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RESEARCH**

APPLICATION NUMBER:

203479Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Final Risk Evaluation and Mitigation Strategy (REMS) Review

Date: February 6, 2013

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Drug Name(s): Versacloz (clozapine oral suspension)

Therapeutic Class: Atypical Antipsychotic

Dosage and Route: 50 mg / mL oral suspension

Application Type/Number: NDA 203479

Applicant/Sponsor: Douglas Pharmaceuticals America LTD

OSE RCM #: 2012-257

*** This document contains proprietary and confidential information that should not be released to the public. ***

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EXECUTIVE SUMMARY

This review documents the Division of Risk Management's final conclusions and recommendations on the proposed Risk Evaluation and Mitigation Strategy (REMS) for Versacloz (NDA 203479), originally submitted on December 29, 2011 (Seq. No. 0000) by Douglas Pharmaceuticals. The final proposed REMS for Versacloz was submitted by Douglas on February 5, 2013. The purpose of the REMS is to mitigate the risk of agranulocytosis associated with the administration of clozapine. The elements of the REMS include Prescriber Certification, Pharmacy Certification, Documentation of Safe Use Conditions, Monitoring Requirement, and a Patient Registry. The amended REMS for Versacloz, dated February 5 and amended Healthcare Provider Enrollment Form submitted February 6, 2013, contain the appropriate and agreed upon revisions as stipulated by the Agency; therefore, DRISK recommends approval of the REMS.

1 INTRODUCTION

This Division of Risk Management (DRISK) review is provided in response to a request by the Division of Psychiatry Products (DPP) to review and comment on Douglas Pharmaceuticals' Risk Evaluation and Mitigation Strategy (REMS) proposal for Versacloz (NDA 203479), originally submitted on December 29, 2011 (Seq. No. 0000). This review documents DRISK's final conclusions and recommendations on the proposed Versacloz REMS, which includes the following elements to assure safe use (ETASU):

- Prescriber Certification
- Pharmacy Certification
- Documentation of Safe Use Conditions
- Monitoring Requirement
- Patient Registry

1.1 BACKGROUND

Clozapine, the first atypical antipsychotic, was approved on September 26, 1989 for the management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia. On December 18, 2002 a second indication for the reduction of risk of recurrent suicidal behavior in schizophrenia or schizoaffective disorder was approved. Clozapine is available in the U.S. as an oral tablet (reference listed drug: Clozaril[®]; including 4 ANDAs) and as an orally disintegrating tablet (reference listed drug: FazaClo[®]).

A serious risk of concern associated with the administration of clozapine is drug-induced agranulocytosis. Because of this risk, clozapine was approved with a boxed warning in the prescribing information and a risk management program with restricted distribution. Each Sponsor of a clozapine product manages and maintains their own risk management program for clozapine. However, all Sponsors of clozapine products are required to maintain a registry of all prescribers, pharmacists, and patients who prescribe, dispense or receive their respective clozapine product. In addition, Sponsors are required to verify patients are not listed on the National NonRechallenge Masterfile (maintained by

Novartis) prior to enrollment. Furthermore, Sponsors must ensure that clozapine is only dispensed to enrolled patients whose white blood cell (WBC) counts and absolute neutrophil count (ANC) results are within the range deemed acceptable by the current clozapine prescribing information. To achieve this objective, health care professionals (HCPs) are responsible for submitting patient lab results as recommended in current clozapine monitoring guidelines contained in the clozapine labeling.

Clozapine was included on the list of products deemed to have in effect an approved 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 were required to submit a REMS proposal by September 21, 2008. All submissions are under review. Currently, no marketed clozapine product has an approved REMS; therefore, clozapine products are marketed under risk minimization action plans (RiskMAPs).

1.2 REGULATORY HISTORY

On December 29, 2011, Douglas submitted a 505(b)2 application for NDA 203479 for Versacloz (clozapine oral suspension), which was accepted for filing on February 14, 2012. The PDUFA date for the application is November 6, 2012. The proposed indication for Versacloz is for the management of treatment resistant schizophrenia and for reducing suicidal behavior in patients with schizophrenia or schizoaffective disorder. The Sponsor's submission included a proposed REMS document and REMS Supporting Document for Versacloz. 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.

The goal of the Sponsor's proposed REMS was to reduce the risk of development of agranulocytosis in patients who are prescribed clozapine oral suspension.

The REMS components initially proposed by the Sponsor were:

- (b) (4)
- Elements to Assure Safe Use
 - Healthcare provider (HCP) certification - Healthcare providers enrollment in a registry
 - Pharmacy certification - Pharmacies/Pharmacist enrollment in a registry
 - Monitoring requirement - Monitoring of WBC count and ANC
 - Patient enrollment in a registry
 - Implementation Plan
 - Timetable for submission of assessments
 - Douglas proposes REMS Assessments will be submitted to FDA (b) (4) following approval of the REMS

The REMS Supporting Document contained registry enrollment forms for prescribers, pharmacies, and patients, and WBC and ANC monitoring forms.

On May 24, 2012, DRISK and DPP met with senior management to discuss the Versacloz application and its impact on other approved clozapine products. It was agreed, if Versacloz is approved, it should be approved with a label and REMS that reflects currently approved labeling and the operating FazaClo registry (Jazz will

maintain the registry for FazaClo and Versacloz). (b) (5)

On July 31, 2012, FDA issued a REMS Notification Letter to each Sponsor of an approved clozapine product and to Douglas as a sponsor of a submitted NDA for a clozapine product. The purpose of the letter was to inform them that the FDA will require a (b) (4)

On August 21, 2012, DRISK interim comments were sent to Douglas. These comments included a draft REMS document which conforms to the framework and regulatory language established by FDAAA.

In addition, the following significant changes to the REMS documents were:

- Prescriber and pharmacy attestations were changed in the REMS document and on REMS enrollment forms to clarify responsibilities of these stakeholders based on the information provided by Douglas in the REMS Supporting Document.
- A patient signature and patient privacy language was added to the Patient Enrollment Form.

Furthermore, the comments to the Sponsor also included clarifying questions involving how (b) (4).

On September 27, 2012, the Sponsor submitted their response to the August 21, 2012 interim comments. Douglas stated that, (b) (4)

On October 12, 2012, FDA held a teleconference with Douglas to discuss their response submitted on September 27, 2012 to the FDA. FDA 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; rather the changes are based on regulatory requirements and standards.

The Agency also stated that (b) (4)

FDA conceded that the Patient Enrollment Form does not need to include a patient signature and patient privacy language. Douglas was reminded that they must be in compliance with the Health Insurance Portability and Accountability Act (HIPAA) regulations in order to protect patient health information.

Douglas was also informed that 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 agreed to discuss the FDA recommendations internally and resubmit as soon as possible.

On October 17, 2012, Douglas submitted a REMS Correspondence Letter (Seq. No. 0023) responding to the July 31, 2012 REMS notification letter, stating the following:

“Douglas commits that the Versacloz™ product will [REDACTED] (b) (4)

On November 1, 2012, FDA communicated the revisions to the following documents which were discussed at the teleconference on October 12, 2012.

- Versacloz REMS document
- Versacloz REMS Supporting Document containing Part I : Versacloz Registry Protocol and Part II: Versacloz REMS Assessment Plan

In addition, FDA requested submission of a screenshot of the Versacloz REMS Registry landing page to review since the original submission did not contain this material.

On November 2, 2012, FDA received a solicited major amendment to the NDA application. The receipt date was within three months of the user fee goal date; therefore, the goal date was extended by three months to provide time for a full review of the submission. The extended user fee goal date is February 6, 2013.

On November 6, 2012, Douglas submitted the REMS document and REMS materials for review (Seq. No. 0027).

On February 4, 2013, FDA communicated the following revisions to the Sponsor based on recommended revisions identified during the internal REMS clearance process:

1. REMS document
 - i. The term “register” was changed to “enroll” per current regulatory standards. As a result of this change in the REMS document, the Healthcare Provider, Pharmacy/Pharmacist and Patient Enrollment Forms were revised accordingly.

ii. As recommended by the Office of Chief Counsel (OCC) the following attestation was added regarding the ability of prescribers to [REDACTED] (b) (5)

[REDACTED]

[REDACTED] (b) (5)

iii. As recommended by OCC, the following healthcare provider and pharmacy attestation was revised to [REDACTED] (b) (5)

[REDACTED]

[REDACTED] (b) (5)

iv. As recommended by OCC, the following statement was revised to define the [REDACTED] (b) (5)

[REDACTED]

[REDACTED] (b) (5)

v. Healthcare providers must routinely complete the WBC count and ANC Monitoring Forms in order to fulfill the Versacloz REMS requirement for monitoring. Therefore, the Sponsor responsibilities regarding ensuring stakeholders are compliant with this requirement were moved from *Section II.A.3.b. Versacloz may be dispensed to patients with documentation of safe*

use conditions to Section II.A.4.a. Each patient using Versacloz is subject to certain monitoring.

- vi. The Patient Enrollment Form contains baseline laboratory data which the sponsor utilizes in order to assure the patient qualifies for clozapine treatment and thereby meets the Versacloz REMS requirement of documentation of safe use conditions. Therefore, the Sponsor responsibility regarding the Patient Enrollment Form was moved from *Section II.A.4.a. Each patient using Versacloz is subject to certain monitoring* to *Section II.A.3.b. Versacloz may be dispensed to patients with documentation of safe use conditions.*
2. The Healthcare Provider Enrollment Form and Pharmacy/Pharmacist Enrollment Form were updated to include the revised attestations included in the REMS document as described above, as applicable.
3. The name of the Patient Registration Form was revised to Patient Enrollment Form in order to be consistent with the recommendation to change “register” to “enroll” in the Versacloz REMS document
4. The REMS Supporting document was revised to include the aforementioned revisions.

On February 5, 2013, the Sponsor resubmitted the REMS with the requested revisions.

On February 6, 2013, FDA communicated to the Sponsor, via email, a revision to the Healthcare Provider Enrollment Form. Attestation 5 was revised by changing “they” to “I”. The Sponsor resubmitted this form on February 6, 2013 (Seq. No. 0032).

2 MATERIALS REVIEWED

2.1 SUBMISSIONS

February 6, 2013: Final Proposed REMS (Seq. No. 0032)

- Healthcare Provider Enrollment Form

February 5, 2013: Final Proposed REMS (Seq. No. 0031)

- REMS document
- Pharmacy/Pharmacist Enrollment Form
- Patient Enrollment Form
- WBC Count and ANC Monitoring Form
- Multi-Patient WBC count and ANC Monitoring Form
- REMS Website
- REMS Supporting document

November 6, 2012: Proposed REMS (Seq. No. 0027)

December 29, 2012: Proposed REMS (Seq. No. 0000)

- Cover letter for New Drug Application
- REMS documents
- REMS Supporting document
- Versacloz Patient Registry Protocol

2.2 OTHER MATERIALS INFORMING OUR REVIEW

- Interim Comments on REMS: Set #1 (KLehrfeld, August 17, 2012)
- Information Request communicating DRISK interim comments to Sponsor (August 21, 2012)
- Meeting minutes from October 12, 2012 teleconference with Douglas to discuss the proposed Versacloz REMS (October 16, 2012)
- Information Request containing the following materials, which were revised after teleconference on October 12, 2012 and communicated to sponsor via email. (November 1, 2012)
 - Versacloz REMS document
 - Versacloz REMS Supporting Document containing Part I : Versacloz Registry Protocol and Part II: Versacloz REMS Assessment Plan
 - Versacloz REMS website landing page
- Versacloz Prescribing Information, internal version January 13, 2013

3 RESULTS OF REVIEW OF PROPOSED VERSACLOZ RISK EVALUATION AND MITIGATION STRATEGY

3.1 OVERVIEW OF CLINICAL PROGRAM

This 505(b)2 application for NDA 203479 relies on the Agency's previous findings of safety and efficacy of the reference drug Clozaril (clozapine tablets), NDA 19758, as noted in the December 29, 2011 NDA Cover Letter. Douglas stated the following in a cover letter (dated December 29, 2012):

“In support of the application, Douglas conducted the following bioequivalence study:

Study #ZPS-411: Multiple-dose, multi-center, randomized, bioequivalence study of clozapine in multiples of 100 mg as 50 mg/mL clozapine suspension (Douglas, America) in a two way crossover comparison with multiples of 100 mg as Clozaril 100 mg tablet (Novartis, USA) in stable patients under fasting and fed conditions and at steady state.

