

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203479Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 203479

SUPPL # 000

HFD # 130

Trade Name Versacloz

Generic Name Clozapine oral suspension, 50 mg/mL

Applicant Name Douglas Pharmaceuticals America LTD

Approval Date, If Known February 6, 2013

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

Douglas' 505(b)(2) NDA application relies on the Agency's previous finding of safety and efficacy of the listed drug Clozaril (clozapine tablets), NDA 19758. This NDA does not contain any clinical studies other than bioequivalence data. As such, no exclusivity request is made in this application.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

YES
Explain:

! NO
! Explain:

Investigation #2

!
!

YES
Explain:

! NO
! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

=====

Name of person completing form: Sharonjit Sagoo, Pharm.D.
Title: Regulatory Project Manager
Date: February 6, 2013

Name of Office/Division Director signing form: CAPT Mitchell V. Mathis, M.D.
Title: Director (acting), DPP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

SHARONJIT K SAGOO
02/06/2013

MITCHELL V Mathis
02/06/2013

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 203479

Supplement Number: 000

NDA Supplement Type (e.g. SE5):
Original

Division Name: Division of
Psychiatry Products

PDUFA Goal Date:
11/06/2012

Stamp Date: 1/6/2012

Proprietary Name: Versacloz

Established/Generic Name: Clozapine oral suspension 50 mg/mL

Dosage Form: Oral suspension

Applicant/Sponsor: Douglas Pharmaceuticals

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

(1) N/A - original NDA

(2) _____

(3) _____

(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1

(Attach a completed Pediatric Page for each indication in current application.)

Indication: Treatment resistant schiznophrenia

1: Is this application in response to a PREA PMR?

Yes Continue

No Please proceed to Question 2.

If Yes, NDA/BLA#: _____

Supplement #: _____

PMR #: _____

Does the division agree that this is a complete response to the PMR?

Yes. Please proceed to Section D.

No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

*** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

Yes. PREA does not apply. **Skip to signature block.**

No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
 - No: Please check all that apply:
 - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
	minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief**

justification):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

] Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications.

Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)Reason(s) for full waiver: **(check, and attach a brief justification for the reason(s) selected)**

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

neck subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):
 Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
	minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan emplate); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

action F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

{Revised: 6/2008}

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 203479	NDA Supplement # 000	If NDA, Efficacy Supplement Type: NA
Proprietary Name: Versacloz Established/Proper Name: Clozapine Dosage Form: Oral suspension		Applicant: Douglas Pharmaceuticals LTD Agent for Applicant (if applicable): VersaPharm Inc.
RPM: Sharonjit Sagoo		Division: HFD-130 / Division of Psychiatry Products
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Clozaril (NDA 19758)</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>This product is a different dosage form (oral suspension).</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input checked="" type="checkbox"/> This application relies on (explain) BE study in rate and extent of absorption to the listed drug product Clozaril (clozapine tablets)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check: 02-06-13</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>February 6, 2013</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None

The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<p><input type="checkbox"/> Received</p>
<p>❖ Application Characteristics³</p> <p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies</p> <p>REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input checked="" type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required</p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<p><input type="checkbox"/> Yes, dates</p>
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>❖ Public communications (<i>approvals only</i>)</p>	
<p>• Office of Executive Programs (OEP) liaison has been notified of action</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>• Press Office notified of action (by OEP)</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>• Indicate what types (if any) of information dissemination are anticipated</p>	<p><input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other</p>

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10- year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input checked="" type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i> 	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>CONTENTS OF ACTION PACKAGE</p>	
<p>❖ Copy of this Action Package Checklist⁴</p>	<p>Included</p>
<p>Officer/Employee List</p>	
<p>❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Documentation of consent/non-consent by officers/employees</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Action Letters</p>	
<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>Action(s) and date(s) AP 02-06-13</p>
<p>Labeling</p>	
<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	<p>02-06-13</p>
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<p>12-29-11</p>
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	<p>N/A</p>

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	02-06-13
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	12-29-11
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	N/A
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	02-06-13
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	06-22-12; Proprietary Name Review 06-25-12; Proprietary Name Denied 09-17-12; Proprietary Name Review 03-23-12; Acknowledge Proprietary Name Withdrawal 02-04-13; Proprietary Name Review
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM 03-12-12 <input checked="" type="checkbox"/> DMEPA 02-01-13; 08-09-12 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 11-01-12 DMPP/PLT 02-06-13 DRISK <input checked="" type="checkbox"/> ODPD (DDMAC) 11-02-13; 10-19-12 <input checked="" type="checkbox"/> SEALD 01-31-13 <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews Nonclinical 10-19-12 PMHS 10-09-12
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	RPM Filing Review 02-15-12
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input type="checkbox"/> Not a (b)(2) 01-23-13; 09-24-12 <input type="checkbox"/> Not a (b)(2) 02/06/13
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>September 5, 2012</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>)	Included
❖ Internal memoranda, telecons, etc.	Included
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • Regulatory Briefing (<i>indicate date of mtg</i>) • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) • EOP2 meeting (<i>indicate date of mtg</i>) • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	<input checked="" type="checkbox"/> No mtg <input checked="" type="checkbox"/> N/A or no mtg <input checked="" type="checkbox"/> No mtg <input checked="" type="checkbox"/> No mtg
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> • Date(s) of Meeting(s) • 48-hour alert or minutes, if available (<i>do not include transcript</i>) 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 02-06-13
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 02-06-13
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 1
Clinical Information⁶	
❖ Clinical Reviews	
<ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) • Clinical review(s) (<i>indicate date for each review</i>) • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	See CDTL Review 02-06-13 01-16-13 <input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See Clinical Review 01-16-13
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable

⁶ Filing reviews should be filed with the discipline reviews.

