization, 4) retaining appropriate preservation conditions, and 5) accurately controlling the pH of the suspension.

The sponsor proposed a single pivotal bioequivalence study to support the application. They sought confirmation that there would not be a requirement to conduct an efficacy and safety study. The Division agreed with the design of the bioequivalence study. This would be a multicenter, randomized, double-blind, multiple-dose (at steady state) bioequivalence, 2-period, 2-sequence crossover study in patients with schizophrenia who have been stably treated with clozapine (multiples of 100 mg per day). The Division requested one study in the fasted state and one study in the fed state. The Division also confirmed that the sponsor would not be required to conduct an efficacy and safety study. We agreed on the required stability data.

3. Chemistry Manufacturing and Controls

Thomas Wong, Ph.D. filed his initial ONDQA Chemistry Manufacturing and Controls review on August 23, 2012. At that time, Dr. Wong stated that he could not support approval of the application, because the Office of Compliance had not provided a final recommendation regarding the inspection of the manufacturing site. Dr. Wong reviewed data on the following: the drug substance, DMF, drug product, excipients, manufacturing process and process controls, impurities, validation of analytical procedures, the container closure system (stability), and the syringe for oral administration.

Clozapine USP is a tricyclic dibenzodiazepine derivative. It is a yellow, crystalline powder that is almost insoluble in water. The drug product is an immediate-release oral suspension of clozapine. The strength is 50 mg per mL. The suspension is packaged in a

(b) (4) mL (b) (4) amber glass bottle; each bottle contains 100 mL (b) (4).

3.1 Drug Substance and Drug Product

Dr. Wong reviewed the following data on the drug substance: the DMF, particle size distribution, excipients, preservatives, pH requirements, and stability. For the assessment of the drug product, Dr. Wong reviewed data on the following: chemical stability through pH control, suspension stability, preservation, flocculation of the suspension, dissolution profile, impurity profile, inhibition of clozapine crystal growth, (b) (4), and (b) (4). Dr. Wong concluded that the sponsor provided adequate data on the drug substance and drug product, and the results are acceptable.

3.2 Manufacturing Process and Process Controls

Clozapine suspension is manufactured using a (b) (4).
(b) (4)
Dr. Wong reviewed data on the following manufacturing process parameters: batch analysis, (b) (4), content uniformity, transfer of the suspension, stability of the suspension, (b) (4), and finished product testing. Dr. Wong concluded that the results are acceptable. The stability data support the sponsor's proposal for a 24-month expiry; the proposed commercial packaging configuration, storage at room temperature 25C° (77F°), and protection from light are acceptable.

3.3 Container Closure System

Clozapine suspension (50 mg per mL) is packed into amber glass bottles (type (b) (4) fitted with a (b) (4). The exhibit batches were packed into (b) (4) mL amber glass bottles (type (b) (4). Stability studies to date demonstrated that amber glass bottles (type (b) (4) provide good protection for the product. The appearance and the levels of drug substance and impurities have remained constant. Dr. Wong concluded that the results are acceptable.

3.4 Microbiological Attributes

Clozapine 50 mg/mL suspension is a non-sterile, orally administered, dosage form containing antimicrobial preservatives. It is a Category 3 product in reference to the USP Chapter <51>.

The sponsor conducted the following antimicrobial effectiveness testing on the finished drug product: Total microbial aerobic count, total yeast counts, moulds count and Escherichia coli testing. Shelf life limits for both paraben contents of (b) (4) % to (b) (4) % were established based on antimicrobial effectiveness studies. Dr. Wong concluded that the

results of the microbial enumeration test and tests for specified organisms (Esherichia coli) are acceptable and within the drug product specification.

3.5 Compatibility and Oral Dispenser Device (Syringe)

The drug product does not require reconstitution; however, an oral dispenser is required for measuring and administering the dose. The drug product may be (b) (4). Dr. Wong concluded that the sponsor conducted appropriate compatibility studies. The oral dispenser consists of a white, transparent, (b) (4) barrel with a white (b) (4) plunger. Dr. Wong concluded that the results were acceptable from the compatibility/suspension stability testing with the 1 mL and (b) (4) syringes for 14 days. The data from the storage studies indicated that the syringe containing the clozapine suspension must be shaken gently before administration of the dose.

