NDA 203479/ S-16

SUPPLEMENT APPROVAL

Tasman Pharma Incorporated
Attention: Heather Luna, MS, RAC
Vice President, Regulatory Affairs
1035 Louis Drive
Warminster, PA 18974

Dear Ms. Luna:

Please refer to your supplemental new drug application (sNDA) dated July 20, 2021, received July 20, 2021, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for NDA 203479 Versacloz (clozapine) oral suspension

This Prior Approval supplemental new drug application provides for proposed modifications to the approved Clozapine Risk Evaluation and Mitigation Strategy (REMS).

We have completed our review of this supplemental application, as amended. It is approved effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for clozapine products of which Versacloz is a member was originally approved on September 15, 2015, and the most recent REMS modification was approved on February 18, 2021. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your proposed modifications to the REMS include changes to the frequency of the submission of patient monitoring via a new Patient Status Form and changes to the pharmacy operations to verify safe use conditions for a REMS dispense authorization. In addition, the third part of the goal has been revised from “ensuring compliance with the monitoring schedule for absolute neutrophil count (ANC) prior to dispensing clozapine” to “ensuring prescribers submit documentation that periodic monitoring of patients is performed to identify severe neutropenia.” You also proposed additional minor changes to the operation of the REMS program, including certain changes to the audit frequency and information dissemination requirements.

Your proposed modified REMS, submitted to Drug Master File (DMF) 030496 on July 16, 2020, amended and appended to this letter, is approved.

To support continued treatment of patients during the 117 calendar day transition period, the current REMS website, call center, operations, and requirements should remain in effect until the modifications detailed in this letter are fully functional.

- Beginning 26 calendar days after the date of this letter, re-enrollment in the modified REMS for prescribers, patients, pharmacies, and wholesalers-distributors opens.
- The modifications to the approved REMS must be fully functional within 117 calendar days of the date of this letter with the following exceptions:
    - The ANC result provided on the modified Patient Enrollment Form will be valid for 147 calendar days from the date of this letter.
    - Previously enrolled patients who have not re-enrolled in the modified REMS, with a current ANC, can be dispensed clozapine for 207 calendar days from the date of this letter.

The REMS uses a shared system for the elements to assure safe use, an implementation system, and a timetable for assessments of the REMS. This shared system, known as the Clozapine REMS, currently includes products listed on the FDA REMS website, available at: https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm .

Other products may be added in the future if additional NDAs or ANDAs are approved.

The timetable for submission of assessments of the REMS must be revised to every 18 months from the date of this letter.

The REMS assessment plan must include, but is not limited to, the following:

Program Outreach and Communication

1. **Clozapine REMS Outreach and Communication (18-month assessment post modification approval only)**

    a. The number of professional societies sent the Pharmacy Professional Society Letter or Healthcare Professional Society Letter by date and by method of distribution
        i. Include which professional societies distributed the letter(s) or the content of the letter(s) to their respective members

    b. The number of Pharmacy Letters (by type of pharmacy), Healthcare Provider Letters and Wholesaler-Distributor Letters sent to each stakeholder, respectively, by date(s) and method(s) of distribution. Provide a list of the documents included with each distribution including the revision date

        i. The number and percentage of emailed letters successfully delivered, opened, and unopened

ii. The number and percentage of mailed letters successfully delivered and returned as undeliverable

iii. The number and percentage of faxed letters successfully delivered and returned as undeliverable

c. Date(s) and names of professional meetings where Clozapine REMS materials were disseminated or displayed

d. Report on any communication activities used to inform stakeholders of the modified Clozapine REMS during the transition period of the REMS modification

Program Implementation and Operations

2. REMS Program Implementation and Operations (18-month assessment post-modification only)

a. Date when the modified Clozapine REMS website went live and was fully operational

b. Date when the REMS Contact Center for the modified Clozapine REMS went live and was fully operational

c. Date(s) when healthcare providers could become certified in the modified Clozapine REMS via online or by fax

d. Date(s) when inpatient and outpatient pharmacies could be certified in the modified Clozapine REMS via online or by fax

e. Date when wholesalers-distributors could be authorized in the modified Clozapine REMS via fax

f. Date(s) when patients can be enrolled in the modified Clozapine REMS via website, fax or the REMS Contact Center

g. Stakeholder Transition

i. For each stakeholder category (prescribers, prescriber designees, inpatient pharmacies, outpatient pharmacies, patients, wholesalers/distributors) report:

a) Number transitioned into the modified Clozapine REMS

b) Number certified or enrolled in the REMS program prior to implementation of the modified Clozapine REMS