<ul style="list-style-type: none"> ❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and Supporting Statement <i>(indicate date(s) of submission(s))</i> • REMS Memo(s) and letter(s) <i>(indicate date(s))</i> • Risk management review(s) and recommendations (including those by OSE and CSS) <i>(indicate date of each review and indicate location/date if incorporated into another review)</i> 	02-06-13 02-06-13 REMS Memo <input type="checkbox"/> None 02-06-13; 08-17-12
❖ OSI Clinical Inspection Review Summary(ies) <i>(include copies of OSI letters to investigators)</i>	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Biostatistics <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 08/07/12
❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input type="checkbox"/> None 08/07/12
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
<ul style="list-style-type: none"> • ADP/T Review(s) <i>(indicate date for each review)</i> • Supervisory Review(s) <i>(indicate date for each review)</i> • Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i> 	<input checked="" type="checkbox"/> None <input checked="" type="checkbox"/> None <input type="checkbox"/> None 10/09/12 10/19/12
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested

Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		<input type="checkbox"/> None 09-04-12 Biopharmaceutics Review 08-23-12 Product Quality Review 02-06-12 Product Quality Memo
❖ Microbiology Reviews		
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>		<input type="checkbox"/> Not needed 08-22-12
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		
		<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		08-23-12 Product Quality Review
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		
Facilities Review/Inspection		
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷)</i>		Date completed: 02-06-13 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>		<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per 08-23-12 review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication **AND** a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

Sagoo, Sharonjit

From: Sagoo, Sharonjit
Sent: Tuesday, January 29, 2013 8:20 AM
To: John Franolic
Subject: RE: NDA 203479
Signed By: Sharonjit.Sagoo@fda.hhs.gov

Hi John,

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

Please review and indicate if you agree to conduct this study to the following schedule:

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

Best regards,
Sharon

*Sharonjit Sagoo, Pharm.D.
LT, U.S. Public Health Service
Regulatory Project Manager
Division of Psychiatry Products
Center for Drug Evaluation and Research, FDA
Office of Drug Evaluation 1
Ph: (301) 796-0431
Email: sharonjit.sagoo@fda.hhs.gov*

From: John Franolic [mailto:JFranolic@versapharm.com]
Sent: Monday, October 22, 2012 2:06 PM
To: Sagoo, Sharonjit
Subject: NDA 203479

Hi Sharon-

Can you tell me if we should expect to receive any feedback on our Sept 19, 2012 (Seq 0019) response to DMEPA request letter dated June 20, 2012, prior to our Complete Response letter?

It seems this is the last major issue that remains unresolved (i.e., proposal to conduct the Human Factors Validation Study (b) (4))

Regards
John

John Franolic, Ph.D.
Vice President of Regulatory Affairs
VersaPharm Incorporated
Phone: 770-373-5635
Phone (alternate): 914-269-9415
Fax: 770-373-5655
Email: jfranolic@versapharm.com

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

/s/

SHARONJIT K SAGOO
01/29/2013

Sagoo, Sharonjit

From: Sagoo, Sharonjit
Sent: Monday, January 28, 2013 11:09 AM
To: 'John Franolic'
Subject: NDA 203479 Versacloz - carton and container labeling

Hi John,

Please refer to your NDA 203479 for Versacloz. Also refer to your September 28, 2012 submission providing for revised carton and container labeling. Our recommendations are below:

- A. Container Label
 - 1. Remove the proprietary name and established name from the storage conditions.
 - 2. There is a typographical error in the storage statement that reads: "Do not refrigerator freeze". Revise the statement to read: "Do not refrigerate or freeze".
- B. Carton Labeling
 - 3. See comment A.1 above.
 - 4. Add the following statement to the storage conditions, "Suspension is stable for 100 days after initial bottle opening" and place it below the "Protect from Light" statement.

Please make the changes listed above and submit revised carton and container labeling by COB Wednesday, January 30, 2013.

Feel free to contact me with any questions.

Best regards,
Sharon

*Sharonjit Sagoo, Pharm.D.
LT, U.S. Public Health Service
Regulatory Project Manager
Division of Psychiatry Products
Center for Drug Evaluation and Research, FDA
Office of Drug Evaluation 1
Ph: (301) 796-0431
Email: sharonjit.sagoo@fda.hhs.gov*

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

/s/

SHARONJIT K SAGOO
01/28/2013

Sagoo, Sharonjit

From: Sagoo, Sharonjit
Sent: Friday, November 23, 2012 9:14 AM
To: 'John Franolic'
Subject: RE: NDA 203479
Signed By: Sharonjit.Sagoo@fda.hhs.gov

Hi John,

Please be informed that the Agency asked Pharmaceutical International, Inc. to submit additional information in support of its response to the FDA form 483 by Jan 04, 2013.

