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APPLICATION NUMBER:

203479Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number	203-479
Priority or Standard	Standard
Related IND	108466
Submission Date	29 Dec 2011
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PDUFA Goal Date	06 February 2013
Division/Office	CDER/DPP
Reviewer Name	Mark Ritter, MD
Review Completion Date	16 January 2013
Established Name	Clozapine oral suspension
Trade Name	VersaCloz
Therapeutic Class	Antipsychotic
Applicant	Douglas Pharmaceuticals
Formulation	Oral Suspension
Dosing Regimen	Initial dosing: 12.5mg once/twice daily with weekly increases of 25-100mg/week up to maximum dose of 900mg/day depending upon efficacy and safety/tolerability.
Indications	1. Treatment-Resistant Schizophrenia 2. Recurrent Suicidal Behavior in Patients with Schizophrenia or Schizoaffective Disorder
Intended Population	Patients with Schizophrenia or Schizoaffective Disorder

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1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT

1.1 Recommendation on Regulatory Action

This reviewer recommends that the Agency APPROVE this NDA application. In lieu of the company's failure to conduct a usability study that was recommended by the Division of Medication Error Prevention and Analysis (DMEPA), I recommend that the sponsor submit 15-day expedited safety reports to the Agency for cases of unintentional overdosage and underdosage of the suspension and other medication errors associated with suspension packaging and oral syringe use.

1.2 Risk Benefit Assessment

The active medication, clozapine, has been marketed in the United States since 1989. A risk of neutropenia and agranulocytosis is associated with clozapine use. Labeling for this 505 (b)(2) application will include identical boxed warnings and identical language from the Warnings and Precautions section of the label from Clozaril NDA 19-758.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The sponsor has accepted the FDA-proposed Versacloz Risk Evaluation and Mitigation Strategy (REMS). The Agency has requested that Douglas Pharmaceuticals participate in the development of (b) (4)

1.4 Recommendations for Postmarketing Requirements and Commitments

The Agency will require the sponsor to conduct a Validation Human Factors Study as a postmarketing commitment. The study must assess the usability of the oral syringe, bottle, and bottle adaptor that are components of the marketed kit. We will continue to work with the sponsor on the design of the human factors protocol.

2 INTRODUCTION AND REGULATORY BACKGROUND

2.1 Product Information

Versacloz is a suspension form of the medication clozapine for oral administration. The strength of the suspension will be 50mg/ml.

The sponsor has developed and marketed a European Union formulation of clozapine oral suspension for the European and Australasian markets since 2003. In 2006 the New Zealand product was found to be bioequivalent to a European innovator product. Currently the New Zealand formulation is approved in New Zealand and Australia as Clopine, as well as in the United Kingdom, Ireland and Germany under different names.

Because of differences in EU/Australasian formulation of Clozaril and the U.S formulation of Clozaril, the sponsor has re-formulated the suspension to be bioequivalent to U.S. Clozaril 100mg tablets.

2.2 Tables of Currently Available Treatments for Proposed Indications

Clozapine is currently available in the U.S. as tablets and orally-disintegrating tablets. Currently clozapine is approved in the United States for the treatment of: 1) Treatment-Resistant Schizophrenia; and 2) Recurrent Suicidal Behavior in Patients with Schizophrenia or Schizoaffective Disorder

2.3 Availability of Proposed Active Ingredients in the United States

Clozapine was first marketed as Clozaril (NDA 19758) and approved for sale in the U.S. on 26 September 1989.

Since approval, clozapine has been approved in generic form under the following ANDAs:

- ANDA 75713- Sponsor Caraco Pharmaceuticals; approved 15 Nov 2002
- ANDA 74949- Sponsor Teva Pharmaceuticals; approved 26 Nov 1996
- ANDA 76809- Sponsor Teva Pharmaceuticals; approved 16 Dec 2005
- ANDA 75417- Sponsor Mylan Pharmaceuticals; approved 27 May 1999

In addition, an orally disintegrating form of clozapine has been marketed under the brand name Fazaclon NDA 21590 by Jazz Pharmaceuticals and approved for sale in the U.S. on 10 Feb 2004.