In his review filed on 23 August 2012, Dr. Wong did not recommend approval because (1) the Office of Compliance had not issued a final overall recommendation regarding the cGMP inspections, and (2) the sponsor had not provided data on the accuracy of the dose delivered by the oral syringes.

4. ONDQA/Division of Good Manufacturing Practice Assessment

Linda Ng, Ph.D., Senior Policy Advisor (ONDQA, New Drug Manufacturing Assessment, Division of Good Manufacturing Practice Assessment) performed the ONDQA/Good Manufacturing Practice review (filed on November 2, 2012). In October 2012, the District Office of Compliance conducted a pre-approval inspection of the finished product manufacturing facility: Pharmaceuticals International, Inc. (10819 Gilroy Road, Hunt Valley, Maryland, 21031). This is the manufacturing site for raw materials release, in-process testing, finished product release and stability, and finished dose packaging of Versacloz. Dr. Ng noted that this is the firm's first suspension product. The inspector observed containment issues at the facility and product-specific deficiencies regarding the suspensions, emulsions, and the parameters set in the manufacturing batch record. OC issued a Form 483 to cover multiple products.

In her initial review (filed on November 2, 2012), Dr. Ng stated that the master production and control records were deficient; they did not include complete manufacturing and instructions. Specifically, the Master Production Record and Master Packaging and Labeling Record for Clozapine 50mg/ml, Suspension USP did not include the following elements:

1. Speed of (b) (4) during (b) (4) mixing at the beginning of each (b) (4)
2. Specific (b) (4) to be used during mixing in the (b) (4)
3. Minimum holding tank fill volume required for (b) (4)
4. Height and position of (b) (4) in (b) (4) during

Filling

5. Maximum hold time prior to filling

Furthermore, there were no data to support the proposed mixing times stated in the Master Packaging and Labeling Record instructions which read, “At the beginning of each filling day: (b) (4)

[REDACTED]”

On 31 October 2012, the District Office made a recommendation of Withhold. The CDER Office of Compliance filed the Establishment Evaluation Request Detail Report (EES) on November 1, 2012. The Office of Manufacturing and Product Quality (OMPQ) reviewed the establishment inspection report (EIR) and the FDA 483 for the inspection. OMPQ concurred with the BLT-District Office recommendation of Withhold.

Dr. Ng and CDER/OC/OMPQ/DGMPA/NDMAB concurred with these findings and recommendations. There was a lack of complete manufacturing and control instructions in the master production record, and there were no data to support these instructions for suspension manufacturing. As of 13 January 2013, Pharmaceuticals International Inc. and Douglas had not provided a response to the FDA 483. They provided an engineering study proposal (dated October 18, 2012) to evaluate the process characterization of (b) (4) and to evaluate bulk hold characteristics during bottle filling at their facility. However, the sponsor had not provided a timeline for completion of these activities. The sponsor was required to submit acceptable data from the engineering studies to support the manufacturing instructions.

The CDER Office of Compliance also inspected the drug substance manufacturer: (b) (4) DMF (b) (4). The inspector assessed the manufacture and full release/stability testing of the active pharmaceutical ingredient. The data were acceptable, and OC provided a recommendation of Acceptable for the manufacturer of the API.

As of February 4, 2013, the sponsor has submitted adequate data regarding the CMC deficiencies. Dr. Ng has reviewed the data, and she has concluded that the data are acceptable. Dr. Ng has given a recommendation of “Acceptable,” and she supports approval of the application. The Office of Compliance has provided a recommendation of Acceptable.

5. Microbiology

Vinayak B. Pawar, Ph.D. performed the microbiology review (filed on August 22, 2012). Dr. Pawar reviewed the microbiology data on manufacturing processes for the drug substance, drug product, and the container closure system. The drug substance is non-sterile clozapine oral suspension. Clozapine oral suspension is manufactured using a (b) (4)

[REDACTED]

The drug product contains anti-microbial preservatives.

The Office of Pharmaceutical Science requested that the sponsor provide test methods and acceptance criteria to demonstrate the absence of *Burkholderia cepacia* species in the product. The sponsor provided adequate data to demonstrate that *B. cepacia* is not present in the water system or drug product. Dr. Pawar concluded that the data from all relevant microbiology studies are acceptable. There are no microbiology deficiencies. Dr. Pawar recommends approval of the application. I agree with Dr. Pawar's conclusions and recommendations.