Feel free to contact me with any questions.

Best regards,
Sharon

*Sharonjit Sagoo, Pharm.D.
LT, U.S. Public Health Service
Regulatory Project Manager
Division of Psychiatry Products
Center for Drug Evaluation and Research, FDA
Office of Drug Evaluation 1
Ph: (301) 796-0431
Email: sharonjit.sagoo@fda.hhs.gov*

From: John Franolic [mailto:JFranolic@versapharm.com]
Sent: Thursday, November 01, 2012 4:59 PM
To: Sagoo, Sharonjit
Subject: NDA 203479

Hi Sharon-

Douglas Pharmaceuticals America confirms that they wish to go for the "Major Amendment" option, thereby extending the PDUFA date by 3 months.

Please find attached an advance electronic copy of the letter which acknowledges PII's inspections status. I will submit to the NDA tomorrow as a General Correspondence.

Regards
John

John Franolic, Ph.D.
Vice President of Regulatory Affairs
VersaPharm Incorporated
Phone: 770-373-5635
Phone (alternate): 914-269-9415
Fax: 770-373-5655
Email: jfranolic@versapharm.com

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

/s/

SHARONJIT K SAGOO
11/23/2012



NDA 203479

**REVIEW EXTENSION –
MAJOR AMENDMENT**

VersaPharm Inc.
Attention: John Franolic, Ph.D.
Vice President of Regulatory Affairs
1775 West Oak Parkway, Suite 800
Marietta, GA 30062-2260

Dear Dr. Franolic:

Please refer to your January 6, 2012, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Versacloz (clozapine oral suspension) 50 mg/mL.

On November 2, 2012, we received your November 1, 2012, solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is February 6, 2013.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by January 16, 2013.

If you have any questions, contact Sharonjit Sagoo, Regulatory Project Manager, at sharonjit.sagoo@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

THOMAS P LAUGHREN
11/05/2012



NDA 203479

GENERAL ADVICE

VersaPharm Inc.
Attention: John Franolic, Ph.D.
Vice President of Regulatory Affairs
1775 West Oak Parkway, Suite 800
Marietta, GA 30062-2260

Dear Dr. Franolic:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Versacloz, (clozapine oral suspension) 50 mg/mL.

We also refer to your February 6, 2012 submission to your IND 108466, containing the human factors study protocol (ZPS-483 (Version 1)) entitled: "Validation Human Factors Study: "A Study to Evaluate the Dose Dispensing Procedure for (b)(4) (Clozapine) Suspension (Douglas Pharmaceuticals America LTD) Using Patients Stabilized on Clozapine".

We also refer to our June 20, 2012 Information Request letter and your July 16, 2012 submission requesting clarifications, and your September 14, 2012 email response.

The Division of Medication Error Prevention and Analysis has reviewed the referenced material. Our responses and recommendations are below:

1. June 20, 2012 Information Request Comment:

The protocol states that the study will be conducted (b)(4). However, the patient population (b)(4) may not be representative of that in the United States. As such, we cannot assume that the results can be extrapolated to the U.S. population. Therefore, the study should be conducted in the United States.

Applicant Response:

The delays experienced in responding to the 20 June FDA letter (and providing a protocol), are primarily due to finding ways to address this issue (the recommendation to conduct the revised 'Validation Human Factors Study (VHFS)' in the United States and (b)(4)). Since the request was made, we have been attempting to identify a (b)(4)

It is difficult to understand FDA's concern since both (b)(4) and the United States have English as the official language, with a wide range of other languages spoken, similar rates of schizophrenia, and similar education level and poverty statistics (% without a high school qualification: 15% USA¹ v (b)(4), % poverty: 13.8% USA¹ v (b)(4)). The study can be repeated in (b)(4) with a protocol available within (b)(4) and study completion within (b)(4)

(b) (4). Furthermore it would include participant information relating to what appears to be the root cause of the FDA's concerns (and dealt with in FDA issue C.1 – i.e., the gathering and provision of information relating to education level, percent men versus women, etc.). We request FDA to reconsider the recommendation to conduct this repeat VHFS in the US as we do not feel that the data sourced out of (b) (4) would be any less relevant to US product usage than VHFS data sourced within the United States.

Considering the above, would FDA reconsider its recommendation and allow the study to be conducted (b) (4)?

Response to Applicant:

We continue to recommend the study be conducted in the United States. Although there may be similarity in some patient characteristics between the populations of (b) (4) and the US population, differing healthcare systems, cultural influences, and variability in the types of products and devices that patients are exposed to differs between the countries. Therefore, patient behaviors in (b) (4) may not mirror those of patients in the US under similar circumstances.

Applicant Response (cont'd):

Alternatively, after (b) (4) we hope to have the protocol in place by the end of (b) (4). The study would likely complete by the end of (b) (4). FDA's email of 07 Sep appeared to indicate that FDA would forego review of the revised protocol and encourage Douglas to move forward and conduct the study. Please confirm that FDA does not wish to review the revised protocol prior to initiation of the study.

While improvements would have benefitted the (b) (4) VHFS study, it does provide sufficient assurance that patients can effectively dose themselves when dosing is demonstrated to them as per the instructions to pharmacists. In addition the oral suspension is marketed in Australia, New Zealand and the EU without inaccurate dosing being an issue.