3. REMS Certification and Enrollment Statistics (provide the two previous, current and cumulative reporting periods beginning with the post-modification 18-month assessment)

a. Healthcare Providers (number and percent)

i. Healthcare Providers who are newly certified

ii. Active prescribers (i.e. who have prescribed clozapine at least once during the reporting period)

iii. Healthcare providers in incomplete status

a) Include a summary of reasons certification is incomplete

iv. For metrics 3.a.i. through iii, stratify by credentials, (e.g. Doctor of Medicine, Doctor of Osteopathic Medicine, Nurse Practitioner, Physician Assistant, Other) and geographic region (as defined by US Census)

v. A summary of the methods of prescriber certification (e.g. online, fax)

vi. Prescribers who were unable to become certified, accompanied by a summary of the reasons they were unable to be certified

b. Prescriber Designees (number and percent)

i. Newly enrolled

ii. Active (associated with active prescriber)

iii. Prescriber designees in incomplete status

a) Include a summary of reasons certification is incomplete

iv. A summary of the methods of prescriber designee certification (e.g. online, fax)

v. Unable to become certified, accompanied by a summary of the reasons they were unable to be certified

c. Patients (number and percent)

i. Newly enrolled

ii. Active patients (i.e. received at least one dispense/authorization of clozapine during the reporting period)

iii. For metrics 3.c.i. and 3.c.ii, stratify by demographics (age, gender, ethnicity, race and geographic region [as defined by US Census]), benign ethnic neutropenia or hospice patient

iv. Of those newly enrolled, the number of unique patients who:

a) Had a yes response on their enrollment form to, Is this patient actively on clozapine therapy?

v. Patient Treatment Status by Patient Type (general population, BEN patients, hospice patients) for the reporting period and cumulatively:

a) Active

b) Interrupted

c) Discontinued

vi. A summary of the methods of patient enrollment (e.g. via online, fax or REMS Contact Center)

vii. Number of patients who were unable to become enrolled (i.e. incomplete status, cancelled), accompanied by a summary of the reasons they were unable to be enrolled

viii. Beginning with the 18-month assessment report: a nationally estimated number of patients that received a dispensed prescription for clozapine (all dosage forms) from U.S. outpatient retail pharmacies for the reporting period. Provide rationale for discrepancies between this estimate and the number of unique patients enrolled in the clozapine REMS and receiving at least one REMS Dispense Authorization during the reporting period.

d. Pharmacies (number and percent)

i. Newly certified in the modified Clozapine REMS

ii. Active pharmacies (i.e. have dispensed clozapine at least once during the reporting period)

iii. Pharmacies in incomplete status

a) Include a summary of reasons certification is incomplete

iv. For metrics 3.d.i. through 3.d.iii, stratify by pharmacy type (inpatient, outpatient) and by geographic region (as defined by US Census)

v. A summary of the methods of pharmacy enrollment (e.g. via online or fax)

vi. Number of pharmacies that were unable to become certified (i.e. incomplete, cancelled), accompanied by a summary of the reasons they were unable to be enrolled

e. Wholesalers-distributors

i. Newly authorized

ii. Active (have shipped clozapine at least once during the reporting period)

4. Clozapine Utilization Data (provide two previous, current and cumulative reporting periods)

a. Number of prescriptions/transactions authorized for dispensing and those dispensed stratified by

i. Prescriber credentials and geographic region

ii. Pharmacy type (inpatient, outpatient)

iii. Patient demographics (age, gender, ethnicity, race, and geographic region [as defined by US Census])

iv. Identify the source of this information

5. REMS Infrastructure and Performance

a. REMS Program Website (provide two previous, current and cumulative reporting periods)

i. Number of visits and unique visits to the REMS website

ii. Number of REMS materials downloaded or printed for each material

iii. A summary of the Clozapine REMS website utilization

The Important Program Update on the Clozapine REMS Website is used to communicate important program changes to stakeholders. This section on the website will provide frequent updates to stakeholders regarding the

program. A summary of the number of updates communicated in this section of the website will be provided during the assessment reporting period.