The manufacturing site for the finished product is Pharmaceuticals International Incorporated: 10819 Gilroy Road, Hunt Valley, MD 21031; FDA Registration #: 1000513101.

6. Nonclinical Pharmacology/Toxicology

Elzbieta Chalecka-Franaszek, Ph.D. performed the Pharmacology/Toxicology review (filed on October 9, 2012). The NDA was submitted as a 505(b)(2) application. The Division and the sponsor had agreed that no additional nonclinical safety data were required for this NDA. There are no outstanding nonclinical issues. Dr. Chalecka-Franaszek recommends approval of the application. I agree with Dr. Chalecka-Franaszek's conclusions and recommendations.

The pharmacology/toxicology team has recommended labeling revisions. In the Use in Specific Populations-Pregnancy section, Dr. Chalecka-Franaszek revised language regarding nonclinical reproduction studies. She also provided updated pharmacology data in the Clinical Pharmacology section (Mechanism of Action and Pharmacodynamics). Dr. also Chalecka-Franaszek provided updated data in the Nonclinical Toxicology section (Carcinogenesis, Mutagenesis, and Impairment of Fertility). We have included Dr. Chalecka-Franaszek's recommendations in labeling.

7. Office of Clinical Pharmacology

Andre Jackson, Ph.D. performed clinical pharmacology review (filed on August 7, 2012). Dr. Jackson reviewed the pharmacokinetic data from the pivotal bioequivalence study. He concluded that the sponsor provided acceptable data demonstrating bioequivalence between clozapine oral suspension and the clozapine tablets. I agree with Dr. Jackson's conclusions.

7.1 Bioequivalence Study

Study ZPS 41-C11-005-LBB was a multicenter (3), randomized, double-blind, multiple-dose, two-treatment, two-period, two-sequence crossover bioequivalence study performed under fasting and fed conditions at steady state. The study included 30 subjects currently treated with clozapine for a psychotic disorder. Subjects must have

been clinically stable (for at least 3 months) on clozapine (multiples of 100 mg administered once daily in the evening). There were 25 male and 5 non-pregnant female patients. The study was conducted in New Zealand. The mean age was 38 (range: 24 to 57); the mean body weight was 94 kg (range: 52 to 136 kg); and the mean BMI was 31 (range: 22 to 42). The ethnicities were primarily European descent (n=16) and Maori (n=11). All subjects completed the study.

Subjects were confined to the clinical site from at least 10 hours prior to drug administration on days 10 and 21, until after the 48-hour post-dose PK sampling on days 12 and 23 for each group. The two treatments were clozapine oral suspension (50 mg per mL) and Clozaril[®] tablets (100 mg). The tablets or suspension were administered with 240 mL of water at ambient temperature. Doses were administered in the evening, under fasting and fed conditions at steady state. On Day 10 of each study period, subjects fasted for at least 8 hours prior to administration of the Test or Reference formulation. On Day 11 of each study period, after fasting for at least 7.5 hours and within 5-minutes of consuming a USFDA standardized high-fat meal over a 30-minute period, subjects were administered a multiple dose of either the test or reference formulation as determined by the randomization scheme. PK samples were drawn at the following times: prior to dose administration on study days 1, 7, 8, 9 and post-dose at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 14, 16, 20 and 24 hours on study Days 10 and 11 of each study period. There was no washout period between the two treatment periods.

The pharmacokinetic assessment parameters were: $AUC_{(0-t)}$, C_{max} , C_{min} , T_{max} , and DF. Clozapine plasma concentrations and pharmacokinetic data were normalized to a 100 mg dose so that the results were comparable. The bioequivalence criteria were the 90% confidence interval (CI) of the ratio (Test/Reference formulation) of least squares means from the ANOVA of the log-transformed data.

Pharmacokinetic Results:

Dr. Jackson concluded that the PK results demonstrated that under fasting and fed conditions, the 90% confidence intervals for the log transformed $\text{Log}_{10} AUC(0\text{-tau})$ and $\text{Log}_{10} C_{max}$ of the plasma clozapine concentrations were within the acceptable limits of 80-125% of the reference product. Dr. Jackson noted that for AUC and C_{max} , the small food effect for clozapine suspension was similar to that for clozapine tablets.