Whether the study is conducted (b) (4) or the US, would the FDA accept a proposal to complete the requested study as a post-approval commitment to be reported by an agreed date with FDA?

Response to Applicant:

Given the fact that we are requesting the study be conducted in the US and you have not, as of September 24, 2012 (b) (4) and will not be able to conduct the study before the NDA PDUFA date, we accept the proposal to complete the requested study as a post-approval commitment to be reported by an agreed date by FDA. We previously provided feedback regarding your validation study protocol which should be considered in your revision of your protocol. There is no requirement for you to submit your revised protocol for our review.

2. June 20, 2012 Information Request Comment:

The study protocol states the study participant will (b) (4)

[Redacted]

Applicant Response:

Phase I of the revised study protocol will (b) (4)

[Redacted]

(b) (4)

[Redacted]

(b) (4)

Response to Applicant:

(b) (4)

If you have any questions, contact Sharonjit Sagoo, Regulatory Project Manager, at sharonjit.sagoo@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

THOMAS P LAUGHREN
10/26/2012

Date: October 12, 2012
Time: 1:10 – 1:35 PM
Meeting Type: Requested by Agency
NDA/Drug: 203479/ Versacloz (clozapine) oral suspension
Contents: Teleconference with Douglas to discuss Versacloz REMS.

Participants:

FDA ATTENDEES

Thomas Laughren, M.D.	Division Director, DPP
Mitchell Mathis, M.D.	Deputy Directory, DPP
Robert Levin, M.D.	Clinical Team Leader, DPP
Claudia Manzo, Pharm.D.	Division Director, DRISK
Reema Mehta, Pharm.D., MPH	Team Leader, DRISK
Kim Lehrfeld, Pharm.D., BCPS	Reviewer, DRISK
Jason Bunting, Pharm.D.	Reviewer, DRISK
Jasminder Kumar, Pharm.D.	Pharmacist Intern, DRISK
Sarah Seager Stewart, JD	Attorney, OCC
Nancy Clark Dickinson, Pharm.D.	REMS Lead, ORP
Loretta Holmes, BSN, Pharm.D.	Reviewer, DMEPA
Irene Chan, Pharm.D., BCPS	Team Leader, DMEPA
Kendra Biddick	Consumer Safety Officer, OC
Tracy Salaam, Pharm.D.	Safety Evaluator, OSE/DPVI
Sandra Griffith, Pharm.D.	Regulatory Project Manager, OSE
Victor Crentsil, M.D.	Safety Team Leader, DPP
Terry Harrison, Pharm.D.	Safety Project Manager, DPP
Sharonjit Sagoo, Pharm.D.	Regulatory Project Manager, DPP

SPONSOR ATTENDEES

John Franolic	VP of Regulatory Affairs, VersaPharm
Mike Johnston	Director, Regulatory Affairs, Jazz Pharmaceuticals
Nichole Lepere	Manager, Drug Safety & Pharmacovigilance, Jazz Pharmaceuticals

Background

- In a submission received 01/06/12 Douglas provided a REMS and REMS supporting document for Versacloz.
- Douglas has entered into a business agreement with Jazz Pharmaceuticals 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 09/12/08 for FazaClo (clozapine orally disintegrating tablet).
- The Agency issued an Information Request letter on 08/21/12 with comments per DRISK's 08/17/12 review and requested that Douglas submit the revised proposed REMS for Versacloz with attached materials and the REMS Supporting Document.
- In the sponsor's 09/27/12 response, Douglas stated that, (b) (4)

- The language in the REMS document and associated forms must reflect the elements to assure safe use framework established by FDAAA. The language provided by the Agency attempts to fit the currently-operating registry into that framework.
- The Agency-provided language with respect to the prescriber and pharmacist certification reflects our current approach to articulating prescriber and pharmacist responsibilities under ETASU A and B. Our intent is that the requirements for the stakeholders (Prescribers, Pharmacists, and Patients) remain the same.
- The current VersaCloz attestations are the same for both prescribers and pharmacists. This can lead to confusion among stakeholders and may result in REMS requirements not being complied with. The attestations must be changed in the REMS document and on the enrollment forms in order for the REMS to be approved.

Discussion

- The Agency explained its rationale and regulatory policy regarding the current standard for the REMS and associated forms. The Agency stated that the proposed changes are not operationally changing the REMS. These changes are a legal necessity.
- Douglas expressed that implementing the requested changes would introduce variables that are not in place for all clozapine sponsors and they proposed using the existing REMS and elements (b) (4).
- The Agency stated that the (b) (4).
- In discussion regarding the Patient Enrollment Form, the Agency stated that we are willing to concede that the Patient Enrollment Form does not need to include a patient signature or patient privacy language. The Agency reminded Douglas that they must be in compliance with HIPAA regulations and protect patient health information.
- Douglas raised concern regarding variance in enrollment forms and potential confusion that this may place on prescribers. The Agency stated that current registries have different forms that variance in their forms should not present an issue for prescribers.
- The Agency reiterated that the REMS is a legally binding document and that it is necessary to dictate specific responsibilities. The currently proposed forms have the same responsibilities for prescribers and pharmacists, which may lead to confusion and difficulty for Douglas in monitoring compliance.
- Douglas agreed with making the Agency's proposed changes, using the documents attached to the 08/21/12 Information Request letter as a base. Douglas was reminded to provide their submission as soon as possible in order to facilitate review of their application.