b. Contact Center Report: (provide current and cumulative reporting periods)

   i. Number of contacts, inbound and outbound, by stakeholder type (patient/caregiver, healthcare provider, pharmacy, wholesaler/distributors, other)

   ii. A table summarizing the most frequently asked questions (e.g., enrollment question) and by stakeholder type (patient/caregiver, healthcare provider, pharmacy, wholesaler/distributors, other)

   iii. Summary of reason for contacts (examples may include “Enrollment question,” “Lab query,” etc.) by reporter (authorized representative, pharmacy, healthcare provider, patient/caregiver, wholesaler/distributor).

   iv. If the summary reason for the contact(s) indicates a complaint, provide details on the nature of the complaint(s) and whether they indicate potential REMS burden or patient access issues

   v. Reported lack of certified prescribers and/or pharmacies in a patient's local area

   vi. A summary of frequently asked questions (FAQ) by stakeholder type

   vii. Narrative of any corrective actions resulting from issues identified

c. Infrastructure and Performance (provide current and cumulative reporting periods)

   i. Number of times a backup system was used with reasons(s) for each instance (for example, pharmacy level problem, or REMS database problem) clearly defined and described with description of corrective actions taken

   ii. Number of times unintended system interruptions occurred for each reporting period. Describe the number of stakeholders affected, how the issue was resolved, and steps put into place to minimize the impact of future interruptions

6. REMS Compliance (current reporting period)

a. Audits of inpatient and outpatient pharmacies, wholesalers/distributors, and the REMS program Contact Center will be conducted to ensure that all REMS processes and procedures are in place, functioning, and support the REMS

program, and will be submitted with each assessment report. The audit reports are to include:

i. A copy of the audit plan used for the reporting period

ii. A detailed description of audit findings including the number with no findings, minor, moderate, or serious findings; include information about the root cause of any noncompliance

iii. Number of audited sites in each stakeholder category listed directly above

iv. Number of audits expected, and the number of audits performed

v. Number and types of deficiencies noted for each group of audited stakeholders

vi. Summary of corrective actions taken to address findings, the status of the corrective actions, and any resulting preventative actions that were taken

vii. Include a unique ID for each stakeholder that had deviations to track deviations by stakeholder over time

viii. Documentation of completion of training for relevant staff

ix. The existence of documented processes and procedures for complying with the REMS

x. Verification that at each audited stakeholder's site, the designated authorized representative remains the same. If different, include the number of new authorized representatives and verification of the site's recertification

b. For each non-compliance event, provide the source of the report, a description of the event, the cause of the event, if any patient harm resulted, corrective actions taken and any outcome of actions taken. Also provide a summary of non-compliance identified by stakeholder, including but not limited to:

i. For Prescribers, provide: (reported by month for the 18-month assessment only, then per reporting period)
   a) Number of clozapine prescriptions dispensed that were written by non-certified prescribers:

b) Number of unique prescribers that did not submit their patient's ANCs to the REMS program using the *Patient Status Form* on a monthly basis (within 37 calendar days)

c) Number of prescribers that did not submit the patient's ANC results to the REMS program after treatment discontinuation as indicated per the PI

d) Number of healthcare providers that were de-certified and reasons for de-certification. Include if any healthcare providers were re-certified

ii. For Prescriber designees provide:

a) Number of prescriber designees who were non-compliant with the Clozapine REMS requirements

b) Number of prescriber designees that were de-certified and reasons for de-certification

iii. For Patients provide:

a) Number of patients not enrolled in the REMS who were dispensed clozapine

b) Number of patient(s) who received a prescription(s) for clozapine without getting a blood test as ordered by their prescriber and reasons for such if known

iv. For Pharmacies provide:

a) Number and types of pharmacies for which non-compliance with the REMS is detected

b) Number of prescriptions dispensed by noncertified pharmacies stratified by type (inpatient and outpatient) and actions taken to prevent future occurrences (reported or detected through audit)

c) Number of times a clozapine prescription dispensed because a pharmacy bypassed REMS Dispense Authorization; and, if any such events occurred, describe how these events were identified, the root cause of the failure, and any corrective actions taken

d) Number of clozapine prescriptions dispensed to non-enrolled patients and the actions taken to prevent future occurrences

e) Number of times an inpatient pharmacy dispensed more than a 7-days' supply of clozapine to a patient at discharge