In addition to the bioequivalence study, Douglas has conducted the following patient usability study:

Study #ZPS-411: Assessing the ability of patients to withdraw and dispense the correct dose of suspension into the dispensers using the dispensing instructions in the usability protocol for the correct

dispensing of clozapine 50mg/ mL suspension U.S. by patients (RD 10223).”

3.2 SAFETY CONCERNS

The primary safety issue for Versacloz is agranulocytosis; which is an established safety risk for the drug moiety clozapine that was identified with the approval of Clozaril. Agranulocytosis, defined as an ANC of less than $500/\text{mm}^3$, has been estimated to occur in association with clozapine use at a cumulative incidence at 1 year of approximately 1.3%, based on the occurrence of 15 U.S. cases out of 1743 patients exposed to clozapine during its clinical testing prior to domestic marketing. All of these cases occurred at a time when the need for close monitoring of WBC counts was already recognized. A hematologic risk analysis was conducted based upon the available information in the Clozapine National Registry for U.S. patients. Based upon a cut-off date of April 30, 1995, the incidence rates of agranulocytosis based upon a weekly monitoring schedule rose steeply during the first two months of therapy, peaking in the third month. Among clozapine patients who continued the drug beyond the third month, the weekly incidence of agranulocytosis fell a substantial degree. After 6 months, the weekly incidence of agranulocytosis declines still further; however, it never reaches zero.

Experience from clinical development, as well as from examples in the medical literature, suggests that patients who have developed agranulocytosis during clozapine therapy are at increased risk of subsequent episodes of agranulocytosis. Analysis of WBC count data from the Clozapine National Registry also suggests that patients who have an initial episode of moderate leukopenia ($3000/\text{mm}^3 > \text{WBC count} \geq 2000/\text{mm}^3$) are at an increased risk of subsequent episodes of agranulocytosis. Except for bone-marrow suppression during initial clozapine therapy, there are no other established risk factors based on worldwide experience for the development of agranulocytosis in association with clozapine use.

No additional safety concerns were identified from the bioequivalence studies conducted to support the NDA application for Versacloz.

3.3 SPONSOR’S PROPOSED REMS GOALS

The Sponsor initially proposed the following goal for the Versacloz REMS:

 (b) (4)

However, the Sponsor’s proposed goal did not adequately state how the Versacloz Patient Registry operation impacts the reduction of the risk of agranulocytosis. Therefore, the goal was revised to include 2 objectives of the Versacloz Patient Registry. The final goal is:

- To minimize the risk of agranulocytosis associated with the use of Versacloz by:
- Ensuring compliance with the monitoring schedule for White Blood Cell Count (WBC) and Absolute Neutrophil Count (ANC) prior to dispensing Versacloz

- Preventing re-exposure of patients who have previously experienced agranulocytosis or severe granulocytopenia/leukopenia with any clozapine products.

3.4 REMS ELEMENTS

The Sponsor initially proposed (b) (4).
The components of the (b) (4) included the following:

(b) (4)

FDA disagreed with the inclusion of (b) (4) the final Versacloz REMS for the following reasons:

(b) (4)

Therefore, (b) (4) was removed from the final agreed upon REMS; however, the call center and REMS website were moved to more appropriate sections of the REMS document.

The Sponsor proposed the following 4 elements to assure safe use (ETASU): Prescriber Certification, Pharmacy Certification, Patient Registry, Monitoring Requirement. The currently operating clozapine registries and clozapine deemed REMS essentially have these 4 ETASU plus Documentation of Safe Use Conditions. Prescribers and pharmacies must submit enrollment forms to the patient registry, which include attestations to comply with the clozapine registry requirements. HCPs must enroll patients in the clozapine registry by completing a patient enrollment form. The Sponsors of clozapine products are required to verify and document safe use conditions by checking the NNRM prior to enrolling a patient in the respective clozapine registry. Ongoing monitoring of WBC and ANC results are required to be submitted to the registry throughout clozapine therapy. For these reasons, these 5 ETASU are included in the Versacloz REMS. The following sections describe the final agreed upon ETASU (Section 3.4.1) and Implementation System (Section 3.4.2) for the Versacloz REMS.

3.4.1 Elements to Assure Safe Use

3.4.1.1 Healthcare providers who prescribe Versacloz will be specially certified

- a. Douglas Pharmaceuticals America LTD will ensure that healthcare providers who prescribe Versacloz are specially certified.
- b. The healthcare provider enrollment process comprises the following steps that must be completed prior to prescribing Versacloz:
 - i. The healthcare provider completes the Healthcare Provider Enrollment Form. In signing the Healthcare Provider Enrollment Form, each healthcare provider indicates they understand that clozapine is available only through the Versacloz REMS Program, entitled Versacloz Patient Registry, and are aware of and attest to the following requirements:
 - a) Review the Versacloz package insert and understand the risk of death associated with agranulocytosis or severe granulocytopenia/leukopenia when prescribing Versacloz.
 - b) Enroll all applicable patients in the Versacloz Patient Registry. When enrolling a patient, healthcare providers will be matched with an enrolled pharmacy and be defined as an “affiliated treatment pair” by completing the appropriate section of the Patient Enrollment Form.
 - c) Understand the recommendations for prescribing and monitoring as described in the Versacloz package insert.
 - d) Understand Versacloz should only be prescribed to new patients after verifying an acceptable baseline WBC count ($\geq 3500/\text{mm}^3$) and ANC ($\geq 2000/\text{mm}^3$) test results, submitting the Patient Registration Form with baseline labs within 7 days of blood draw and only after receiving a Patient Registration Number (PRN) from the Versacloz Patient Registry.
 - e) Understand that no more than a 7 day supply of Versacloz should be prescribed to a patient who has been continually on clozapine treatment with a different clozapine formulation (i.e. clozapine tablets, clozapine orally disintegrating tablets) prior to initiating Versacloz but who is not currently enrolled in the Versacloz Patient Registry, and understand that Versacloz should not be prescribed in such circumstances until verification that the patient has an acceptable baseline WBC count ($\geq 3500/\text{mm}^3$) and ANC ($\geq 2000/\text{mm}^3$). They understand they should prescribe Versacloz to a patient a second time only after receiving a valid PRN from the Versacloz Patient Registry
 - f) Complete the Patient WBC Count and ANC Monitoring Form and provide the affiliated pharmacist with the completed form and a valid prescription for each dispensation of Versacloz.

- g) Follow the process for a patient discontinued from Versacloz, regardless of the reason for discontinuation:
 - i. Indicate discontinuation of Versacloz on the Patient WBC Count and ANC Monitoring Form
 - ii. Notify the Versacloz Patient Registry by submitting the completed Patient WBC Count and ANC Monitoring Form to the Versacloz Patient Registry.
 - iii. Notify the affiliated pharmacy by submitting the completed Patient WBC Count and ANC Monitoring Form to the affiliated pharmacy
 - iv. Submit the required WBC count and ANC test results to the Versacloz Patient Registry weekly for at least 4 weeks from the day of discontinuation or until the patients labs return to normal (WBC>3500mm³ and ANC>2000/mm³).
- h) Understand the list of patients enrolled in the Versacloz Patient Registry will be used to verify the patient's rechallenge status against the Clozapine National Non-Rechallenge Masterfile. Furthermore, any patient permanently discontinued from Versacloz for meeting the non-rechallenge criteria (WBC count <2000/mm³ and/or ANC <1000mm³) will be reported to the Clozapine National Non-Rechallenge Masterfile
- i) Understand the Versacloz Patient Registry will be audited to monitor adherence to prescribing and monitoring requirements, and enrolled healthcare providers and pharmacies will be promptly notified of any discrepancies or missing information by Douglas Pharmaceuticals America LTD.
- c. Douglas Pharmaceuticals America LTD will:
 - i. Ensure that healthcare provider enrollment can successfully be completed via the Versacloz REMS website, or by mailing or faxing the forms.
 - ii. Ensure that, as part of the enrollment process, the following materials that are part of the Versacloz REMS program are available to healthcare providers. These materials are appended:
 - *Healthcare Provider Enrollment Form*
 - iii. Ensure that the *Healthcare Provider Enrollment Form* is complete before a healthcare provider's enrollment is activated in the Versacloz REMS program.
 - iv. Ensure that healthcare providers are notified when they are successfully enrolled in the Versacloz REMS program, and therefore, are certified to prescribe Versacloz.
 - v. Monitor enrollment requirements for healthcare providers and institute corrective action and/or inactivate non-compliant

healthcare providers. Upon initial activation, healthcare providers remain active until inactivation occurs.

3.4.1.2 Versacloz ^{(b) (4)} dispensed by pharmacies that are specially certified

- a. Douglas Pharmaceuticals America LTD will ensure that pharmacies that dispense Versacloz are specially certified.
- b. The pharmacy enrollment process comprises the following steps that must be completed prior to dispensing Versacloz:
 - i. The lead pharmacist will complete the Pharmacy Enrollment Form. In signing the Pharmacy Enrollment Form, the lead pharmacist indicates that all pharmacists with dispensing privileges at the pharmacy understand that Versacloz is only available to certified pharmacies after enrolling in the Versacloz REMS program, entitled Versacloz Patient Registry, and are aware of and attest to the following requirements:
 - a) Review the Versacloz package insert and understand the risk of death associated with agranulocytosis or severe granulocytopenia/leukopenia prior to dispensing Versacloz.
 - b) Enroll all applicable patients in the Versacloz Patient Registry. When enrolling a patient, healthcare providers will be matched with an enrolled pharmacy and be defined as an “affiliated treatment pair” by completing the appropriate section of the *Patient Enrollment Form*.
 - c) Understand the recommendations for prescribing and monitoring as described in the package insert.
 - d) Understand Versacloz should only be dispensed to a new patient after verifying an acceptable baseline WBC count ($\geq 3500/\text{mm}^3$) and ANC ($\geq 2000/\text{mm}^3$) test results and only after receiving a Patient Registration Number (PRN) from the Versacloz Patient Registry.
 - e) Understand that no more than a 7 day supply of Versacloz should be dispensed to a patient who has been continually on clozapine treatment with a different clozapine formulation (i.e. clozapine tablets, clozapine orally disintegrating tablets) prior to initiating Versacloz but is not currently enrolled in the Versacloz Patient Registry, and understand that Versacloz should not be dispensed in such circumstances until verification that the patient has an acceptable baseline WBC count ($\geq 3500/\text{mm}^3$) and ANC ($\geq 2000/\text{mm}^3$). They understand they should dispense Versacloz to a patient a second time only after receiving a valid PRN from the Versacloz Patient Registry.
 - f) Understand the importance of providing the Versacloz Patient Registry with all WBC count and test results for all enrolled patients within:

- 7 days from blood draw to patients on weekly monitoring schedule
 - 14 days from blood draw to patients on bi weekly monitoring schedule
 - 28 days from blood draw to patients on monthly monitoring schedule
- g) Understand the list of patients enrolled in the Versacloz Patient Registry will be used to verify a patient's rechallenge status against the Clozapine National Non-Rechallenge Masterfile. Furthermore, any patient permanently discontinued from Versacloz for meeting the non-rechallenge criteria (WBC count $<2000/\text{mm}^3$ and/or $\text{ANC}<1000/\text{mm}^3$) will be reported to the Clozapine National Non-Rechallenge Masterfile.
- h) Understand the Versacloz Patient Registry will be audited to monitor adherence to prescribing, monitoring and timeliness requirements and enrolled healthcare providers and pharmacies will be promptly notified of any discrepancies or missing information by Douglas Pharmaceuticals America LTD.
- c. Douglas Pharmaceuticals America LTD will:
- i. Ensure that pharmacy enrollment can successfully be completed via the Versacloz REMS website, or by mailing or faxing the forms.
 - ii. Ensure that, as part of the enrollment process, the following materials that are part of the Versacloz REMS program are available to pharmacies. These materials are appended:
 - *Pharmacy Enrollment Form*
 - iii. Ensure that the *Pharmacy Enrollment Form* is complete before a pharmacy's enrollment is activated in the Versacloz REMS program.
 - iv. Ensure that pharmacies are notified when they are successfully enrolled in the Versacloz REMS program, and therefore, are certified to dispense Versacloz.
 - v. Monitor enrollment requirements for pharmacies/pharmacists and institute corrective action and/or inactivate non-compliant pharmacies/pharmacists. Upon initial activation, pharmacies/pharmacists remain active until inactivation occurs.