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

/s/

SHARONJIT K SAGOO
10/16/2012



NDA 203479

INFORMATION REQUEST

VersaPharm Inc.
Attention: John Franolic, Ph.D.
Vice President of Regulatory Affairs
1775 West Oak Parkway, Suite 800
Marietta, GA 30062-2260

Dear Dr. Franolic:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VersaCloz, (Clozapine oral suspension) 50 mg/mL.

We also refer to your submission dated December 29, 2011 and received January 6, 2012, containing the Risk Evaluation and Mitigation Strategy (REMS) and REMS Supporting Document for VersaCloz.

The Division of Risk Management has completed their preliminary review of your REMS proposal and has the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

A) General Comments

1. Please explain how VersaCloz will be [REDACTED] (b) (4)
[REDACTED].
 - 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)

B) 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.

C) 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.*

D) Implementation System

1. The implementation section of the submitted REMS contains the following language concerning (b) (4).



E) 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.

F) 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.

G) REMS Supporting Document

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

If you have any questions, contact Sharonjit Sagoo, Regulatory Project Manager, at sharonjit.sagoo@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures:

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

17 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

THOMAS P LAUGHREN
08/21/2012



NDA 203479

INFORMATION REQUEST

VersaPharm Inc.
Attention: John Franolic, Ph.D.
Vice President of Regulatory Affairs
1775 West Oak Parkway, Suite 800
Marietta, GA 30062-2260

Dear Dr. Franolic:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VersaCloz, (Clozapine oral suspension) 50 mg/mL.

We also refer to your March 23, 2012 submission containing the Container Label and Carton Labeling; and your May 4, 2012 submission containing Insert Labeling and Instructions for Use.

The Division of Medication Error Prevention and Analysis has completed their evaluation of these submissions and we have the following comments and requests:

A. General Comments for Container Label and Carton Labeling

1. Since VersaCloz is not a name that has been involved in drug name confusion or wrong drug errors, the capitalization of the letter "C" is inappropriately applied. Ensure the proprietary name, Versacloz, is presented without a capital "C".
2. The dosage form statement ("oral suspension") lacks prominence due to its small size and (b) (4) color which is difficult to see against the white background. The font for the dosage form statement should match the font used for the active ingredient statement (clozapine, USP) in size, typography, and color.
3. The statement of strength lacks prominence due to its small size and thin white font against the blue background. Increase the size of the statement of strength and use a heavier font weight.
4. The (b) (4) graphic above the proprietary name is distracting. Delete the graphic to minimize clutter and allow additional room for more important information on the principal display panel (PDP).
5. The net quantity statement is too prominent due to its size. Decrease the size of the net quantity statement and debold the font.
6. Add the statement "For Oral Administration Only" to the principal display panel (PDP). Postmarketing experience has demonstrated that wrong route of administration errors have occurred in the clinical setting when oral liquid products have been inadvertently administered as injections.

7. Under “*How should I store VERSACLOZ?*” in the Patient Instructions for Use, the statement “Do not refrigerate or freeze” is present. This statement is not on the container label, carton labeling, or in the Prescribing Information. Ensure the storage conditions statements are consistent throughout all of the labels and labeling.

B. Container Label

1. The statement “Each mL contains 50 mg of clozapine” and the storage conditions are on the principal display panel (PDP). Relocate these statements to one of the side panels since they are not necessary on the PDP and add clutter to the PDP as well.
2. The statement “The prescribed amount of suspension should be drawn from the bottle using the oral dispenser provided” is located under the dispensing instructions to the pharmacist. However, this statement should be prominent for patients. Move the statement to the principal display panel. Additionally, we recommend revising the term “oral dispenser” to read “oral syringe”.
3. According to data that you submitted to the Agency, the product should be shaken for at least 10 seconds in order to ensure a (b) (4) suspension. Therefore, revise the statement “Shake Well Before Use” to read: “Shake Well for 10 Seconds Before Use”. Additionally, change from upper case to title case lettering for improved readability. To retain prominence, maintain the bold font or consider the use of color or some other means.

C. Carton Labeling

1. The statement “Each mL contains 50 mg of clozapine” is on the principal display panel (PDP). Delete it from the PDP since it is redundant and it adds clutter to the PDP.
2. The list of carton contents is not optimally worded for clarity. Revise to read as follows:

This Carton Contains:

One 1 mL oral syringe

One 9 mL oral syringe

One bottle adaptor

This recommendation may change based on the final packaging presentation for this product.

3. Revise the statement “Shake well before use” to read “Shake Well For 10 Seconds Before Use” and relocate the statement to the PDP. Additionally, change from upper case to title case lettering for improved readability. To retain prominence, maintain the bold font or consider the use of color or some other means.
4. Currently, the section “Dispensing Instructions—Attention Pharmacists:” precedes and is attached to the approved Patient Labeling (Patient Information and Patient Instructions for Use). The pharmacist is required to tear off this section of the labeling prior to giving the Patient Information and Instructions for Use to the patient. Having the dispensing instructions for the pharmacist inside the package is error-prone because pharmacists may

not always look in the carton to find the dispensing instructions or be aware that these instructions are inside the package. Since these instructions are more detailed, replace the existing dispensing instructions on the carton with those that are attached to the Patient Labeling.