For the suspension, the T_{max} in the fasted and fed state was 2.18 and 3.12 hours, respectively. For the tablet, the T_{max} in the fasted and fed state was 2.53 and 4.94 hours, respectively. The presence of food delayed the rate of absorption for both formulations; however, the effect was much larger for the tablet compared to the suspension. Dr. Jackson concluded that these differences in T_{max} are not clinically significant, because clozapine will be administered at steady state. I agree with Dr. Jackson's conclusions and recommendations.

The results of the bioequivalence analyses are summarized in the tables 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) |

| | <i>Clozapine 50 mg/ml suspension (II) vs Clozaril® 100 mg tablet (I)</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

Summary Results:

Fed 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) | 3059.15±1280.21 (702.48-7540.92) | 3090.08±1214.51 (967.96-6970.06) |
| C _{max} (ng/ml) | 220.16±82.73 (82.92-525.20) | 220.48±74.49 (107.39-466.41) |
| C _{min} (ng/ml) | 72.58±40.41 (10.73-219.46) | 71.81±38.54 (9.10-193.64) |
| DF (%) | 122.82±36.76 (64.79-246.64) | 122.46±36.80 (66.34-243.70) |
| T _{max} (hr) | 3.12±2.29 (1.00-12.00) | 4.94±2.84 (1.00-14.00) |

| | 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}) | 0.321 | 99.68 | - | (0.934,1.018)* |
| Log ₁₀ (C _{max}) | 0.604 | 99.72 | - | (0.937,1.035)* |
| Log ₁₀ (C _{min}) | 0.366 | 100.34 | - | (0.988,1.041) |
| AUC _{0-t} | 0.671 | 99.00 | 97.50 | (0.950,1.030) |
| C _{max} | 0.959 | 99.86 | 98.49 | (0.951,1.046) |
| C _{min} | 0.556 | 101.08 | 101.40 | (0.980,1.042) |
| DF | 0.922 | 100.29 | - | (0.954,1.052) |
| T _{max} | 0.004 | 63.17 | - | (0.434,0.830) |
| T _{max} ^a | - | - | - | (0.478,0.756) |

7.2 Office of Compliance Inspection Findings of CMC Facilities

Arindam Dasgupta, Ph.D., from the Bioequivalence Branch, Division of Bioequivalence and GLP Compliance (DBGLPC), Office of Scientific Investigations, performed the review of the inspections findings (filed on July 27, 2012). DBGLPC conducted inspections of the clinical and analytical portions of the bioequivalence study (C11-005-LBB (ZPS 411). The inspections were conducted by the ORA and scientific investigators at Zenith Technology Corporation Ltd. (Site #1), Dunedin, New Zealand. The ORA investigator conducted the inspection of the clinical site #2: Waikato Hospital, Hamilton, New Zealand (by CG). The audits included a thorough review of study records, examination of facilities and equipment, and interviews and discussions with the firms’

management and staff. The Agency issued Form FDA-483 for several, relatively minor observations. Following review and evaluation of the Form FDA-483 observations and responses from the inspected sites, Dr. Dasgupta concluded that the clinical and analytical data generated for study C11-005-LBB (ZPS 411) were not affected by the cited deficiencies; the data for the clinical and analytical portions of study are acceptable. I agree with Dr. Dasgupta's conclusions and recommendations.

8. Biopharmaceutics Review

Deepika Arora Lakhani, Ph.D. performed the biopharmaceutics review. Dr. Lakhani reviewed data on the dissolution method and acceptance criteria. The robustness of the dissolution method was evaluated by assessing the effect of changing dissolution parameters (paddle speed). The discriminating capacity of the dissolution method was evaluated by varying the amount of xantham gum ((b) (4) agent) and (b) (4) agent) in the formulation. Dr. Lakhani concluded that the proposed dissolution method discriminates for xantham gum concentration, and it is acceptable. The following dissolution method for clozapine oral suspension is acceptable: USP Apparatus II, Paddle speed: 50 rpm, Volume/Temp: 900 ml / 37°C, Medium: pH 4.0 Acetate Buffer. FDA recommended specific dissolution acceptance criteria ($Q = \frac{(b)}{(4)}\%$ at 15 minutes); the sponsor agreed with the recommendation. There are no outstanding biopharmaceutics deficiencies. Dr. Lakhani recommends approval of the NDA. I agree with Dr. Lakhani's conclusions and recommendations.