3.4.1.3

(b) (4) Versacloz (b) (4) be dispensed (b) (4) documentation of safe-use conditions

- a. Douglas Pharmaceuticals America LTD will ensure that no patient is able to be enrolled with the Versacloz Patient Registry or provided a PRN if

the patient is in the Clozapine National Non-Rechallenge Masterfile to assure safe-use conditions.

- i. Douglas Pharmaceuticals America LTD will ensure that the following will be completed upon receipt of the completed patient enrollment form:
 - a) Review the form for completeness and clarity.
 - b) Verify that the patient is not included in the Clozapine National Non- Rechallenge Masterfile.
 - c) Confirm that the patient's WBC count and ANC test results, which have been obtained within 1 week of the registration date, are acceptable (WBC count $\geq 3500/\text{mm}^3$ and ANC $\geq 2000/\text{mm}^3$.)
 - d) Notify the pharmacist of patient non-rechallenge and registration status and provide a PRN by mail, fax, or e-mail.
 - e) Separately notify the patient's healthcare provider of the patient's non- rechallenge status and his/her PRN by mail, fax, or e-mail.
 - f) Provide notification of monitoring schedule when appropriate data are available to the registry.
- ii. Douglas Pharmaceuticals America LTD will ensure that, as part of the enrollment process, the following enrollment form that is part of the Versacloz REMS program is available to enrolled healthcare providers and pharmacies. These materials are appended:
 - *Patient Enrollment Form*

3.4.1.4 Each patient using Versacloz will be subject to certain monitoring

- a. Douglas Pharmaceuticals America LTD will ensure that required routine laboratory results (WBC and ANC) are received from enrolled healthcare providers and pharmacies according to the patient's appropriate monitoring schedule as described in the Versacloz package insert.
 - i. Douglas Pharmaceuticals America LTD will ensure that the *Patient WBC Count and ANC Monitoring Form* can successfully be completed via the Versacloz REMS website, by phone, or by mailing or faxing the forms.
 - ii. Douglas Pharmaceuticals America LTD will ensure that, as part of the monitoring process, the following materials that are part of the Versacloz REMS program are available to enrolled healthcare providers and pharmacies. These materials are appended:
 - *Single Patient WBC Count and ANC Monitoring Form*
 - *Multiple Patient WBC Count and ANC Monitoring Form*
- b. Douglas Pharmaceuticals America LTD will ensure that any patient for which they receive confirmed blood test results that meet the non-rechallenge criteria (WBC count below $2000/\text{mm}^3$ and/or ANC below $1000/\text{mm}^3$) will be reported to the Clozapine National Non-Rechallenge Masterfile within 48 hours.

- c. Douglas Pharmaceuticals America LTD will ensure that certified healthcare providers submit WBC count and ANC values for any patient who experiences confirmed blood test results that meet the non-rechallenge criteria (WBC count below 2000/mm³ and/or ANC below 1000/mm³) until laboratory results return to normal (WBC>3500mm³ and ANC>2000/mm³) and for at least 4 weeks from day of discontinuation of therapy.

3.4.1.5 Each patient using Versacloz will be enrolled in a registry

- a. Douglas Pharmaceuticals America LTD will ensure that certified healthcare providers enroll each patient in the Versacloz Registry. The registry will collect patient demographics, patient's affiliated treatment team (MD and RPh), all required routine labs (ANC and WBC), patient monitoring schedule (weekly, bi-weekly, monthly), and non-rechallengeable status.
- b. Douglas Pharmaceuticals America LTD will ensure that the patient enrollment can successfully be completed via the Versacloz REMS website, by phone, or by mailing or faxing the forms.

3.4.2 Implementation System

1. Douglas Pharmaceuticals America LTD will maintain a database of all enrolled entities (healthcare providers, pharmacies, and patients) and will monitor and evaluate implementation of the Versacloz REMS program requirements.
2. Douglas Pharmaceuticals America LTD will monitor distribution data and prescription data to ensure that only enrolled healthcare providers are prescribing and enrolled pharmacies are dispensing Versacloz. Corrective action or inactivation will be instituted by Douglas Pharmaceuticals America LTD if non-compliance is found.
3. Audit the Versacloz Patient Registry to monitor adherence to prescribing and monitoring requirements and promptly notify enrolled healthcare providers and pharmacies of any discrepancies and obtain missing information.
4. Douglas Pharmaceuticals America LTD will maintain a call center to support patients, healthcare providers, pharmacies, and distributors in interfacing with the Versacloz REMS program.
5. Douglas Pharmaceuticals America LTD will ensure that all materials listed in or appended to the Versacloz REMS program will be available through the Versacloz REMS program website, www.versaclozregistry.com or by calling the Versacloz REMS call center at **1-877-329-2256**.
6. If there are substantive changes to the Versacloz REMS program, Douglas Pharmaceuticals America LTD will update all affected materials and notify pharmacies, prescribers, and distributors of the changes, as applicable. Notifications for patients will be sent to the patient's healthcare provider. Substantive changes to the Versacloz REMS program are defined as:
 - Significant changes to the operation of the Versacloz REMS program.
 - Changes to the package insert that affect the risk-benefit profile of Versacloz

7. Based on monitoring and evaluation of the REMS Elements to Assure Safe Use, Douglas Pharmaceuticals America LTD will take reasonable steps to improve implementation of these elements and to maintain compliance with the Versacloz REMS program requirements, as applicable.

3.4.3 Timetable for Submission of Assessments

The Timetable for Submission of Assessments proposed by the Sponsor for the submission of the Versacloz REMS Assessment to the FDA was at [REDACTED] (b) (4) [REDACTED] after approval. FDA's currently requires assessment of REMS with ETASU more frequently. Therefore, the timetable for submission of assessments was revised to the following:

Douglas will submit REMS Assessments to the FDA at a minimum, by 6 months, and annually thereafter from the date of approval of the initial REMS.

3.5 REMS ASSESSMENT PLAN

The Assessment Plan proposed by the Sponsor was not comparable to current FDA approved REMS Assessment Plans for REMS with ETASU. Therefore, with consultation from DRISK's REMS Assessment Team, The Office of Compliance (OC) and DPP, a revised REMS Assessment Plan was drafted. The FDA's proposed Assessment Plan was accepted by the Sponsor on November 6, 2012 and is as follows:

The elements to assure safe use will be evaluated by the following assessments:

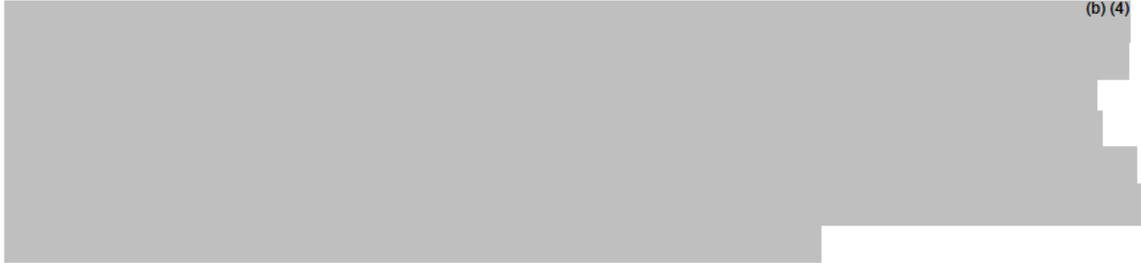
- Assessment of enrollment and discontinuation statistics for prescribers, pharmacies, and patients:
 - The number of patients enrolled in the Versacloz REMS (during the reporting period and cumulative).
 - The number of person-years for enrolled patients.
 - The number of patients who received Versacloz that were not enrolled (during the reporting period and cumulative).
 - The number of patients who stopped receiving Versacloz (during the reporting period and cumulative).
 - The number of prescribers enrolled in Versacloz REMS (during the reporting period and cumulative).
 - The number of pharmacies enrolled in Versacloz REMS (during the reporting period and cumulative).
- Assessment of Versacloz Patient Registry Healthcare Providers Enrollment Forms, Pharmacy/Pharmacist Enrollment Forms, and Patient Registration Forms:

- Number of incomplete enrollment forms and summary of most frequent missing information
- Summary of annual accuracy audit from Versacloz Registry Protocol including a narrative summary of any corrective action taken
- Assessment of prescribing and dispensing of Versacloz for ineligible patients, including a narrative summary of corrective action taken.
- Assessment of nonenrolled prescribers and pharmacists who prescribe or dispense Versacloz, including a narrative summary of corrective action taken.
- Assessment of prescriber and pharmacy compliance including:
 - Compliance with submission of WBC count and ANC within the appropriate timeframe depending on patient monitoring frequency (7, 14, 28-days) by assessing WBC count/ANC alerts and whether appropriate follow-up action was taken and by assessing of lab value late list reports and whether appropriate follow-up action was taken
 - Compliance with submission of patient information to the Versacloz REMS after discontinuation of clozapine due to agranulocytosis
 - Compliance with changes in the frequency of monitoring as recommended dependent upon changes in a patients WBC count and ANC values.
- Number of communications with Clozapine National Non-Rechallenge Masterfile (NNRM) including narrative reports of any patient who received Versacloz while listed on the NNRM.
- Summaries of MedWatch forms submitted to FDA.
- An assessment of wholesaler's compliance with limiting distribution of Versacloz to registered pharmacies.
- Summaries of Versacloz quarterly safety meetings including issues discussed at the meeting and actions taken as a result.

4 DISCUSSION

The final proposed REMS for Versacloz was submitted by Douglas on February 5, 2013. The purpose of the REMS is to mitigate the risk of agranulocytosis associated with the administration of clozapine. No additional risks were identified during the review of the application that warranted mitigation through a REMS.

Based on available data, the currently operating clozapine registries are adequately mitigating the risk of agranulocytosis. The clozapine registries have been in operation since 1989 and have demonstrated a decrease in incidence of agranulocytosis. As of 1996, the 1% to 2% incidence of agranulocytosis evident in clinical trials before the registry was established has subsequently been reduced to a rate of 0.38%¹



The Versacloz REMS will be managed by Jazz Pharmaceuticals; therefore, the proposed REMS reflects the currently operating FazaClo Patient Registry. The Versacloz REMS reflects current labeling and contains the necessary elements to mitigate the risk of agranulocytosis associated with the administration of clozapine. Therefore, DRISK recommends the Versacloz REMS submitted on February 5, 2013 be approved.