Additionally, pharmacists may be required to dispense partial bottles. Therefore, the packaged bottle of oral suspension, oral syringes, bottle adapter, and FDA approved patient labeling may not be available to dispense to all patients. Provide information on the carton labeling that instructs pharmacists on what to do in this situation. In order to accommodate this additional information, consider moving storage information and other statements from the back panel to the side panel(s). Additionally, consider removing redundant statements.

If you have further questions or need clarifications, please contact Sandra Griffith, Project Manager, at 301-796-2445.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

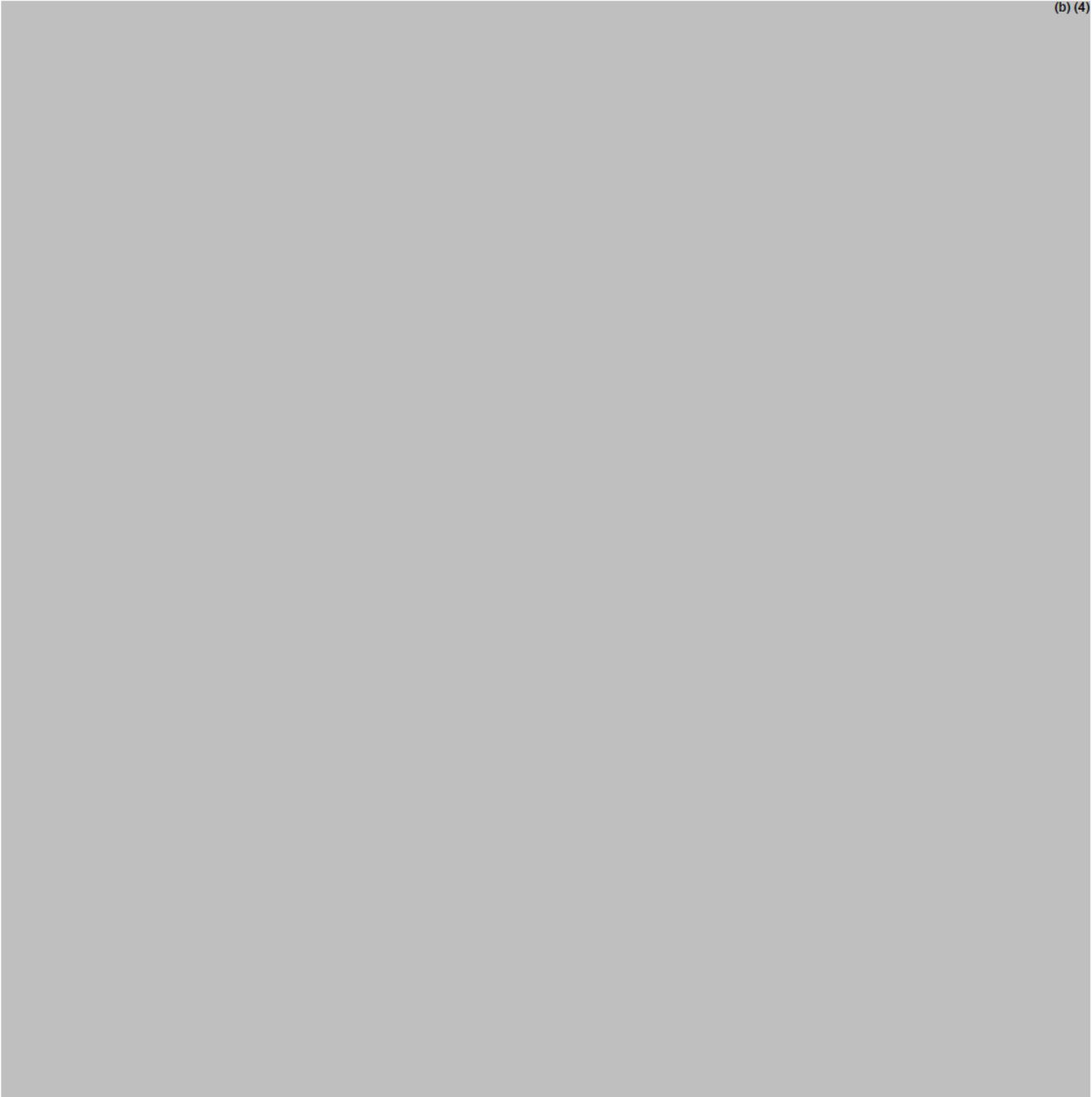
THOMAS P LAUGHREN
08/16/2012

Sagoo, Sharonjit

From: Sagoo, Sharonjit
Sent: Thursday, July 26, 2012 2:33 PM
To: 'John Franolic'
Subject: NDA 203479 VersaCloz - Responses to 7/16/12 submission

Hello Dr. Franolic,

Reference is made to your NDA 203479 for VersaCloz (clozapine oral suspension) and your July 16, 2012 submission requesting clarifications prior to responding to the Agency's June 20, 2012 Information Request. Our responses are below:



(b) (4)

Please contact me if there are any further questions.