9. Clinical Review

Mark Ritter, M.D. performed the clinical review (filed on January 16, 2013). He reviewed the pharmacokinetic and safety data from the bioequivalence study. Dr. Ritter also considered the reviews from other members of the review team (ONDQA, Office of Clinical Pharmacology, and Biopharmaceutics). Dr. Ritter concluded that the sponsor demonstrated bioequivalence between clozapine oral suspension (Versacloz) and the reference formulation (clozapine tablets). Dr. Ritter recommends approval of the application. I agree with Dr. Ritter's conclusions and recommendations.

Subjects (N=30) must have been previously stably treated with clozapine for at least 3 months before entering the study. Thus, they had tolerated treatment with clozapine. There were no deaths, serious adverse reactions, or discontinuations related to adverse events. There were no new or unexpected safety findings compared to the known safety and tolerability profile of clozapine. There were no significant differences in adverse events or other safety parameters between study drug treatments. The most common adverse events were sedation, dizziness, confusion, constipation, and blurred vision. These were evenly distributed between treatment conditions. There were no clinically significant clinical laboratory or ECG findings.

10. Division of Risk Management (DRISK) and the Versacloz REMS

Kim Lehrfeld, Pharm.D., BCPS reviewed the sponsor's proposed REMS. Dr. Lehrfeld has recommended substantial revisions to the Versacloz REMS. I agree with the

revisions, and the Division has incorporated all of Dr. Lehrfeld's recommended revisions in the FDA Versacloz REMS.

The clozapine label includes a boxed warning and a detailed warning for drug-induced agranulocytosis, which can lead to serious infection and death. Because of this risk, Clozaril (the innovator product) was approved with a risk management program. The risk management programs for all clozapine products require sponsors to maintain a registry of all prescribers, pharmacists, and patients who prescribe, dispense or receive clozapine. In addition, sponsors are required to ensure that clozapine is only dispensed to enrolled patients whose WBC and ANC results are within the acceptable range (as defined in clozapine labeling). To achieve this objective, healthcare providers are required to submit patients' clinical laboratory results, as recommended in current clozapine monitoring guidelines and clozapine labeling.

Clozapine was included on the list of products required to have an approved REMS (deemed REMS) [under section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) with the passage of the Food and Drug Administration Amendments Act (FDAAA) in 2007]. Therefore, all sponsors with clozapine products were required to submit a REMS proposal by September 21, 2008. All REMS submissions are under review. Currently, no marketed clozapine products have an approved REMS. Therefore, clozapine products are marketed under risk minimization action plans (RiskMAPs).

The goal of the Douglas proposed REMS is to reduce the risk of developing agranulocytosis in patients who are prescribed clozapine oral suspension. The components of the Versacloz REMS include elements to assure safe use (ETASU), a communication plan, an implementation plan, and a timetable for submission of assessments. The Versacloz REMS includes the following elements to assure safe use (ETASU):

- Prescriber Certification for enrollment in the registry
- Pharmacy and Pharmacist Certification for enrollment in the registry
- Patient Enrollment in a Registry
- Monitoring Requirements (for WBC and ANC)
- Documentation of Safe Use Conditions

Throughout the review cycle, Dr. Lehrfeld and DRISK reviewed drafts of the sponsor's proposed REMS documents, and they have provided comments to the sponsor. DRISK recommended substantial changes to the REMS documents. They revised the prescriber and pharmacy attestations in the REMS document and REMS enrollment forms to clarify the responsibilities of the stakeholders. In addition, DRISK added a patient signature and patient privacy language to the Patient Enrollment Form.