5 CONCLUSION

In conclusion, the amended REMS for Versacloz (clozapine oral suspension) submitted February 5, 2013 and amended Healthcare Provider Enrollment Form submitted February 6, 2013 contain the appropriate and agreed upon revisions on the REMS components Prescriber Certification, Pharmacy Certification, Documentation of Safe Use Conditions, Monitoring Requirement, and Patient Registry as stipulated by the Agency on February 5, 2013. The REMS Supporting Document outlines the information and content that the applicant will use to assess the effectiveness of the Versacloz REMS in achieving the goals.

Therefore, the Versacloz REMS is compliant under FDAAA and acceptable to the Office of Surveillance and Epidemiology, the Division of Risk Management.

6 RECOMMENDATIONS

The Office of Medication Error Prevention and Risk Management, DRISK recommends approval of the Versacloz REMS submitted February 5, 2013.

In addition, we recommend the Versacloz REMS Assessment Plan (Section 3.5 REMS ASSESSMENT PLAN) be included in the REMS Approval Letter (REMS Section).

7 ATTACHMENTS

Versacloz REMS document

Healthcare Provider Enrollment Form

¹ 2 Honigfeld G, Arellano F, Sethi J, et al. Reducing clozapine-related morbidity and mortality: 5 years of experience with the Clozaril National Registry. *J Clin Psychiatry* 1998;59(suppl 3):3-7

Pharmacy/Pharmacist Enrollment Form

Patient Enrollment Form

WBC Count and ANC Monitoring Form

Multi-patient WBC Count and ANC Monitoring Form

Versacloz REMS Website landing page screenshot

Versacloz REMS Supporting Document

Initial REMS Approval: XX/XX/XXXX

NDA 203479

Versacloz™ (clozapine) oral suspension

Class of Product: Atypical Antipsychotic

NDA Holder:

**Douglas Pharmaceuticals America LTD
Corner Central Park Drive and Te Pai Place, Lincoln Auckland,
NEW ZEALAND**

0011 649 835 0660 (Telephone)

0011 649 835 0690 (Facsimile)

US Agent:

**VersaPharm Incorporated
1775 West Oak Parkway, Suite 800
Marietta, GA 30062
Contact: John Franolic
Phone: 770-373-5635
Facsimile: 770-373-5655**

**VERSACLOZ™ RISK EVALUATION
AND MITIGATION STRATEGY (REMS)**

I. GOAL

To minimize the risk of agranulocytosis associated with the use of Versacloz by:

- Ensuring compliance with the monitoring schedule for White Blood Cell Count (WBC) and Absolute Neutrophil Count (ANC) prior to dispensing Versacloz
- Preventing re-exposure of patients who have previously experienced agranulocytosis or severe granulocytopenia/leukopenia with any clozapine products.

II. REMS ELEMENTS

A. Elements To Assure Safe Use

1. Healthcare providers who prescribe Versacloz are specially certified.

- a. Douglas Pharmaceuticals America LTD will ensure that healthcare providers who prescribe Versacloz are specially certified.
- b. The healthcare provider enrollment process comprises the following steps that must be completed prior to prescribing Versacloz:
 - i. The healthcare provider completes the Healthcare Provider Enrollment Form. In signing the Healthcare Provider Enrollment Form, each healthcare provider indicates they understand that clozapine is available only through the Versacloz REMS Program, entitled Versacloz Patient Registry, and are aware of and attest to the following requirements:
 - a) Review the Versacloz package insert and understand the risk of death associated with agranulocytosis or severe granulocytopenia/leukopenia when prescribing Versacloz.
 - b) Enroll all applicable patients in the Versacloz Patient Registry. When enrolling a patient, healthcare providers will be matched with an enrolled pharmacy and be defined as an “affiliated treatment pair” by completing the appropriate section of the Patient Enrollment Form.
 - c) Understand the recommendations for prescribing and monitoring as described in the Versacloz package insert.
 - d) Understand Versacloz should only be prescribed to new patients after verifying an acceptable baseline WBC count ($\geq 3500/\text{mm}^3$) and ANC ($\geq 2000/\text{mm}^3$) test results, submitting the Patient Registration Form with baseline labs within 7 days of blood draw and only after receiving a Patient Registration Number (PRN) from the Versacloz Patient Registry.
 - e) Understand that no more than a 7 day supply of Versacloz should be prescribed to a patient who has been continually on clozapine treatment with a different clozapine formulation (i.e. clozapine tablets, clozapine orally disintegrating tablets) prior to initiating Versacloz but who is not currently enrolled in the Versacloz Patient Registry, and understand that Versacloz should not be prescribed in such circumstances until verification that the patient has an acceptable baseline WBC count ($\geq 3500/\text{mm}^3$) and ANC

- ($\geq 2000/\text{mm}^3$). They understand they should prescribe Versacloz to a patient a second time only after receiving a valid PRN from the Versacloz Patient Registry
- f) Complete the Patient WBC Count and ANC Monitoring Form and provide the affiliated pharmacist with the completed form and a valid prescription for each dispensation of Versacloz.
 - g) Follow the process for a patient discontinued from Versacloz, regardless of the reason for discontinuation:
 - i. Indicate discontinuation of Versacloz on the Patient WBC Count and ANC Monitoring Form
 - ii. Notify the Versacloz Patient Registry by submitting the completed Patient WBC Count and ANC Monitoring Form to the Versacloz Patient Registry.
 - iii. Notify the affiliated pharmacy by submitting the completed Patient WBC Count and ANC Monitoring Form to the affiliated pharmacy
 - iv. Submit the required WBC count and ANC test results to the Versacloz Patient Registry weekly for at least 4 weeks from the day of discontinuation or until the patients labs return to normal ($\text{WBC} > 3500/\text{mm}^3$ and $\text{ANC} > 2000/\text{mm}^3$).
 - h) Understand the list of patients enrolled in the Versacloz Patient Registry will be used to verify the patient's rechallenge status against the Clozapine National Non-Rechallenge Masterfile. Furthermore, any patient permanently discontinued from Versacloz for meeting the non-rechallenge criteria ($\text{WBC count} < 2000/\text{mm}^3$ and/or $\text{ANC} < 1000/\text{mm}^3$) will be reported to the Clozapine National Non-Rechallenge Masterfile. .
 - i) Understand the Versacloz Patient Registry will be audited to monitor adherence to prescribing and monitoring requirements, and enrolled healthcare providers and pharmacies will be promptly notified of any discrepancies or missing information by Douglas Pharmaceuticals America LTD.
- c. Douglas Pharmaceuticals America LTD will:
- i. Ensure that healthcare provider enrollment can successfully be completed via the Versacloz REMS website, or by mailing or faxing the forms.
 - ii. Ensure that, as part of the enrollment process, the following materials that are part of the Versacloz REMS program are available to healthcare providers. These materials are appended:
 - *Healthcare Provider Enrollment Form*
 - iii. Ensure that the *Healthcare Provider Enrollment Form* is complete before a healthcare provider's enrollment is activated in the Versacloz REMS program.
 - iv. Ensure that healthcare providers are notified when they are successfully enrolled in the Versacloz REMS program, and therefore, are certified to prescribe Versacloz.

- v. Monitor enrollment requirements for healthcare providers and institute corrective action and/or inactivate non-compliant healthcare providers. Upon initial activation, healthcare providers remain active until inactivation occurs.

2. Pharmacies that dispense Versacloz are specially certified.

- a. Douglas Pharmaceuticals America LTD will ensure that pharmacies that dispense Versacloz are specially certified.
- b. The pharmacy enrollment process comprises the following steps that must be completed prior to dispensing Versacloz:
 - i. The lead pharmacist will complete the Pharmacy Enrollment Form. In signing the Pharmacy Enrollment Form, the lead pharmacist indicates that all pharmacists with dispensing privileges at the pharmacy understand that Versacloz is only available to certified pharmacies after enrolling in the Versacloz REMS program, entitled Versacloz Patient Registry, and are aware of and attest to the following requirements:
 - a) Review the Versacloz package insert and understand the risk of death associated with agranulocytosis or severe granulocytopenia/leukopenia prior to dispensing Versacloz.
 - b) Enroll all applicable patients in the Versacloz Patient Registry. When enrolling a patient, healthcare providers will be matched with an enrolled pharmacy and be defined as an “affiliated treatment pair” by completing the appropriate section of the *Patient Enrollment Form*.
 - c) Understand the recommendations for prescribing and monitoring as described in the package insert.
 - d) Understand Versacloz should only be dispensed to a new patient after verifying an acceptable baseline WBC count ($\geq 3500/\text{mm}^3$) and ANC ($\geq 2000/\text{mm}^3$) test results and only after receiving a Patient Registration Number (PRN) from the Versacloz Patient Registry.
 - e) Understand that no more than a 7 day supply of Versacloz should be dispensed to a patient who has been continually on clozapine treatment with a different clozapine formulation (i.e. clozapine tablets, clozapine orally disintegrating tablets) prior to initiating Versacloz but is not currently enrolled in the Versacloz Patient Registry, and understand that Versacloz should not be dispensed in such circumstances until verification that the patient has an acceptable baseline WBC count ($\geq 3500/\text{mm}^3$) and ANC ($\geq 2000/\text{mm}^3$). They understand they should dispense Versacloz to a patient a second time only after receiving a valid PRN from the Versacloz Patient Registry.

- f) Understand the importance of providing the Versacloz Patient Registry with all WBC count and test results for all enrolled patients within:
 - 7 days from blood draw to patients on weekly monitoring schedule
 - 14 days from blood draw to patients on bi weekly monitoring schedule
 - 28 days from blood draw to patients on monthly monitoring schedule
- g) Understand the list of patients enrolled in the Versacloz Patient Registry will be used to verify a patient's rechallenge status against the Clozapine National Non- Rechallenge Masterfile. Furthermore, any patient permanently discontinued from Versacloz for meeting the non-rechallenge criteria (WBC count $<2000/\text{mm}^3$ and/or $\text{ANC}<1000\text{mm}^3$) will be reported to the Clozapine National Non-Rechallenge Masterfile.
- h) Understand the Versacloz Patient Registry will be audited to monitor adherence to prescribing, monitoring and timeliness requirements and enrolled healthcare providers and pharmacies will be promptly notified of any discrepancies or missing information by Douglas Pharmaceuticals America LTD.
- c. Douglas Pharmaceuticals America LTD will:
 - i. Ensure that pharmacy enrollment can successfully be completed via the Versacloz REMS website, or by mailing or faxing the forms.
 - ii. Ensure that, as part of the enrollment process, the following materials that are part of the Versacloz REMS program are available to pharmacies. These materials are appended:
 - *Pharmacy Enrollment Form*
 - iii. Ensure that the *Pharmacy Enrollment Form* is complete before a pharmacy's enrollment is activated in the Versacloz REMS program.
 - iv. Ensure that pharmacies are notified when they are successfully enrolled in the Versacloz REMS program, and therefore, are certified to dispense Versacloz.
 - v. Monitor enrollment requirements for pharmacies/pharmacists and institute corrective action and/or inactivate non-compliant pharmacies/pharmacists. Upon initial activation, pharmacies/pharmacists remain active until inactivation occurs.