Best regards,
Sharon

*Sharonjit Sagoo, Pharm.D.
LT, U.S. Public Health Service
Regulatory Project Manager
Division of Psychiatry Products
Center for Drug Evaluation and Research, FDA
Office of Drug Evaluation 1
Ph: (301) 796-0431
Email: sharonjit.sagoo@fda.hhs.gov*

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

/s/

SHARONJIT K SAGOO
07/26/2012

Sagoo, Sharonjit

From: Sagoo, Sharonjit
Sent: Thursday, June 21, 2012 9:13 AM
To: 'John Franolic'
Subject: RE: NDA 203479 - Questions
Attachments: 6-19-12 DMEPA_Information Request.pdf

Hi John,

1. The Division of Medication Error Prevention and Analysis has reviewed the human factors study protocol. The review team has concluded that the proposed study protocol is inadequate and you are required to submit a revised protocol. Please reference the attached letter for our comments.

2. Per 21 CFR 314.50(d)(5)(vi)(b), the applicant shall, under section 505(i) of the act, update its pending application with new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling 4 months after the initial submission. The CFR - Code of Federal Regulations Title 21 can be found in the FDA website <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm>.

If there are no further safety updates, simply state so in the Safety Update submission.

Please contact me if there are any questions.

Best regards,
Sharon

*Sharonjit Sagoo, Pharm.D.
LT, U.S. Public Health Service
Regulatory Project Manager
Division of Psychiatry Products
Center for Drug Evaluation and Research, FDA
Office of Drug Evaluation 1
Ph: (301) 796-0431
Email: sharonjit.sagoo@fda.hhs.gov*

From: John Franolic [mailto:JFranolic@versapharm.com]
Sent: Tuesday, June 19, 2012 2:39 PM
To: Sagoo, Sharonjit
Subject: NDA 203479 - Questions

Hi Sharon-

I had a couple of questions regarding our NDA 203479/IND 108466 for Clozapine Oral Suspension.

1. **Validation Human Factors Study:** On Feb 6, 2012 we submitted an IND Amendment (Seq 0005) with a

request for FDA to evaluate our protocol for the repeat of the Validation Human Factors study. We have not yet received feedback from the Agency. We were planning on starting this study in late [REDACTED] (b) (4)

[REDACTED] Will the Agency provide feedback on this protocol in the near future?

2. **Safety Update:** The original NDA submission dated Dec 28, 2011 (Module 1.11) contained a safety update of literature reference to Clozapine through Sept 30, 2011, and AERS database summary through March 31, 2011 (as per available data at the time). Do we need to provide further safety updates to the NDA at this time or sometime prior to our PDUFA date?

Regards,
John

John Franolic, Ph.D.
Vice President of Regulatory Affairs
VersaPharm Incorporated
Phone: 770-373-5635
Phone (alternate): 914-269-9415
Fax: 770-373-5655
Email: jfranolic@versapharm.com

This message and any attachment is for the addressee only. This e-mail may contain confidential or legally privileged information that is intended only for the individual or entity named as the recipient. If you are not the intended recipient, you are hereby notified that any disclosure, copying, distribution, or reliance upon the contents of this e-mail is strictly prohibited. If you have received this e-mail in error, please contact the sender, so that VersaPharm Incorporated can arrange for proper delivery, and then please delete this message. Thank you.



NDA 203479

INFORMATION REQUEST

VersaPharm Inc.
Attention: John Franolic, Ph.D.
Vice President of Regulatory Affairs
1775 West Oak Parkway, Suite 800
Marietta, GA 30062-2260

Dear Dr. Franolic:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VersaCloz, (Clozapine oral suspension) 50 mg/mL.

We also refer to your February 6, 2012 submission to your IND 108466, containing the human factors study protocol (ZPS-483 (Version 1)) entitled: "Validation Human Factors Study: "A Study to Evaluate the Dose Dispensing Procedure for (b) (4) (Clozapine) Suspension (Douglas Pharmaceuticals America LTD) Using Patients Stabilized on Clozapine".

The Division of Medication Error Prevention and Analysis has reviewed the human factors study protocol. The review team has concluded that the proposed study protocol is not adequate to validate the usability of the dispensing syringes and Instructions for Use (IFU) for clozapine oral suspension. You are required to submit a revised protocol based on our comments. We must reach agreement on the final protocol prior to implementation of the study.

We have the following comments and requests:



(b) (4)



B. Overall Study Design

(b) (4)



(b) (4)



C. Study Participants

(b) (4)



(b) (4)



D. Recommendation for Overall Study Design

(b) (4)



E. Data Collection

(b) (4)



F. Data Analysis

(b) (4)