On October 12, 2012, FDA held a teleconference with Douglas to discuss their response submitted on September 27, 2012. The Agency explained the rationale and regulatory policy regarding the current standard for the REMS document and associated forms. FDA

stated that the proposed changes do not change the REMS operationally; the changes are based on regulatory standards. For approval of this application, the sponsor must accept the Agency's revised language in the Versacloz REMS and supporting documents. In particular, the sponsor must accept the language regarding the prescriber and pharmacist certification, which reflects FDA's current approach to articulating prescriber and pharmacist responsibilities under ETASU A and B. The Agency agreed with Douglas that it's not necessary for the Patient Enrollment Form to include a patient signature and patient privacy language. We reminded Douglas that they must be in compliance with the Health Insurance Portability and Accountability Act (HIPAA) regulations, in order to protect patient health information. The REMS document is a legally binding document between the Agency and Douglas; therefore, the documents must reflect Douglas' responsibility and not a contracted entity.

Douglas accepted the FDA Versacloz REMS. Douglas submitted the final REMS document and REMS materials on November 6, 2012.

Douglas has entered into a business agreement with Jazz Pharmaceuticals (formerly Azur Pharma) for the clozapine registry. Jazz will manage the registry program on behalf of Douglas for Versacloz.

11. Division of Medication Error Prevention and Analysis (DMEPA)

Loretta Holmes, BSN, Pharm.D. performed the DMEPA labeling review (filed on August 9, 2012). Dr. Holmes reviewed: 1) product packaging (component kit), 2) container labels, 3) carton labeling, 4) insert labeling, and 5) Instructions for Use. DMEPA has concerns about the sponsor's proposed kit, which contains bottles and oral syringes. With the proposed kit, there is a risk of medication errors and inaccurate dosing. The product will be supplied in bottles containing 100 mL of Versacloz. The concentration of the clozapine suspension is 50 mg per mL. Dr. Holmes notes that the amount of Versacloz dispensed by the pharmacist to an individual patient may be limited to less than 100 mL, because the patient's individual dose and the frequency of WBC and ANC monitoring determines the amount that can be dispensed under the REMS. Thus, it may be necessary for the pharmacist to dispense partial bottles. Dr. Holmes states that it's not clear what is expected of the pharmacist regarding the dispensing of partial bottles, especially because the proposed product will be supplied with only one 1 mL oral syringe and one 9 mL oral syringe. The supplied bottle adaptor will is specifically designed to fit with the original packaged container, and it may not be suitable for use with other bottles provided directly by a pharmacy. Additionally, only one set of Patient Information and Patient Instructions for Use will be enclosed in the carton, which increases the risk that the medication will be dispensed to a patient without the accompanying FDA-approved patient labeling.

Dr. Holmes discussed these concerns in her review of the sponsor's proposed human factors protocol (usability study) submitted by Douglas. Throughout the review cycle, the Division conveyed DMEPA's comments on the usability study to the sponsor, in response to the sponsor's questions and proposed amendments to the protocol. At this point, the sponsor has not conducted the recommended usability study.

Dr. Holmes notes that the patient must shake the bottle of clozapine suspension for at least 10 seconds in order to produce a (b) (4) suspension. Therefore, these instructions must be incorporated into the “Shake Well” statements on the labels and in labeling. Dr. Holmes concluded that the strength and dosage form proposed for Clozapine Oral Suspension are reasonable, given the proposed indication, dosage and administration for this product. However, DMEPA identified deficiencies in the proposed container labels, carton labeling, insert labeling, and instructions for use:

1. The prominence of important information is inadequate.
2. The layout and format of information are not optimal.
3. Some aspects of the label and labeling statements are not clear.
4. There is a lack of information for the pharmacist regarding the dispensing of partial bottles.
5. Proposed labeling includes error-prone abbreviations and symbols.

Dr. Holmes concluded that the proposed label and labeling should be improved to increase the readability and prominence of important information on the labels in order to promote the safe use of the product, to mitigate any confusion, and to clarify information. The packaging design is not optimal, because it does not allow pharmacists to easily dispense partial bottles and provide patients with the materials necessary to use the medication as labeled (i.e., extra supply of oral syringes and instructions for use). The Division has conveyed these comments to the sponsor, and we have provided detailed recommendations for the human factors/usability study. DMEPA will continue to work with the sponsor regarding the proposed packaging.

Dr. Holmes has recommended important revisions in the following sections of labeling: Dosage and Administration, Patient Counseling Information, How Supplied/Storage and Handling, and Patient Information. The Division agrees with all of Dr. Holmes’ recommendations, and we have incorporated the revisions in the label. The sponsor has accepted these revisions.