3. Versacloz may be dispensed to patients with documentation of safe-use conditions.

- a. Douglas Pharmaceuticals America LTD will ensure that no patient is able to be enrolled with the Versacloz Patient Registry or provided a PRN if the patient is in the Clozapine National Non-Rechallenge Masterfile to assure safe-use conditions.
 - i. Douglas Pharmaceuticals America LTD will ensure that the following will be completed upon receipt of the completed patient enrollment form:

- a) Review the form for completeness and clarity.
 - b) Verify that the patient is not included in the Clozapine National Non- Rechallenge Masterfile.
 - c) Confirm that the patient's WBC count and ANC test results, which have been obtained within 1 week of the registration date, are acceptable (WBC count $\geq 3500/\text{mm}^3$ and ANC $\geq 2000/\text{mm}^3$.)
 - d) Notify the pharmacist of patient non-rechallenge and registration status and provide a PRN by mail, fax, or e-mail.
 - e) Separately notify the patient's healthcare provider of the patient's non- rechallenge status and his/her PRN by mail, fax, or e-mail.
 - f) Provide notification of monitoring schedule when appropriate data are available to the registry.
- ii. Douglas Pharmaceuticals America LTD will ensure that, as part of the enrollment process, the following enrollment form that is part of the Versacloz REMS program is available to enrolled healthcare providers and pharmacies. These materials are appended:
 - *Patient Enrollment Form*

4. Each patient using Versacloz is subject to certain monitoring.

- a. Douglas Pharmaceuticals America LTD will ensure that required routine laboratory results (WBC and ANC) are received from enrolled healthcare providers and pharmacies according to the patient's appropriate monitoring schedule as described in the Versacloz package insert.
 - i. Douglas Pharmaceuticals America LTD will ensure that the *Patient WBC Count and ANC Monitoring Form* can successfully be completed via the Versacloz REMS website, by phone, or by mailing or faxing the forms.
 - ii. Douglas Pharmaceuticals America LTD will ensure that, as part of the monitoring process, the following materials that are part of the Versacloz REMS program are available to enrolled healthcare providers and pharmacies. These materials are appended:
 - *Single Patient WBC Count and ANC Monitoring Form*
 - *Multiple Patient WBC Count and ANC Monitoring Form*
- b. Douglas Pharmaceuticals America LTD will ensure that any patient for which they receive confirmed blood test results that meet the non-rechallenge criteria (WBC count below $2000/\text{mm}^3$ and/or ANC below $1000/\text{mm}^3$) will be reported to the Clozapine National Non-Rechallenge Masterfile within 48 hours.
- c. Douglas Pharmaceuticals America LTD will ensure that certified healthcare providers submit WBC count and ANC values for any patient who experiences confirmed blood test results that meet the non-rechallenge criteria (WBC count below $2000/\text{mm}^3$ and/or ANC below $1000/\text{mm}^3$) until laboratory results return to normal (WBC $> 3500/\text{mm}^3$ and ANC $> 2000/\text{mm}^3$) and for at least 4 weeks from day of discontinuation of therapy.

5. Each patient using Versacloz is enrolled in a registry.

- a. Douglas Pharmaceuticals America LTD will ensure that certified healthcare providers enroll each patient in the Versacloz Registry. The registry will collect patient demographics, patient's affiliated treatment team (MD and RPh), all required routine labs (ANC and WBC), patient monitoring schedule (weekly, bi-weekly, monthly), and non-rechallengeable status.
- b. Douglas Pharmaceuticals America LTD will ensure that the patient enrollment can successfully be completed via the Versacloz REMS website, by phone, or by mailing or faxing the forms.

D. Implementation System

1. Douglas Pharmaceuticals America LTD will maintain a database of all enrolled entities (healthcare providers, pharmacies, and patients) and will monitor and evaluate implementation of the Versacloz REMS program requirements.
2. Douglas Pharmaceuticals America LTD will monitor distribution data and prescription data to ensure that only enrolled healthcare providers are prescribing and enrolled pharmacies are dispensing Versacloz. Corrective action or inactivation will be instituted by Douglas Pharmaceuticals America LTD if non-compliance is found.
3. Audit the Versacloz Patient Registry to monitor adherence to prescribing and monitoring requirements and promptly notify enrolled healthcare providers and pharmacies of any discrepancies and obtain missing information.
4. Douglas Pharmaceuticals America LTD will maintain a call center to support patients, healthcare providers, pharmacies, and distributors in interfacing with the Versacloz REMS program.
5. Douglas Pharmaceuticals America LTD will ensure that all materials listed in or appended to the Versacloz REMS program will be available through the Versacloz REMS program website, www.versaclozregistry.com or by calling the Versacloz REMS call center at **1-877-329-2256**.
6. If there are substantive changes to the Versacloz REMS program, Douglas Pharmaceuticals America LTD will update all affected materials and notify pharmacies, prescribers, and distributors of the changes, as applicable. Notifications for patients will be sent to the patient's healthcare provider. Substantive changes to the Versacloz REMS program are defined as:
 - Significant changes to the operation of the Versacloz REMS program.
 - Changes to the package insert that affect the risk-benefit profile of Versacloz
7. Based on monitoring and evaluation of the REMS Elements to Assure Safe Use, Douglas Pharmaceuticals America LTD will take reasonable steps to improve implementation of these elements and to maintain compliance with the Versacloz REMS program requirements, as applicable.

E. Timetable for Submission of Assessments

Douglas Pharmaceuticals America LTD will submit REMS Assessments to the FDA at a minimum, by 6 months, and annually thereafter from the date of approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Douglas

Pharmaceuticals America LTD will submit each assessment so that it will be received by the FDA on or before the due date.

Instruction: This form is used to enroll a healthcare provider in the Versacloz Patient Registry. Submitting this completed form indicated you have read and agree to the statement of OBLIGATIONS below. All forms must be signed and dated by the Healthcare Provider.

Healthcare Provider statement of OBLIGATIONS:

1. I will review the Versacloz package insert and understand the risk of death associated with agranulocytosis when prescribing Versacloz
2. I will enroll all applicable patients in the Versacloz Patient Registry. When enrolling a patient, providers will be matched with an enrolled pharmacy and be defined as an “affiliated treatment pair” by completing the appropriate section of the Patient Enrollment Form.
3. I understand the recommendations for prescribing and monitoring as described in the package insert.
4. I understand Versacloz should only be prescribed to a new patient after verifying an acceptable baseline WBC count ($\geq 3500/\text{mm}^3$) and ANC ($\geq 2000/\text{mm}^3$) test results and only after receiving a Patient Registration Number (PRN) from the VersaCloz Patient Registry.
5. I understand that no more than a 7 day supply of VersaCloz should be prescribed to a patient who has been continually on clozapine treatment with a different clozapine formulation (i.e. clozapine tablets, clozapine orally disintegrating tablets) but is not currently enrolled in the VersaCloz Patient Registry, and understand that Versacloz should not be prescribed until verification that the patient has an acceptable baseline WBC count ($\geq 3500/\text{mm}^3$) and ANC ($\geq 2000/\text{mm}^3$). I understand I should prescribe Versacloz to a patient a second time only after receiving a Patient Registration Number (PRN) from the Versacloz Patient Registry.
6. I will complete the Patient WBC Count and ANC Monitoring Form and provide the affiliated pharmacist with the completed form and a valid prescription for each dispensation of Versacloz.
7. I will follow the process for a patient discontinued from Versacloz, regardless of the reason for discontinuation:
 - i. Indicate discontinuation of Versacloz on the Patient WBC Count and ANC Monitoring Form
 - ii. Notify the VersaCloz Patient Registry by submitting the completed Patient WBC Count and ANC Monitoring Form to the Versacloz Patient Registry
 - iii. Notify the affiliated pharmacy by submitting the completed Patient WBC Count and ANC Monitoring Form to the affiliated pharmacy.
 - iv. Submit the required WBC count and ANC test results to the Versacloz Patient Registry weekly for at least 4 weeks from the day of discontinuation or until the patients labs return to normal (WBC $>3500/\text{mm}^3$ and ANC $>2000/\text{mm}^3$)
8. I understand the list of patients enrolled in the Versacloz Patient Registry will be used to verify the patient’s rechallenge status against the Clozapine National Non-Rechallenge Masterfile. Furthermore, any patient permanently discontinued from Versacloz for meeting the non-rechallenge criteria (WBC $<2000/\text{mm}^3$ and/or ANC $<1000/\text{mm}^3$) will be reported to the Clozapine National Non-Rechallenge Masterfile.
9. I understand the Versacloz Patient Registry will be audited to monitor adherence to prescribing, monitoring and timeliness requirements and registered healthcare providers and pharmacies will be promptly notified of any discrepancies or missing information by Douglas Pharmaceuticals America Ltd.

Healthcare Provider Signature	Date: (MM/DD/YYYY)
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* The blood work draw date may not be more than 7 days old in order for the pharmacist to dispense the drug, regardless of the patients’ monitoring schedule

Healthcare Provider Name (PLEASE PRINT)

Last:	FIRST	M.I.	Suffix.
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Healthcare Provider ID # (optional)

Medical Facility Information (Please Print)

Facility Name:		
Address:		
City:	State:	Zip:
Phone:	Fax:	E-mail:

Please answer the following question:

1. Are you currently enrolled in any other clozapine registry? Yes No

If yes, please indicate the name of the registry:

Please mail or Fax completed form to:

Versacloz Patient Registry
1818 Market Street, Suite 2350
Philadelphia, PA 19103

Phone: 1-877-329-2256
Fax: 1-877-798-0229

Versacloz Patient Registry

Patient Enrollment Form

Instruction: This form is used to register a patient in the Versacloz Patient Registry. Submitting this completed form indicates you have read and agree to the statement of OBLIGATIONS, have determined that Versacloz treatment is not contraindicated for this patient, and assigns one Healthcare Provider and one pharmacist as the Affiliated Treatment pair for this patient.

A. Patient Information:

Initials: (F/M/L)	<input type="text"/>	<input type="text"/>	Birth Date: (DD/MM/YYYY)	<input type="text"/>	Zip Code:	<input type="text"/>
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Patient Social Security	<input type="text"/>	<input type="text"/>	<input type="text"/>	-	<input type="text"/>	<input type="text"/>	-	<input type="text"/>	<input type="text"/>	<input type="text"/>	Gender: Male <input type="checkbox"/>	Female <input type="checkbox"/>
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Race: **Caucasian** **African-American** **Asian** **Hispanic** **Other**

Blood Draw Date: (MM/DD/YYYY)	Dosage:	Total WBC Count (per mm ³)	ANC (per mm ³)
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

QUESTIONS		Yes	No
1.	Has the patient ever been treated with clozapine (brand or generic)?	<input type="checkbox"/>	<input type="checkbox"/>
2.	Is the patient currently enrolled in any other clozapine registry?	<input type="checkbox"/>	<input type="checkbox"/>
3.	Has the patient's clozapine treatment been interrupted in this time?	<input type="checkbox"/>	<input type="checkbox"/>
4.	Is the patient currently on every two weeks WBC count and ANC monitoring?	<input type="checkbox"/>	<input type="checkbox"/>
5.	Is the patient currently on every four weeks WBC count and ANC monitoring?	<input type="checkbox"/>	<input type="checkbox"/>
6.	If weekly WBC count and ANC monitoring, indicate how many weeks without treatment interruption since this treatment has started:	<input type="text"/>	

B. Affiliated Treatment Pair Information: *Only one Treatment Pair can be assigned by enrolled patient*

Healthcare Provider		Pharmacy / Pharmacist	
Name:	<input type="text"/>	Name:	<input type="text"/>
ID# (optional):	<input type="text"/>	DEA or ID#:	<input type="text"/>
Facility Name:	<input type="text"/>	Pharmacy Name:	<input type="text"/>
Address:	<input type="text"/>	Address:	<input type="text"/>
Phone:	<input type="text"/>	Phone:	<input type="text"/>
Fax:	<input type="text"/>	Fax:	<input type="text"/>
Email:	<input type="text"/>	Email:	<input type="text"/>
Acknowledgement	Date:	Acknowledgement	Date:

Pharmacist: Once this form is received from the Affiliated Healthcare Provider this completed form should be mailed or Faxed to the:

Versacloz Patient Registry
1818 Market Street, Suite 2350
Philadelphia, PA 19103

Phone: 1-877-329-2256
Fax: 1-877-798-0229

Alternatively, the data may be phoned into the Registry at 1-877-329-2256 or the information may be entered into the Versacloz database via the internet at www.versaclozregistry.com

C. To be completed by the Registry Staff: DO NOT DISPENSE TREATMENT UNTIL Notified of Patient Eligibility with PRN

Patient Registration Number	<input type="text"/>	Assignment of PRN indicated that the registry staff has verified that this patient is not on the Clozapine National Non-Rechallenge Masterfile
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Versacloz Patient Registry

WBC Count and ANC Monitoring Form

Instructions: This form is used to submit WBC count and ANC monitoring information according to the Versacloz Patient Registry protocol and package insert. Multiple dates of information may be logged on one form for one patient if data submission is via fax. In this case, complete log and resubmit form every time according to schedule. Multiple forms will be required if data submission is via mail. **NOTE: FORM MUST BE SUBMITTED TO REGISTRY AT EVERY DISPENSATION TIME.**

- > The patient's Affiliated Healthcare Provider must complete this form after verifying the patient's required blood counts are within normal limits and timeframe according to Versacloz product labeling and healthcare provider evaluates patient.
- > The Affiliated Healthcare Provider must provide Affiliated Pharmacist with completed WBC Count and ANC Monitoring Form and valid prescription for each dispensation of Versacloz to meet monitoring requirements.
- > The Affiliated Pharmacist can dispense Versacloz ONLY after receiving a completed WBC Count and ANC Monitoring Form with valid PRN, a valid prescription, and verifying the WBC count and ANC test results are within normal limits and timeframe according to Versacloz package insert.