2.4 Important Safety Issues With Consideration to Related Drugs

Antipsychotic administration has been associated with increased mortality in patients with dementia-related psychosis. Currently all antipsychotic medications carry a boxed warning for this association.

Metabolic changes, such as hyperglycemia, development of diabetes mellitus, dyslipidemia and weight gain, are associated with antipsychotic medication use and thus all currently approved antipsychotics carry a warning regarding the association between antipsychotic use and metabolic changes that may increase cardiovascular/cerebrovascular risk.

In addition, antipsychotic medications carry a labeled warning for the potential appearance of neuroleptic malignant syndrome (NMS)

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The sponsor submitted a pre-IND meeting request for IND 108,466 on 19 April 2010 with background materials submitted 25 May 2010. The purpose of this meeting was to gain Agency guidance on 505 b(2) development of an oral suspension formulation of clozapine (currently marketed in Australasia) to treatment refractory schizophrenic patients that have difficulty swallowing medications or “cheek” medications.

The Agency provided preliminary comments to the sponsor before the type-B meeting on 29 June 2010. We requested that the sponsor conduct a food effect study as part of the bioequivalence study. However the sponsor challenged the requirement, stating that for the recently approved orally disintegrating tablet, the sponsor was not required to conduct a food effect study. We requested that the sponsor submit a scientific justification for not conducting a food effect study.

It was further agreed to by both the Agency and sponsor that no additional clinical or non-clinical safety data was required from the sponsor to support a 505 b(2) NDA applications other than a detail safety summary of the RLD NDA 19-758, one year literature and AERS database searches followed by periodic safety updates.

With regard to the patient registry, the sponsor had entered into a co-marketing agreement with another sponsor of an FDA-approved clozapine product to utilize an existing Patient Registry program to monitor for agranulocytosis, to which the Agency gave approval for.

The Agency had no objections to the packaging and dosing devices proposed in the internal meeting. The sponsor stated that the container closure, adaptor, and dosing syringes were to be identical to the approved European product. However, the Division of Medication Error Prevention and Analysis (DMEPA) provided post-meeting feedback to the sponsor with regard to packaging issues and development of an oral syringe for use with the oral suspension product. In addition, DMEPA recommended that the sponsor conduct a usability study to ensure that patients can easily understand and accurately use the syringe that will accompany the product.

Finally, the Agency stated that we would likely require that the sponsor provide a MedGuide to insure safe and accurate dosing of the product.

2.6 Other Relevant Background Information

The bioequivalence study ZPS-411 was conducted at two facilities in New Zealand:

Dunedin Facility

Clinical Site: 3rd Floor Radio Otago House
248 Cumberland Street
Dunedin, New Zealand

Waikato Facility

Clinical Site:

Puna-A-Tane, Puna Maatai, Puawai
Regional Forensics Psychiatric Service
Henry Bennett Centre
Waikato Hospital
Selwyn Street
Hamilton, New Zealand

Te Whare Taurima
Waikato Hospital
Selwyn Street
Hamilton, New Zealand

3 ETHICS AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Integrity

An investigation by the Division of Scientific Investigations was performed by Arindam Dasgupta, PhD. on 27 July 2012. An inspection of the clinical and analytical portions of the bioequivalence study was conducted. Although some deficiencies were noted during the inspection, it was the reviewer's opinion that the clinical and analytical data generated for the bioequivalence study was not affected by the cited deficiencies.

3.2 Compliance with Good Clinical Practices

Study ZPS-411 was conducted according to the Declaration of Helsinki and amendments and 21 CFR parts 50 and 56. All subject information was documented and stored using Good Clinical Practices (GCP) as delineated in the Health Insurance Portability and Accountability Act (HIPAA) of 1997.

3.3 Financial Disclosures

Financial disclosures were collected for all investigators and sub-investigators named in all the clinical studies.