12. Pediatrics and Maternal Health Staff

12.1 Pediatrics Issues

Jeanine Best, MSN, RN, PNP, Senior Clinical Analyst, Pediatric and Maternal Health Staff performed the pediatrics review. Clozapine has not been studied in pediatric patients. The Division requested input on the Pediatric Use section of the label. PMHS recommends the following standard language:

Use in Specific Populations - Pediatric Use:

Safety and effectiveness in pediatric patients have not been established.

The Division agrees and has incorporated this language in the label.

12.2. Pediatric Waiver and Pediatric Equity in Research Committee (PeRC)

The sponsor requested a full waiver of pediatric studies required under the Pediatric Research Equity Act (PREA). On March 29, 2012 the sponsor submitted a revised full waiver request with the justification that it would be impossible or highly impractical to conduct pediatric studies with Versacloz, because the number of pediatric patients with treatment-resistant schizophrenia is exceedingly small. The sponsor also stated that current pediatric use of clozapine is extremely low, because of the significant toxicities of clozapine. The Division agreed with the sponsor, and we recommended that PeRC grant a full waiver of the requirement for pediatric studies using Versacloz. The PeRC agreed with the Division, and they granted a full waiver of the requirement to conduct pediatric studies (for ages 0 to 17).

12.3 Maternal Health Staff (Pregnancy and Nursing Issues)

Upasana Bhatnagar, M.D. performed the Maternal Health Team review. Dr. Bhatnagar reviewed the Pregnancy and Nursing Mothers sections of labeling. She also reviewed the published literature on clozapine use during pregnancy as well as infant exposure to clozapine through ingestion of breast milk. Dr. Bhatnagar noted that the incidence of schizophrenia peaks in women at age 25 to 35 years old, which coincides with peak reproductive age. Women with schizophrenia have an increased risk of unplanned pregnancy. In some women, symptoms worsen during pregnancy and the postpartum period. Therefore, female patients with schizophrenia have the potential to be exposed to clozapine during pregnancy and lactation.

Dr. Bhatnagar found 13 case reports of schizophrenic patients treated with clozapine during pregnancy. There were 18 pregnancies and 19 infants (one set of twins) with reported outcomes. One neonatal death occurred after delivery to a mother who attempted suicide by an overdose with clozapine. Several infants had a diagnosis of Floppy Infant Syndrome (FIS). Dr. Bhatnagar concluded that the pregnancy case reports did not provide sufficient information about exposures, other potentially contributing factors, and follow-up of outcomes.

Dr. Bhatnagar found 5 case reports on clozapine use during breastfeeding. In one case, breast milk from a post-partum patient treated with clozapine was sampled one day and one week after delivery. The concentration of clozapine in the breast milk was higher than the plasma concentration on Day 1 (plasma 14.7 ng/ml, breast milk 63.5 ng/ml) and one week after delivery (plasma 41.4 ng/ml and breast milk 115.6 ng/ml). The authors attributed this to the lipophilic properties of clozapine. In several cases, adverse events were reported with clozapine use during breastfeeding. There were reports of agranulocytosis, speech delay, and sedation (one each). There was little information in these reports. Dr. Bhatnagar concluded that clozapine is present in breast milk of treated women, and it may be present in higher concentrations in the breast milk compared to plasma in some patients. Additionally, although the reported data are minimal, some reports suggest that adverse reactions can be associated with infant exposure to clozapine through breast milk.

Dr. Bhatnagar noted that embryofetal studies in animals did not demonstrate adverse developmental effects. She also concluded that clinical data regarding clozapine use in pregnancy are limited. PMHS-MHT recommends maintaining the current pregnancy category B for clozapine products. The few case reports in the literature are difficult to interpret because of the variations in the dosage used, timing of exposure, and variability of pregnancy outcome data. No specific pattern of adverse events in the fetus is evident from these reports. Thus, the available human data from these reports are not sufficient to inform labeling. In deciding whether to continue or discontinue clozapine treatment in pregnant patients, the clinician must balance the potential risk to the fetus with the risk of worsening psychosis in the untreated mother.

Because of the increased risk for hyperglycemia with clozapine treatment, Dr. Bhatnagar recommends that clinicians consider monitoring pregnant women for persistent hyperglycemia during treatment with clozapine. Persistent hyperglycemia in gestational diabetes pregnancy is associated with adverse pregnancy outcomes such as congenital malformations and birth injury.