A. Patient Information:

Initials (F/M/L)

Patient Registration Number (PRN):

Patient SSN: - -

B. Affiliated Pair Information (Patient's Affiliated Treatment Pair):

Healthcare Provider DEA or ID#: -

Pharmacy DEA or ID#: -

C. WBC Count, ANC, and Treatment Dispensation Information:

Blood Draw Date (MM/DD/YYYY)	Total WBC Count (per mm ³)	ANC (per mm ³)	Treatment Status After Today's Evaluation C=Continue T=TEMP Discontinue P=PERM Discontinue	Medication Dispense Date (MM/DD/YYYY)	Total Daily Dose (mg/day)	Acceptable to Dispense Treatment? Y = Yes N = No	Monitoring Schedule After Today's Evaluation		
							Weekly	Every Two Weeks	Every Four Weeks

Patient Notes

Pharmacist: Once this form is received from the Affiliated Healthcare Provider this completed form should be mailed or FAXed to the
 Versacloz Patient Registry
 1818 Market Street, Suite 2350
 Philadelphia, PA 19103
 FAX: 1-877-798-0229

Alternatively, the data may be phoned into the Versacloz Patient Registry at 1-877-329-2256, or the information may be entered into the Versacloz database via the Internet at www.versaclozregistry.com

Versacloz™ Risk Evaluation and Mitigation Strategy (REMS)

Versacloz Patient Registry Information

[General Overview](#) | [System Requirements](#) | [Registration and Monitoring Forms](#) | [HIPAA](#) | [Using the Registry FAQ](#) | [Versacloz Patient Registry Demo](#) | [Versacloz Patient Registry Login](#) | [Sign Up for the Versacloz Patient Registry](#)

General Overview

Sign Up for the Versacloz™ Patient Registry



Versacloz™ Patient Registry Login



Prescribing Information

- [Prescribing Information](#)
- [Important Safety Information](#)
- [Download Adobe Acrobat](#)

The Versacloz Patient Registry is a component of a Risk Evaluation and Mitigation Strategy (REMS) required by the United States Food and Drug Administration. Pursuant to this requirement Douglas Pharmaceuticals America Ltd. is required to collect laboratory data, patient identification information and investigate adverse events associated with Versacloz.

The Versacloz Patient Registry:

- Provides a database for WBC and absolute neutrophil count monitoring of patients treated with Versacloz to permit early detection of clozapine-induced leukopenia.
- Provides confidential registration and report process for patients treated with Versacloz.
- Provides ongoing updating of the Clozapine National Non-Rechallenge Masterfile with patients treated with Versacloz who become non-rechallengeable.

The Versacloz Patient Registry under the direction of the Versacloz Patient Registry Coordinating Center, includes a registry team, a professional toll-free call center at 1-877-329-2256, and a registry web-site.

The Versacloz Patient Registry team is composed of dedicated healthcare, registry, call center, administrative support and data management professionals.

The Versacloz Patient Registry Call Center is available 24 hours a day and 365 days a year to support all registry operations. Health care practitioners, pharmacist and patients may contact the call center with any questions related to the Versacloz Patient Registry. Health care practitioners and pharmacists may request registry materials directly through the call center.

Adverse Event Reporting

To report an adverse event please call 1-800-520-5568

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

You may contact the Versacloz Patient Registry at 1-877-329-2256 or at www.versaclozregistry.com. Please see full [Prescribing Information](#), including BOXED Warning, for additional important safety information.

Versacloz™ is a registered trademark of Jazz Pharmaceuticals.



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NDA 203479

Versacloz™ (clozapine) oral suspension

Class of Product: Atypical Antipsychotic

NDA Holder:

**Douglas Pharmaceuticals America LTD
Corner Central Park Drive and Te Pai Place, Lincoln Auckland,
NEW ZEALAND**

0011 649 835 0660 (Telephone)

0011 649 835 0690 (Facsimile)

US Agent:

**VersaPharm Incorporated
1775 West Oak Parkway, Suite 800
Marietta, GA 30062
Contact: John Franolic
Phone: 770-373-5635
Facsimile: 770-373-5655**

REMS SUPPORTING DOCUMENT

Part I - Versacloz™ Patient Registry Protocol

Part II - Versacloz™ REMS Assessment Plan

Versacloz REMS Supporting Document

PART I:

Versacloz

PATIENT REGISTRY PROTOCOL

TITLE:

A Patient Registry for Agranulocytosis Monitoring of VersaCloz Treatment (1) in Patients Failing Standard Therapy for Severe Schizophrenia and (2) in Patients With Schizophrenia or Schizoaffective Disorder Who Are at Risk of Re-experiencing Suicidal Behavior

Note: The Versacloz Patient Registry is a component of a restricted distribution program under a Risk Evaluation and Mitigation Strategy (REMS) required by the United States Food and Drug Administration (FDA).

PROTOCOL: 00

Douglas Pharmaceuticals America LTD
Corner Central Park Drive and Te Pai Place, Lincoln Auckland,
NEW ZEALAND

CONFIDENTIAL

SIGNATURE PAGE

PROTOCOL: 00

APPROVAL SIGNATURES

Title	Signature	Date

30 pages have been withheld immediately following this page as b4 (CCI/TS)

Appendix H: Registry Forms

Versacloz Patient Registry

Patient Enrollment Form

Instruction: This form is used to register a patient in the Versacloz Patient Registry. Submitting this completed form indicates you have read and agree to the statement of OBLIGATIONS, have determined that Versacloz treatment is not contraindicated for this patient, and assigns one Healthcare Provider and one pharmacist as the Affiliated Treatment pair for this patient.

A. Patient Information:

Initials: (F/M/L)			Birth Date: (DD/MM/YYYY)		Zip Code:	
-----------------------------	--	--	------------------------------------	--	------------------	--

Patient Social Security		Gender: Male <input type="checkbox"/>	Female <input type="checkbox"/>
--------------------------------	--	--	--

Race:	Caucasian <input type="checkbox"/>	African-American <input type="checkbox"/>	Asian <input type="checkbox"/>	Hispanic <input type="checkbox"/>	Other <input type="checkbox"/>
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Blood Draw Date: (MM/DD/YYYY)	Dosage:	Total WBC Count (per mm ³)	ANC (per mm ³)

QUESTIONS	Yes	No
1. Has the patient ever been treated with clozapine (brand or generic)?		
2. Is the patient currently enrolled in any other clozapine registry?		
3. Has the patient's clozapine treatment been interrupted in this time?		
4. Is the patient currently on every two weeks WBC count and ANC monitoring?		
5. Is the patient currently on every four weeks WBC count and ANC monitoring?		
6. If weekly WBC count and ANC monitoring, indicate how many weeks without treatment interruption since this treatment has started:		

B. Affiliated Treatment Pair Information: *Only one Treatment Pair can be assigned by enrolled patient*

Healthcare Provider		Pharmacy / Pharmacist	
Name:		Name:	
ID# (optional):		DEA or ID#:	
Facility Name:		Pharmacy Name:	
Address:		Address:	
Phone:		Phone:	
Fax:		Fax:	
Email:		Email:	
Acknowledgement	Date:	Acknowledgement	Date:

Pharmacist: Once this form is received from the Affiliated Healthcare Provider this completed form should be mailed or Faxed to the:

Versacloz Patient Registry
1818 Market Street, Suite 2350
Philadelphia, PA 19103

Phone: 1-877-329-2256
Fax: 1-877-798-0229

Alternatively, the data may be phoned into the Registry at 1-877-329-2256 or the information may be entered into the Versacloz database via the internet at www.versaclozregistry.com

C. To be completed by the Registry Staff: DO NOT DISPENSE TREATMENT UNTIL Notified of Patient Eligibility with PRN

Patient Registration Number		Assignment of PRN indicated that the registry staff has verified that this patient is not on the Clozapine National Non-Rechallenge Masterfile
------------------------------------	--	--

Versacloz Patient Registry

Healthcare Provider Enrollment Form

Instruction: This form is used to enroll a healthcare provider in the Versacloz Patient Registry. Submitting this completed form indicated you have read and agree to the statement of OBLIGATIONS below. All forms must be signed and dated by the Healthcare Provider.

Healthcare Provider statement of OBLIGATIONS:

1. I will review the Versacloz package insert and understand the risk of death associated with agranulocytosis when prescribing Versacloz
2. I will enroll all applicable patients in the Versacloz Patient Registry. When enrolling a patient, providers will be matched with an enrolled pharmacy and be defined as an “affiliated treatment pair” by completing the appropriate section of the Patient Enrollment Form.
3. I understand the recommendations for prescribing and monitoring as described in the package insert.
4. I understand Versacloz should only be prescribed to a new patient after verifying an acceptable baseline WBC count ($\geq 3500/\text{mm}^3$) and ANC ($\geq 2000/\text{mm}^3$) test results and only after receiving a Patient Registration Number (PRN) from the VersaCloz Patient Registry.
5. I understand that no more than a 7 day supply of VersaCloz should be prescribed to a patient who has been continually on clozapine treatment with a different clozapine formulation (i.e. clozapine tablets, clozapine orally disintegrating tablets) but is not currently enrolled in the VersaCloz Patient Registry, and understand that Versacloz should not be prescribed until verification that the patient has an acceptable baseline WBC count ($\geq 3500/\text{mm}^3$) and ANC ($\geq 2000/\text{mm}^3$). They understand they should prescribe Versacloz to a patient a second time only after receiving a Patient Registration Number (PRN) from the Versacloz Patient Registry.
6. I will complete the Patient WBC Count and ANC Monitoring Form and provide the affiliated pharmacist with the completed form and a valid prescription for each dispensation of Versacloz.
7. I will follow the process for a patient discontinued from Versacloz, regardless of the reason for discontinuation:
 - i. Indicate discontinuation of Versacloz on the Patient WBC Count and ANC Monitoring Form
 - ii. Notify the VersaCloz Patient Registry by submitting the completed Patient WBC Count and ANC Monitoring Form to the Versacloz Patient Registry
 - iii. Notify the affiliated pharmacy by submitting the completed Patient WBC Count and ANC Monitoring Form to the affiliated pharmacy.
 - iv. Submit the required WBC count and ANC test results to the Versacloz Patient Registry weekly for at least 4 weeks from the day of discontinuation or until the patients labs return to normal (WBC $>3500/\text{mm}^3$ and ANC $>2000/\text{mm}^3$)
8. I understand the list of patients enrolled in the Versacloz Patient Registry will be used to verify the patient’s rechallenge status against the Clozapine National Non-Rechallenge. Furthermore, any patient permanently discontinued from Versacloz for meeting the non-rechallenge criteria (WBC $<2000 \text{ mm}^3$ and/or ANC $<1000/\text{mm}^3$) will be reported to the Clozapine National Non-Rechallenge.
9. I understand the Versacloz Patient Registry will be audited to monitor adherence to prescribing, monitoring and timeliness requirements and registered healthcare providers and pharmacies will be promptly notified of any discrepancies or missing information by Douglas Pharmaceuticals America Ltd.