The Clinical Investigator for ZPS-411 was Dr N A Hung. Trial physicians include DrS^(b)₍₄₎

4 SIGNIFICANT ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry Manufacturing and Controls

On 27 August 2012, a review of this NDA was conducted by Dr. Lakhani of the Office of New Drug Quality and Assessment (ONDQA). Several communications regarding paddle speeds and proposed dissolution methods were transmitted between the Agency

and Sponsor during the NDA review cycle. After consensus was obtained, a final test of the batches passed the requisite tests.

The application was deemed as acceptable based on the dissolution method used and within accepted criteria.

Dr. Thomas Wong from ONDQA completed his initial review of the NDA on August 23, 2012. At that time, he could not support approval, because the Office of Compliance had not issued a final recommendation regarding the cGMP inspections.

On 2 Nov 2012, Linda Ng, Ph.D., Senior Policy Advisor of the New Drug Manufacturing Assessment Branch, Division of Good Manufacturing Practice Assessment, concurred with the Baltimore District Office's recommendation of Withhold. The District Office issued an FDA Form 483 to Pharmaceuticals International, Inc. in White Marsh, MD for various violations of Good Manufacturing Practices (GMP). There were deficiencies for multiple products, including Versacloz.

The sponsor was granted a major amendment extension on 5 Nov 2012 after the sponsor submitted a request for a major amendment on 2 Nov 2012. The PDUFA goal date was then extended for three months while the manufacturing facility corrects the issues identified on the FDA form 483.

4.2 Clinical Microbiology

Not applicable for this submission.

4.3 Preclinical Pharmacology/Toxicology

Elzbieta Chalecka-Franaszek, Ph.D. completed a review of the NDA on 9 Oct 2012. No additional nonclinical safety data was required for this NDA as indicated in the IND 108466 meeting minutes dated 20 July 2010. Hence the submitted NDA did not submit any new preclinical studies but referenced pre-clinical studies under the 505(b)(2) regulatory pathway. After review of the NDA, there were no objections to approve NDA 203479 from a pharmacology/toxicology perspective.

4.4 Clinical Pharmacology

Andre Jackson, Ph.D. from the Office of Clinical Pharmacology reviewed the NDA and deemed the NDA acceptable on 7 August 2012. The 50mg/ml clozapine suspension was found to be bioequivalent to the 100mg Clozaril tablet at steady state under fasting and fed conditions.

4.4.1 Mechanism of Action

The mechanism of antipsychotic action of clozapine is not well understood. However clozapine is an atypical antipsychotic that binds with high affinity to dopaminergic receptors as an antagonist. Excessive dopamine levels in the brain has been consistently been shown to correlate with positive symptomatology in patients with schizophrenia.

4.4.2 Pharmacodynamics

Clozapine is a D1, D2, D3 and D4 receptor antagonist preferentially at striatal dopamine receptors. In addition, clozapine is noted to be an antagonist at adrenergic, cholinergic, histaminergic and serotonergic receptors. Some of clozapine’s adverse reactions are related to these other antagonist properties of the drug.

4.4.3 Pharmacokinetics

The sponsor has referenced the distribution, metabolism and excretion data from the reference listed product. In summary, the mean half-life after a single dose of 75mg was 8 hours (range 4-12 hours). Clozapine is almost completely metabolized prior to excretion with 50% excreted in urine and 30% in feces. The desmethyl metabolite (norclozapine) has only limited pharmacological activity.

Clozapine is highly protein bound (97%). Although an interaction between clozapine and other highly protein bound drugs has not been fully evaluated, it is theoretically possible.

5 SOURCES OF CLINICAL DATA

Data used to support efficacy for this 505 b-2 application consisted of one bioequivalence study and a usability study.

5.1 Tables of Clinical Studies

Table 1: Versacloz Table of Studies

Phase 1 Bioequivalence Study	
ZPS-411	A two-week, outpatient-inpatient, multicenter, randomized, two-period, two-treatment, two sequence open-label crossover study of 30 schizophrenic patients (ages 18-55 years of age) with a current psychotic illness who were stabilized on multiples of 100mg Clozaril for at least 3 months who received tablets for 11 days then received cross-over suspension treatment for 11 days with patients being confined to the study center on days 10 and 11 and days 21 and 22 for blood sampling.