Dr. Bhatnagar recommends advising nursing mothers discontinue clozapine or discontinue breastfeeding. Case reports indicate that clozapine is present in the breast milk of lactating patients receiving clozapine, and clozapine may be actively secreted into breast milk. Serious adverse reactions associated with exposure to clozapine through breast milk have been reported; although the data are extremely limited. Because these data are insufficient to determine the long-term effects on infants exposed to clozapine through breast milk, clinicians must counsel patients about the potential risks to the infant, balanced with the risk of discontinuing clozapine treatment in the mother. Dr. Bhatnagar has provided detailed language for the pregnancy and nursing mothers sections of labeling. The Division has agreed with the recommendations, and we have included this language in labeling. I agree with Dr. Bhatnagar's conclusions and recommendations.

13. Patient Labeling Team

Robin Duer, MBA, BSN, RN, (Senior Patient Labeling Reviewer, Division of Medical Policy and Programs), performed the review of the sponsor's proposed Patient Labeling and Patient's Instructions for Use. Dr. Duer substantially revised the sponsor's proposed documents, in order to make them consistent with the revised Versacloz PLR label and to enhance patient comprehension of the information. The Division has incorporated Dr. Duer's recommendations in the Patient Information and the Patient's Instructions for Use.

14. Labeling Review

The Division substantially revised most sections of the sponsor's proposed PLR label. There are many changes in the following sections: Boxed Warnings, Dosage and Administration, Contraindications, Warnings and Precautions, Adverse Reactions, Drug Interactions, Specific Populations, Clinical Pharmacology, Nonclinical, and the Clinical Studies sections. On February 5, 2013 we reached agreement with the sponsor on labeling.

15. Conclusions and Recommendations

15.1 Recommended Action

The sponsor conducted an adequate bioequivalence study comparing clozapine oral suspension (Versacloz) with the reference product, Clozaril Tablets. The sponsor has demonstrated that Versacloz suspension is bioequivalent to the reference product. There were no new or unexpected clinical safety findings compared to the known safety and tolerability profile of clozapine. Reviewers from all disciplines have concluded that the sponsor has provided acceptable data, and they support approval of the NDA. There are no unresolved issues. I agree with all reviewers' conclusions and recommendations, and I recommend approval of the NDA.

15.2 Recommended Postmarketing Commitment

I recommend that the Division require a postmarketing actual-use human factors study to assess the ability of patients with schizophrenia to correctly measure doses using the approved kit and Instructions for Use. The kit includes a bottle, a syringe for oral administration, and a bottle adapter. The sponsor has agreed to conduct the study as a PMC. The approval letter outlines the PMC:

You are required to conduct an actual use human factors study in the U.S. in patients with schizophrenia. The study should include patients who are new to clozapine and patients who are stabilized on clozapine. The study should assess patients' ability to correctly measure doses using the approved Instructions for Use and packaging components.

The sponsor has agreed to meet the following timeline:

Final Protocol Submission: April 30, 2013
Study completion date: August 30, 2013
Final Report Submission: October 31, 2013

15.3 Postmarketing Enhanced Pharmacovigilance Reporting

The Division will require the sponsor to submit 15-day expedited reports for cases of adverse events, medication errors, and product complaints related to the use of the bottles, oral syringes, and bottle adapters. The Division has made the following request, and the sponsor has agreed to meet the reporting requirements:

Submit both serious and non-serious outcomes as expedited reports within 15 days of receipt for the following:

All reports of medication errors, including overdoses or underdoses of the drug, and any adverse events resulting from the medication errors.

A summary evaluation of these medication error reports should be included in your submission of periodic reports for each reporting period.

Submit as expedited reports within 15 days of receipt for the following:

All consumer inquiries or reports of product complaints related to the use of the oral syringes or product packaging

A summary evaluation of these consumer inquiries and product complaints should be included in your submission of periodic reports for each reporting period.

15.4 Pediatric Studies

The Agency has waived the requirement for pediatric studies of Versacloz, because the studies would be highly impracticable; the number of pediatric patients with treatment-resistant schizophrenia who might be candidates for treatment with clozapine is exceedingly small.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT L LEVIN
02/06/2013