f) Inpatient pharmacy dispensing for outpatient use (reported or detected through audit)

g) Number of pharmacies suspended or de-certified by pharmacy type, the reasons for such actions, and actions to address non-compliance

v. For Wholesalers/distributors provide:

a) The number of authorized wholesalers/distributors for which non-compliance with the REMS is detected

b) Number of shipments sent to noncertified pharmacies, source of report, and actions taken to prevent future occurrences (reported or detected through audit)

c) Number of wholesalers/distributors suspended or de-authorized, reasons for such action, and actions to address non-compliance

vi. For REMS Dispense Authorizations (RDA) provide:

a) Number of REMS Dispense Authorizations (RDA) without current lab value submitted on a *Patient Status Form*, provided as

1. Total number of unique patients receiving RDA without current lab (i.e., aggregate)
2. Number of RDAs for each unique patient without current lab; provide mean, median and range of RDAs per patient

b) Number of RDAs without any ANC (excluding hospice patients) on the submitted *Patient Status Form* and number of these resulting in clozapine dispensing

c) Number of RDAs without a *Treatment Rationale* provided when the ANC was unacceptable, and number of these resulting in clozapine dispensing

d) False negatives: e.g., all entities are certified, but system generated a prescription rejection notice

e) False positives: e.g., one or all entities were not certified but system verified dispensing/generated an RDA

c. For each non-patient stakeholder referred to in section 6.b. above (18-month assessment only)

i. Describe any moderate or serious non-compliance with the REMS that occurred during the first year of transitioning to the modified REMS

ii. Provide an assessment of stakeholder compliance in following the proposed transition plan in transitioning to the modified REMS

d. Number of unique patients receiving a clozapine prescription under a *Dispense Rationale* stratified by type of *Dispense Rationale* and the number of prescriptions authorized under a *Dispense Rationale* per patient in a 6-month timeframe

i. Summary of outreach to prescribers

ii. Summary of resulting prescriber certifications (for non-certified prescriber *Dispense Rationale*)

iii. Summary of resulting *Patient Status Form* submissions (for no monthly *Patient Status Form* submitted)

iv. Number of unique patients who have exceeded or attempted more than the allowable *Dispense Rationales*

e. Number of prescriptions dispensed under a *Dispense Rationale* stratified by prescriber, type of pharmacy and type of *Dispense Rationale*

f. For each reporting period, include a copy of the non-compliance plan used during that reporting period

Safe Use Behaviors

7. Report on Patient Status Forms (PSF) (provide two previous, current and cumulative reporting periods

a. Number of PSFs expected, received, outstanding, and not due as of the cut-off date by the number of active patients

b. Number of PSFs not received within 37 calendar days after the date of the last PSF submission

c. Number of unique patients for whom clozapine treatment was interrupted due to lack of PSF submission or late submission of a PSF

i. Of those patients who resumed therapy after late submission of the PSF, what was the time between when the PSF was due and a successful RDA

ii. Of these patients, the number for whom clozapine was discontinued

d. (For the 18-month, 3-year, and 4½ year assessment reports only) The most common modes of submission of PSFs to the REMS (e.g. fax, online)

e. The number of PSFs where the prescriber responded "no" to the question, "Are you monitoring the patient as recommended in the Prescribing Information (PI)?"

   i. Number of unique patients

   ii. Number of unique prescribers

f. The percentage of unique patients who had their ANCs reported on their PSF in accordance with their monitoring schedule, reported by month (exclude those patients who had a treatment rationale, hospice patients, and patients for whom a dispense rationale was obtained or the prescriber did not submit a PSF for that month)

   i. For those patients on a weekly monitoring schedule ANCs reported:
      a) 0
      b) 1
      c) 2
      d) 3
      e) 4 or more

   ii. For those patients on every two weeks monitoring schedule ANCs reported:
      a) 0
      b) 1
      c) 2 or more

   iii. For those patients on every four weeks monitoring schedule ANCs reported:
      a) 0
      b) 1 or more