G. Instructions for Use (IFU)

1. The Agency provided recommendations regarding revisions to the patient Instructions for Use (IFU) on March 2, 2012. These recommendations along with any others provided since that time regarding the IFU should be implemented prior to the IFU being used in the validation human factors study. All written materials (e.g., scripts, instructions, questionnaires, etc.) should be included in the revised protocol.
2. Some of the Figures show sweeping semicircular marks that appear to be intended to show direction (e.g., Figures A, G, and K), however, these marks are confusing and do not clearly indicate the action the patient should take. Use arrows or other graphics to better illustrate intended direction or actions.
3. The first figure showing contents of the package and Figure D should be enlarged to clearly show the details of the oral syringes including graduation marks. As currently presented, the graduation marks cannot be easily read in the applicable figures. The pictures of the oral syringes should accurately reflect the actual syringes that will be packaged in the carton.
4. Step 4 in the Instructions for Use (IFU) states that if the dose is lower than 50 mg (1 mL) then the 1 mL syringe should be used; if the dose is greater than 50 mg (1 mL) the larger 9 mL syringe should be used. However, the instructions do not state which syringe should be used if the dose is 50 mg (1 mL). The Instructions for Use should state which syringe should be used to measure a 50 mg (1 mL) dose, and this should be tested in the study in order to determine the ability of study participants to select the correct syringe when a 50 mg (1 mL) dose is prescribed.
5. Step 12 in the Instructions For Use (IFU) states:

(b) (4)

The patient should be instructed to push the liquid medicine into either side of their mouth and to swallow slowly to avoid aspiration. Figure L shows that but the written instruction in Step 12 does not say that.

Please revise Step 12 to say:

“Put the open tip of the syringe into either side of your mouth. Close your lips around the syringe as tightly as you can (see Figure L). Push on the plunger so the liquid slowly goes into your mouth. Swallow the medicine slowly as it goes into your mouth.”

If you have any questions, call Sharonjit Sagoo, Regulatory Project Manager, at (301) 796-0431.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

THOMAS P LAUGHREN
06/20/2012

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

/s/

SHARONJIT K SAGOO
06/21/2012



NDA 203479

INFORMATION REQUEST

VersaPharm Inc.
Attention: John Franolic, Ph.D.
Vice President of Regulatory Affairs
1775 West Oak Parkway, Suite 800
Marietta, GA 30062-2260

Dear Dr. Franolic:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VersaCloz, (Clozapine oral suspension) 50 mg/mL.

We also refer to your February 6, 2012 submission to your IND 108466, containing the human factors study protocol (ZPS-483 (Version 1)) entitled: "Validation Human Factors Study: "A Study to Evaluate the Dose Dispensing Procedure for (b) (4) (Clozapine) Suspension (Douglas Pharmaceuticals America LTD) Using Patients Stabilized on Clozapine".

The Division of Medication Error Prevention and Analysis has reviewed the human factors study protocol. The review team has concluded that the proposed study protocol is not adequate to validate the usability of the dispensing syringes and Instructions for Use (IFU) for clozapine oral suspension. You are required to submit a revised protocol based on our comments. We must reach agreement on the final protocol prior to implementation of the study.

We have the following comments and requests:

A. Study Products (Materials)



(b) (4)



B. Overall Study Design

(b) (4)



(b) (4)



C. Study Participants

(b) (4)



(b) (4)

A large rectangular area of the page is completely redacted with a solid grey fill.

D. Recommendation for Overall Study Design

(b) (4)

A large rectangular area of the page is completely redacted with a solid grey fill.

E. Data Collection

(b) (4)

A large rectangular area of the page is completely redacted with a solid grey fill.

F. Data Analysis

(b) (4)



G. Instructions for Use (IFU)

1. The Agency provided recommendations regarding revisions to the patient Instructions for Use (IFU) on March 2, 2012. These recommendations along with any others provided since that time regarding the IFU should be implemented prior to the IFU being used in the validation human factors study. All written materials (e.g., scripts, instructions, questionnaires, etc.) should be included in the revised protocol.
2. Some of the Figures show sweeping semicircular marks that appear to be intended to show direction (e.g., Figures A, G, and K), however, these marks are confusing and do not clearly indicate the action the patient should take. Use arrows or other graphics to better illustrate intended direction or actions.
3. The first figure showing contents of the package and Figure D should be enlarged to clearly show the details of the oral syringes including graduation marks. As currently presented, the graduation marks cannot be easily read in the applicable figures. The pictures of the oral syringes should accurately reflect the actual syringes that will be packaged in the carton.
4. Step 4 in the Instructions for Use (IFU) states that if the dose is lower than 50 mg (1 mL) then the 1 mL syringe should be used; if the dose is greater than 50 mg (1 mL) the larger 9 mL syringe should be used. However, the instructions do not state which syringe should be used if the dose is 50 mg (1 mL). The Instructions for Use should state which syringe should be used to measure a 50 mg (1 mL) dose, and this should be tested in the study in order to determine the ability of study participants to select the correct syringe when a 50 mg (1 mL) dose is prescribed.
5. Step 12 in the Instructions For Use (IFU) states:

(b) (4)



The patient should be instructed to push the liquid medicine into either side of their mouth and to swallow slowly to avoid aspiration. Figure L shows that but the written instruction in Step 12 does not say that.

Please revise Step 12 to say:

“Put the open tip of the syringe into either side of your mouth. Close your lips around the syringe as tightly as you can (see Figure L). Push on the plunger so the liquid slowly goes into your mouth. Swallow the medicine slowly as it goes into your mouth.”

If you have any questions, call Sharonjit Sagoo, Regulatory Project Manager, at (301) 796-0431.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

THOMAS P LAUGHREN
06/20/2012