Healthcare Provider Signature	Date: (MM/DD/YYYY)
-------------------------------	-----------------------

* The blood work draw date may not be more than 7 days old in order for the pharmacist to dispense the drug, regardless of the patients’ monitoring schedule

Healthcare Provider Name (PLEASE PRINT)

Last:	FIRST	M.I.	Suffix.
-------	-------	------	---------

Healthcare Provider ID # (optional)

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Medical Facility Information (Please Print)

Facility Name:			
Address:			
City:	State:	Zip:	
Phone:	Fax:	E-mail:	

Please answer the following question:

1. Are you currently enrolled in any other clozapine registry? Yes No

If yes, please indicate the name of the registry:

Please mail or Fax completed form to:

Versacloz Patient Registry
1818 Market Street, Suite 2350
Philadelphia, PA 19103

Phone: 1-877-329-2256
Fax: 1-877-798-0229

Versacloz Patient Registry

Pharmacy / Pharmacist Enrollment Form

Instruction: This form is used to enroll a pharmacy / pharmacist in the Versacloz Patient Registry. Submitting this completed form indicated you have read and agree to the statement of OBLIGATIONS below. All forms must be signed and dated by the Pharmacist.

Pharmacy / Pharmacist statement of OBLIGATIONS:

I and all pharmacists with dispensing privileges at this pharmacy will:

1. Review the Versacloz package insert and understand the risk of death associated with agranulocytosis prior to dispensing Versacloz.
2. Enroll all applicable patients in the Versacloz Patient Registry. When enrolling a patient, providers will be matched with an enrolled pharmacy and be defined as an “affiliated treatment pair” by completing the appropriate section of the Patient Enrollment Form.
3. Understand the recommendations for prescribing and monitoring as described in the VersaCloz package insert.
4. Understand VersaCloz should only be dispensed to a new patient after verifying an acceptable baseline WBC count ($\geq 3500/\text{mm}^3$) and ANC ($\geq 2000/\text{mm}^3$) test results and only after receiving a Patient Registration Number (PRN) from the Versacloz Patient Registry.
5. Understand that no more than a 7 day supply of VersaCloz should be dispensed to a patient who has been continually on clozapine treatment with a different clozapine formulation (i.e. clozapine tablets, clozapine orally disintegrating tablets) but is not currently enrolled in the VersaCloz Patient Registry, and understand that Versacloz should not be dispensed in such circumstances until verification that the patient has an acceptable baseline WBC count ($\geq 3500/\text{mm}^3$) and ANC ($\geq 2000/\text{mm}^3$). They understand they should dispense Versacloz to a patient a second time only after receiving a Patient Registration Number (PRN) from the Versacloz Patient Registry.
6. Understand the importance of providing the VersaCloz Patient Registry with all WBC count and test results for all enrolled patients within:
 - 7 days from blood draw to patients on weekly monitoring schedule
 - 14 days from blood draw to patients on bi weekly monitoring schedule
 - 28 days from blood draw to patients on monthly monitoring schedule
7. Understand the list of patients enrolled in the Versacloz Patient Registry will be used to verify a patient’s rechallenge status against the Clozapine National Non-Rechallenge Masterfile. Furthermore, any patient permanently discontinued from Versacloz for meeting the non-rechallenge criteria ($\text{WBC} < 2000 \text{ mm}^3$ and/or $\text{ANC} < 1000 \text{ mm}^3$) will be reported to the Clozapine National Non-Rechallenge.
8. Understand the Versacloz Patient Registry will be audited to monitor adherence to prescribing, monitoring and timeliness requirements and registered healthcare providers and pharmacies will be promptly notified of any discrepancies or missing information by Douglas Pharmaceuticals America Ltd.

Pharmacist Signature	Date (MM/DD/YYYY)
----------------------	----------------------

* The blood work draw date may not be more than 7 days old in order for the pharmacist to dispense the drug, regardless of the patients’ monitoring schedule

Pharmacist Name (PLEASE PRINT)

Last:	FIRST	M.I.	Suffix.
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Pharmacy DEA or ID #

Pharmacy Information (Please Print)

Pharmacy Name:		
Address:		
City:	State:	Zip:
Phone:	Fax:	E-mail:

Please answer the following question:

1. Is your pharmacy currently enrolled in any other clozapine registry? Yes No

If yes, please indicate the name of the registry:

Please mail or Fax completed form to:
 Versacloz Patient Registry
 1818 Market Street, Suite 2350
 Philadelphia, PA 19103

Phone: 1-877-329-2256
 Fax: 1-877-798-0229

Instructions: This form is used to submit WBC count and ANC monitoring information on multiple registry patients where treatment dispensation occurs on the same day. NOTE: DATA SUBMISSION TIMELINES MUST BE MET FOR ALL LISTED PATIENTS – (ie, form received by registry within 7 days of blood draw date for patients on weekly monitoring; 14 days for every two weeks monitoring; and 28 days for every 4 weeks monitoring).

- The Affiliated Healthcare Provider must provide Affiliated Pharmacist with complete WBC count and ANC test results according to individual monitoring schedule and valid prescription for each dispensation of Versacloz to meet monitoring requirements.
- The Affiliated Pharmacist can dispense Versacloz ONLY after receiving a completed WBC Count and ANC Monitoring Form with valid PRN, a valid prescription, and verifying the WBC count and ANC test result are within normal limits and timeframe according to Versacloz package insert.

Date:		Pharmacy Name:		Pharmacy DEA or ID#:													
--------------	--	-----------------------	--	-----------------------------	--	--	--	--	--	--	--	--	--	--	--	--	--

WBC/ANC and Treatment Dispensation Information:

Patient Initials (FML)	Patient SSN/PRN	Affiliated Healthcare Provider DEA or ID#	Blood Draw Date (MM/DD/YYYY)	Total WBC Count (per mm ³)	ANC (per mm ³)	Treatment Status After Today's Evaluation C=Continue T=Temporarily Discontinue P=Permanently Discontinue	Medication Dispense Date (MM/DD/YYYY)	Total Daily Dose (mg/day)	Acceptable to Dispense Treatment? Y=Yes N=No	Monitoring Schedule After Today's Evaluation		
										Weekly	Every Two Weeks	Every Four Weeks

Pharmacist: Once this form is received from the Affiliated Healthcare provider this completed form should be mailed or FAXed to:
Versacloz Patient Registry
 1818 Market Street, Suite 2350 Fax: 1-877-798-0229
 Philadelphia, PA 19103
 Alternatively, the data may be phoned into the Versacloz Patient Registry at 1-877-329-2256, or the information may be entered into the Versacloz database via the Internet at www.versaclozregistry.com

Appendix I: Package Insert

Versacloz REMS Supporting Document

PART II: Versacloz REMS Assessment Plan

Information Needed for Assessments

Elements to Assure Safe Use Assessments:

The elements to assure safe use will be evaluated by the following assessments:

- Assessment of enrollment and discontinuation statistics for prescribers, pharmacies, and patients:
 - The number of patients enrolled in the Versacloz REMS (during the reporting period and cumulative).
 - The number of person-years for enrolled patients.
 - The number of patients who received Versacloz that were not enrolled (during the reporting period and cumulative).
 - The number of patients who stopped receiving Versacloz (during the reporting period and cumulative).
 - The number of prescribers enrolled in Versacloz REMS (during the reporting period and cumulative).
 - The number of pharmacies enrolled in Versacloz REMS (during the reporting period and cumulative).
- Assessment of Versacloz Patient Registry Healthcare Providers Enrollment Forms, Pharmacy/Pharmacist Enrollment Forms, and Patient Registration Forms:
 - Number of incomplete enrollment forms and summary of most frequent missing information
- Summary of annual accuracy audit from Versacloz Registry Protocol including a narrative summary of any corrective action taken
- Assessment of prescribing and dispensing of Versacloz for ineligible patients, including a narrative summary of corrective action taken.
- Assessment of nonregistered prescribers and pharmacists who prescribe or dispense Versacloz, including a narrative summary of corrective action taken.
- Assessment of prescriber and pharmacy compliance including:

- Compliance with submission of WBC count and ANC within the appropriate timeframe depending on patient monitoring frequency (7, 14, 28-days) by assessing WBC count/ANC alerts and whether appropriate follow-up action was taken and by assessing of lab value late list reports and whether appropriate follow-up action was taken
 - Compliance with submission of patient information to the Versacloz REMS after discontinuation of clozapine due to agranulocytosis
 - Compliance with changes in the frequency of monitoring as recommended dependent upon changes in a patients WBC count and ANC values.
- Number of communications with Clozapine National Non-Rechallenge Masterfile (NNRM) including narrative reports of any patient who received Versacloz while listed on the NNRM.
 - Summaries of MedWatch forms submitted to FDA.
 - An assessment of wholesaler's compliance with limiting distribution of Versacloz to registered pharmacies.
 - Summaries of Versacloz quarterly safety meetings including issues discussed at the meeting and actions taken as a result.

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/s/

KIMBERLY LEHRFELD
02/06/2013

REEMA J MEHTA
02/06/2013
Signing on behalf of Claudia Manzo and Mary Willy who concur with the review.

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Drug Evaluation I
Division of Psychiatry Products

NDA/BLA #s: 203479
Products: Versacloz (clozapine) oral suspension 50 mg/mL
APPLICANT: Douglas Pharmaceuticals America Ltd
FROM: Mitchell V. Mathis, M.D., Director (acting), Division of Psychiatry Products
DATE: January 29, 2013

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

Due to an increased risk of agranulocytosis since initial approval of clozapine in 1989, the drug is only available in the U.S. through a restricted distribution program. Under FDAAA, holders of clozapine applications subject to this restricted distribution program are deemed to have in effect an approved REMS. The deemed REMS includes prescriber, pharmacy, and patient enrollment, maintenance of a patient registry and a National Non-Rechallenge Masterfile (NNRM), verification that patients are eligible for treatment by checking the NNRM, and routine reporting of patient laboratory data. FDA has determined that a (b) (4)

[REDACTED]

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for Versacloz (clozapine) oral suspension to ensure that the benefits of the drug outweigh the risks of agranulocytosis. In reaching this determination, we considered the following:

- A. The estimated number of patients in the United States with schizophrenia: The number of patients with schizophrenia in the United States is estimated to be about 3 million.