8. Report on Prescription Rejections

a. Number of prescriptions submitted for authorization stratified by outcome (authorized or rejected) and authorization type (Clozapine REMS Website or Clozapine REMS Contact Center)

b. Mean, median, and range or the duration of time between rejection and subsequent RDA (for the same patient where both occurred in the reporting period), stratified by authorization type (Clozapine REMS Website or Clozapine REMS Contact Center)

c. Provide reasons for all prescription rejections in the reporting period stratified by type of RDA (via Clozapine REMS Website or Clozapine REMS Contact Center)

    i. Provide mean, median, and range or the duration of time between rejection and subsequent RDA (for the same patient where both occurred in the reporting period), stratified by reasons for prescription rejections

9. Report on *Treatment Rationales*

a. Number of Treatment Rationales submitted
    i. Number per unique patient stratified by patient type (general population, BEN, hospice)

b. Mean, median and range of Treatment Rationales submitted per prescriber

10. Report on Notifications and Alerts

a. Number of notifications and alerts sent, stratified by type and stakeholder type (prescriber, pharmacy) and resulting actions by stakeholder (clozapine discontinued, pharmacy became enrolled, etc.)

    i. For overdue *Patient Status Form* and severe neutropenia notifications, provide the number of notifications per unique patient and any actions by stakeholder (clozapine discontinued, clozapine interrupted, Treatment Rationale submitted, etc.) resulting from the notification.

Evaluation of Knowledge

11. Knowledge Assessments (18-month and 3-year assessments post-modification)

a. Number of completed *Clozapine REMS Knowledge Assessment for Prescribers* and *Clozapine REMS Knowledge Assessment for Pharmacies* (KA) for certified prescribers and pharmacy authorized representatives, and pharmacy staff that have elected to take the KA, including method of enrollment and number of attempts to complete, by stakeholder

b. Summary of the most frequently missed KA questions, stratified by prescriber and pharmacy

c. A summary of potential comprehension or perception issues identified with the KA

d. Proposed remediation for *Clozapine and the Risk of Neutropenia: A Guide for Prescribers, Clozapine and the Risk of Neutropenia: A Guide for Pharmacists*, *Clozapine REMS Knowledge Assessment for Prescribers*, or *Clozapine REMS Knowledge Assessment for Pharmacies.*

12. Periodic Surveys of Prescribers, Pharmacists and Patients (beginning with the 3-Year REMS Assessment Report and thereafter with each assessment report)

A Knowledge, Attitude and Behavior (KAB) Survey will be conducted with random samples of prescribers, pharmacists, and patients who have prescribed, dispensed, or received clozapine.

a. An evaluation of knowledge of certified prescribers of the risk of severe neutropenia, appropriate monitoring of clozapine and REMS requirements

b. An evaluation of knowledge of authorized representatives and pharmacists of the risk of severe neutropenia, appropriate monitoring of clozapine and REMS requirements

c. An evaluation of knowledge of patients or caregivers of the risk of severe neutropenia, and the need for appropriate monitoring

Health Outcomes and/or Surrogates of Health Outcomes

13. Safety Surveillance (per previous two reporting periods, current and cumulatively)

a. Total instances of neutropenia for unique patients stratified by patient type (general population, BEN)
   i. Severe: reported as lowest ANC for each unique patient whose ANC drops below 500/μL within each month
   ii. Moderate: reported as lowest ANC for each unique patient whose ANC drops below 1000/μL, but remains at 500/μL or above within each month
   iii. Mild: reported as lowest ANC for each unique patient whose ANC drops below 1500/μL, but remains at 1000/μL or above within each month

b. For each unique patient identified in a.i (severe neutropenia) provide the time to onset from clozapine initiation to date of lab draw for first ANC consistent with severe neutropenia

c. For each unique patient identified in a.i (severe neutropenia), provide the following stratified by general population patients and BEN patients to include the number and percentage of those with severe neutropenia:

i. After clozapine treatment was interrupted for severe neutropenia, report treatment status on the date of the data cutoff for the reporting period
   a) Treatment was discontinued
   b) Received a treatment rationale
   c) Moved to active status
   d) Remained in interrupted status

ii. Had a daily ANC monitored until ≥1,000 µL (general population) or ≥ 500 µL (BEN) as per the PI
   a) Then monitored three times weekly until ANC ≥1,500 µL (general population) or ≥ patient's baseline (BEN) as per the PI

iii. Were rechallenged and outcome of the rechallenge (e.g. treatment discontinued, continued on treatment)

iv. Report the mean, median, maximum and minimum number of treatment status changes for unique patients with severe neutropenia

d. Data from the REMS Patient Registry (REMS Data, Postmarketing Adverse Event Data, REMS Contact Center) of known or suspected adverse events due to clozapine-induced neutropenia (e.g. infection) are to be reported regardless of outcome. Provide an overall analysis and discussion of all cases identified from all sources including but not limited to the following for each case: any associated dates, clozapine dosages, dosage changes and ANC values associated with the adverse event.