- B. Schizophrenia is a major psychiatric illness, which if left untreated, results in enormous personal, family, and social disability.
- C. The use of clozapine in patients with treatment-resistant schizophrenia and/or recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder results in better control of symptoms, decreased hospitalizations, and return to more normal function.
- D. The expected or actual duration of treatment with the drug: The expected duration of therapy with Versacloz is indefinite, although the severity of symptoms may vary over time.
- E. The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug: Clozapine has been highly associated with agranulocytosis, an adverse event for which it has a boxed warning. Agranulocytosis may lead to life-threatening infections and death. Agranulocytosis, defined as an ANC of less than 500/mm³, has been estimated to occur in association with clozapine use at a cumulative incidence at 1 year of approximately 1.3%, based on the occurrence of 15 U.S. cases out of 1743 patients exposed to clozapine during its premarketing clinical testing. Approximately 88% of the cases of agranulocytosis occurred during the first 26 weeks of therapy.

A fatality rate of 32% for clozapine-induced agranulocytosis had been reported in association with clozapine use as of December 31, 1989; however, more than half of these deaths occurred before 1977, prior to the recognition of the risk of agranulocytosis and the need for routine blood monitoring. From February 1990 to August 21, 1997, among approximately 150,409 patients treated with Clozaril in the U.S., 585 new cases of agranulocytosis were reported, of which 19 (3.2%) had a fatal outcome, demonstrating the importance and utility of the restricted distribution program.

- F. Versacloz is not a new molecular entity.

The Versacloz REMS reflects the safety information in the current labeling for clozapine products. The REMS is also consistent with the existing, not yet approved, deemed REMS for other clozapine products and contains the necessary elements to mitigate the risk of agranulocytosis associated with the administration of clozapine.

The components of the REMS will be elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. The elements to assure safe use will require prescriber certification; pharmacy certification; documentation of safe use conditions; monitoring requirements; and a patient registry.

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/s/

SHARONJIT K SAGOO
02/05/2013

MITCHELL V Mathis
02/06/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

**Interim Comments on Risk Evaluation and Mitigation Strategy (REMS)
Set # 1**

Date: August 17, 2012

Reviewer: Kimberly Lehrfeld, PharmD, BCPS
Division of Risk Management

Team Leader: Reema Mehta, PharmD, MPH
Division of Risk Management

Division Director: Claudia Manzo, PharmD
Division of Risk Management

Drug Name(s): VersaCloz (clozapine oral suspension)

Therapeutic Class: Atypical Antipsychotic

Dosage and Route: 50 mg / mL oral suspension

Application Type/Number: NDA 203479

Applicant/sponsor: Douglas Pharmaceuticals America LTD

*** This document contains proprietary and confidential information that should not be released to the public. ***

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1 INTRODUCTION

This is an interim review of the proposed Risk Evaluation and Mitigation Strategy (REMS) for VersaCloz[®] (clozapine oral suspension) submitted by Douglas Pharmaceuticals America LTD on 29 December 2011 (Sequence Number 0000).

2 MATERIALS REVIEWED

- Douglas Pharmaceuticals proposed REMS and REMS Supporting Document for VersaCloz (clozapine oral suspension), received December 29, 2011 (Sequence Number 0000)

3 SUMMARY OF APPLICANT'S PROPOSED REMS

BACKGROUND

Clozapine was included on the list of products deemed to have in effect an approved 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 were required to submit a REMS proposal by September 21, 2008. All submissions are under review. Currently, no marketed clozapine product has an approved REMS; therefore, clozapine products are marketed under approved risk minimization action plans (RiskMAPs).

Douglas submitted NDA 203479 for VersaCloz for the management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia. The sponsor's submission included a proposed REMS for VersaCloz. Douglas has entered into a business agreement with Jazz Pharmaceuticals (formerly Azur Pharma) for the clozapine registry. Jazz will manage the registry program for VersaCloz. The proposed REMS submitted by Douglas for VersaCloz is identical to the proposed REMS submitted by Jazz Pharmaceuticals on September 12, 2008 for FazaClo (clozapine orally disintegrating tablet).

COMPONENTS OF PROPOSED REMS

The goal of the sponsor's proposed REMS is to reduce the risk of development of agranulocytosis in patients who are prescribed clozapine oral suspension. The REMS elements proposed by Douglas are as follows:

- (b) (4)
- Elements to Assure Safe Use
 - Healthcare provider (HCP) certification
 - Pharmacy certification
 - Monitoring requirement
 - Patient enrollment in a registry
 - Implementation Plan
 - Timetable for submission of assessments

Elements to assure safe use (ETASU):

The proposal contains the following elements to assure safe use (ETASU):

- *Healthcare Provider certification (ETASU A)*

Requires healthcare practitioners to review the clozapine oral suspension package insert and agree to prescribing and monitoring only according to product labeling and only with a pharmacy/pharmacist enrolled in the clozapine oral suspension registry.

- *Pharmacy certification (ETASU B)*

Requires pharmacies to review the clozapine oral suspension package insert and agree to prescribing and monitoring only according to product labeling and only with a healthcare practitioner enrolled in the clozapine oral suspension registry.

- *Monitoring requirement (ETASU E)*

Healthcare practitioners and pharmacist will be required to work together to monitor patients during clozapine oral suspension treatment. The *WBC Count and ANC Monitoring Form* is used to record all data necessary for patient monitoring, according to the Clozapine Oral Suspension Patient Registry protocol and package insert. Enrolled health care practitioners are responsible for completion of the form. Prior to dispensing, enrolled pharmacists are responsible for reviewing the data on the form for completeness and accuracy, according to the clozapine oral suspension package insert, and for submitting forms to the registry according to specified data submission timelines.

- *Patient enrollment in a registry (ETASU F)*

All patients must be enrolled in the clozapine oral suspension registry. Healthcare practitioners must submit an enrollment form to the registry and receive a patient registration number (PRN) before prescribing or dispensing clozapine oral suspension.

Douglas will verify the patient is not listed on the National Non-rechallenge Masterfile before enrolling a patient and providing a PRN number for an individual

patient or notifying the associated healthcare practitioners that the patient has been enrolled.

Implementation System

The scope of the FazaClo Patient Registry operations has been broadened to include Clozapine Oral Suspension. The FazaClo Patient Registry was developed and implemented prior to market launch of FazaClo in 2004. Procedures have been established and are maintained for regular data auditing of health care professionals who prescribe or dispense Clozapine Oral Suspension. The proposed implementation system describes audits of the following:

- Prescription and dispensation information to assure there are no discrepancies from approved clozapine oral suspension product labeling
- *WBC and ANC Monitoring Forms* audited to assure timeliness of submission
- Patient lab results to assure a corresponding appropriate monitoring interval
- Enrolled healthcare practitioners enrollment forms to assure accuracy
- Wholesalers audited to assure distribution of clozapine only to enrolled pharmacies

Timetable for submission of assessments

Douglas proposes REMS Assessments will be submitted to FDA [REDACTED] (b) (4) following approval of the REMS.

4 RECOMMENDATIONS FOR THE REVIEW DIVISION

We recommend that the following comments on the VersaCloz proposal be sent to the applicant. Please request that the applicant respond to these comments as soon as possible to facilitate further review within the Prescription Drug User Fee Act (PDUFA) deadline for this NDA/BLA submission.

The comments below are based on DRISK's preliminary review of the REMS proposal for VersaCloz. Appended to this review is the VersaCloz REMS proposal and *Patient Registration Form, Healthcare Provider Enrollment Form, Pharmacy Enrollment Form, Single Patient WBC Count and ANC Monitoring Form, and Multiple Patient WBC Count and ANC Monitoring Form* including our track changes of the forms. The applicant should be reminded that the REMS Supporting Document must be consistent with all changes made to the REMS document.

5 COMMENTS FOR THE APPLICANT

1. Please explain how VersaCloz will be [REDACTED] (b) (4).
 - a. Clarify if the REMS for VersaCloz will be unique from the registry for FazaClo, including the name of the VersaCloz REMS registry that will be utilized to make the distinction.

- b. Will Douglas and Jazz be forming a shared system which will enable stakeholders who enroll in one program to be eligible to prescriber, dispense, or receive both VersaCloz and FazaClo?
 - c. Will the patient registration number (PRN) issued for patients being prescribed FazaClo be the same as the PRN issued for patients being prescribed VersaCloz?
 - d. Will the forms approved for the VersaCloz REMS be used by the FazaClo Patient Registry?
2. The REMS document should clearly indicate who has the final responsibility for each activity within the program; in particular, for responsibilities shared by the prescriber and pharmacist. (See the attached REMS document for revisions)

5.1 GOAL

Revise the REMS goal as follows:

To minimize the risk of agranulocytosis associated with the use of VersaCloz by:

- Ensuring compliance with the monitoring schedule for White Blood Cell Count (WBC) and Absolute Neutrophil Count (ANC) prior to dispensing VersaCloz
- Preventing re-exposure of patients who have previously experienced agranulocytosis or severe granulocytopenis/leukopenia with any clozapine products.

5.2 ELEMENT TO ASSURE SAFE USE

The VersaCloz REMS should contain the following elements to assure safe use (ETASU): Prescriber certification, Pharmacy certification, Monitoring requirement, Documentation of safe use conditions and Patient registry. The attached REMS document reflects this. Additional questions and comments about specific elements are below.

Documentation of safe use conditions

1. Clarify the circumstances under which the pharmacist and the prescriber are responsible for verifying the patient registration number (PRN)? Do they verify the PRN only the first time VersaCloz is prescribed or dispensed or every time VersaCloz is prescribed or dispensed?
2. Describe how a prescriber or pharmacist “verifies” a patient registration number (PRN)?

Patient registry

1. Describe the process for how a prescriber or pharmacist enrolls a patient in the following situations. Include how the process is different online, by phone and by faxing paper forms. Clarify if a healthcare professional can register a patient and choose and affiliated healthcare professional without the affiliated healthcare professionals knowledge or acknowledgement?
 - a. If a patient is new to clozapine treatment?

- b. If a patient is being switched from another clozapine formulation to VersaCloz after being on clozapine treatment continuously prior to the switch?
 - c. If a patient has been off clozapine treatment for 180 days or longer?
 - d. If a patient has been off clozapine treatment for less than 180 days?
2. In reference to the following paragraph, what notifications are being referred to in vi. (underlined text)? Explain what is meant by “appropriate data are available to the registry?”

Douglas will, upon receipt of the completed patient registration form:

- i. Review the form for completeness and clarity*
- ii. Verify that the patient is not included in the Clozapine National Non-Rechallenge Masterfile*
- iii. Confirm that the patient’s WBC count and ANC test results which has been obtained within 1 week of the registration date is in accord with the clozapine product label*
- iv. Notify the pharmacist of patient non-rechallenge and registration status and provide a Patient Registration Number (PRN) by mail, telefax, or e-mail*
- v. Separately notify the patient’s health care provider of the patient’s non-rechallenge status and his/her Patient Registration Number by mail, telefax, or e-mail.*
- vi. Provide notification of monitoring schedule when appropriate data are available to the registry.*

5.3 IMPLEMENTATION SYSTEM

1. The implementation section of the submitted REMS contains the following language concerning wholesalers.



5.4 TIMETABLE FOR SUBMISSION OF ASSESSMENTS

Revise the timetable for submission of assessments to include the submission of assessments every 6 months and annually thereafter from the date of the REMS approval. See attached revised REMS.

5.5 GENERAL COMMENTS

Resubmission Requirements and Instructions: Submit the revised proposed REMS for clozapine oral suspension with attached materials and the REMS Supporting Document. Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word documents.

6 REMS SUPPORTING DOCUMENT

The REMS Supporting Document must be consistent with all changes made to the REMS document.

7 ATTACHMENTS

VersaCloz REMS document

Patient Registration Form

Healthcare Provider Enrollment Form

Pharmacy Enrollment Form

Single Patient WBC Count and ANC Monitoring Form

Multiple Patient WBC Count and ANC Monitoring Form

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

/s/

REEMA J MEHTA
08/17/2012
Checking in on behalf of Kimberly Lehrfeld

CLAUDIA B MANZO
08/17/2012
concur