i. Include all event and prescribing information obtained from the follow-up questions from the REMS Contact Center for each case identified

ii. Number of *Patient Status Forms* that reported a patient had experienced an adverse event due to clozapine-induced neutropenia:
   a) Number and percentage of unique patients

iii. Number of calls made to the REMS Contact Center reporting any adverse event(s) due to clozapine induced neutropenia (e.g. infection)

iv. Include in the analysis prescriber's adherence to baseline and periodic ANC monitoring as described in the PI for each unique case, by case number, in addition to aggregate results

14. Data Sources for Safety Surveillance:

a. Adverse event reports will be processed according to each Applicant's Standard Operation Procedures and criteria outlined in 21 CFR 314.80 The Applicants will process hematologic adverse drug experiences on clozapine collected by the single shared system as follows:

i. All adverse events (hematologic and non-hematologic) will be considered “solicited” events and reported per 21 CFR 314.80(e). In other words, any adverse event collected by the single shared system that is determined to be serious, unexpected, and related will be reported as a 15-Day Alert Report

ii. Individual Case Safety Reports (ICSRs) will be submitted for both serious and non-serious outcomes for all cases of neutropenia (ANC < 1000/µl) for all patients (general population and BEN) per 21 CFR 314.80

iii. Serious, expected events will be reported within the line listing and SOC tabulations in the product’s periodic report

iv. Non-serious neutropenic events (ANC 1000/µl to 1499/µl) not associated with any other adverse event will not be submitted as an Individual Case Safety Report (ICSR). The Clozapine REMS will retain any lab records that fall between 1000/µL and 1499/µL. All ANCs between 1000/µL and 1499/µL will be reported in the REMS Assessment Reports. FDA may request the ICSRs of ANCs that fall within the specified range above, to be provided within a timeline agreed upon with FDA

b. All serious and non-serious adverse events reported for clozapine outside of the single shared system (e.g., an adverse event reported to the sponsor) will be reported in accordance with 21 CFR 314.80

15. **With respect to each goal included in the strategy**, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified (Section 505-1(g)(3)).

16. **Report on Key Performance Indicator:** The key performance indicator (KPI), or the primary metric that will be used to evaluate the success of the Clozapine REMS, is the percentage of patients who received a dispensed prescription for clozapine during the reporting period that had a benefit/risk analysis conducted by the prescriber prior to authorizing clozapine use. Evidence that the benefit/risk analysis has occurred will be fromthe informationsubmitted on the *Patient Enrollment Form* (initial prescription) or the *Patient Status Form* (ongoing prescriptions)

a. Conduct a quarterly analysis of patients prescribed clozapine in the outpatient setting to assess whether a risk/benefit analysis was conducted by the prescriber authorizing clozapine therapy. The threshold for the KPI is as follows:

i. By the last quarter of the 18-month assessment reporting interval prior to data lock, at least 75% of RDAs (excluding those obtained using a dispense rationale or associated with inpatient clozapine use) will be associated with a prescriber having conducted a risk/benefit analysis

ii. Results of each quarterly analysis are to be included in the assessment report

iii. Include a narrative of any process improvement measures or root cause analyses implemented as a result of these quarterly analyses

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use, as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
c) *If the new, proposed indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.
e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rational to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing a REMS modification*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 203479 REMS ASSESSMENT METHODOLOGY
(insert concise description of content in bold capital letters, e.g., ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 203479 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 203479/S-
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 203479/S-
PRIOR APPROVAL SUPPLEMENT

PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 203479/ S-
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 203479/ S-
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISION FOR NDA 203479

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Ermias Zerislassie, Regulatory Project Manager, at 301-796-2770.

Sincerely,

{See appended electronic signature page}

Marc Stone, M.D.
Deputy Director for Safety
Division of Psychiatry
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):

- REMS

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/s/

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CAROLYN N TIEU on behalf of KATE H OSWELL
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