5.2 Review Strategy

Table 2 below provides a listing of documents that were reviewed during the NDA review process.

Table 2: Items Utilized in this review

SUBMISSION DATE	ITEMS REVIEW
29 Dec 2011	-Study reports: ZPS-411 -Proposed labeling -Financial Disclosure Certification -Application Summary -Case Report Tabulations (.xpt files) -Case Report Forms
4 May 2012	-Revised labeling

6 REVIEW OF BIOEQUIVALENCE STUDY

Based on the 20 July 2010 meeting minutes for IND 108,466, the sponsor and Agency agreed that the submitted NDA would not contain clinical data other than a bioequivalence study between the sponsor's product and Clozaril tablets. Therefore under the 505(b)(2) regulatory pathway, the Agency has relied on previous efficacy studies and data from the two Clozaril programs for the two indications.

Bioequivalence Summary

The primary endpoint for the clinical study submitted for this NDA submission is to establish bioequivalence of the innovator product to the reference listed drug (RLD). Efficacy of clozapine has been established through clinical trial testing of the reference listed drug product Clozaril.

6.1.1 Rationale for Selection of Studies for Review

The sponsor has only conducted one study to establish bioequivalence of the suspension product to the RLD.

6.1.2 Study Summary

Methods/Study Design/Analysis Plan

Study ZPS-411 "Multiple-dose, multi-center, randomized, bioequivalence (BE) study of clozapine in multiples of 100mg as 50mg/ml Clozapine suspension in a two way crossover comparison with multiples of 100mg as Clozaril 100mg tablets in stable patients under fasting and fed conditions and at steady state."

Objectives:

The primary objective of this study was:

- To evaluate the bioequivalence of the test formulation, Clozapine 50mg/ml suspension relative to the reference formulation, Clozaril 100mg tablets, in adult patients under fasting and fed conditions at steady state in a randomized, double-blind, multiple dose, two-way cross-over study.

The secondary objective was to assess the overall safety of the patients with regards to adverse events and standard laboratory evaluations.

Bioequivalence Endpoint:

Bioequivalence would be established if the 90% confidence interval or the ratio of Test: Reference formulation of the least squares means from the ANOVA of the AUC_{0-t} and C_{max} for clozapine is between 0.80 and 1.25.

Study Design:

The study was an open-label, multiple-dose, multicenter, randomized, double-blind bioequivalence study using two treatments (100mg/day Clozaril tablets, 100mg clozapine suspension) two periods (days 1-11; days 12-22), two sequences (tabs days 1-11-suspension days 12-22; suspension days 1-11; tabs days 12-22). The study included 30 adult patients with schizophrenia. They received medication in under fasted conditions for days 1-9 and 12-20 and under fed conditions (200ml of whole milk) days 11 and 22.

Patients took the study medication as outpatients until study day 10 for period 1 and study day 21 for period 2. Patients were confined to the study center from 9:00 a.m. on study day 10 until 8:00 p.m. on study day 12. In similar fashion, patients were to be confined to the study center from 9:00 a.m. on study day 21 until 8:00 p.m. on study day 23.

Fasting Period: On days 10 and 21, patients were required to fast from 12 noon until 1 a.m. the next day with a standard meal provided 9 hours prior to dosing at 11am with a light supper provided at 1am on the day following dosing,

Fed Period: Prior to the evening dose on study days 11 and 22, patients will fast from 12 noon to 7:30pm and then receive a standard meal prior to dosing on study days 11 and 22.

Pharmacokinetic Sampling:

Fasting Days 10 and 21: Patients will receive their dose of study medication at 20:00 and then undergo clinical blood sampling from an intravenous catheter at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5 hours during the fasting phase then receive a light supper. Patients will then continue to undergo clinical blood sampling at hours 6, 8, 10 and 12 hours post dose followed by breakfast and sampling at 14, 16 and 20 hours post dose.

Fed Days 11 and 22: Patients will eat a standardized high fat meal 30 minutes prior to dosing and then undergo clinical blood sampling from an intravenous catheter at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5 hours during the fasting phase then receive a light supper. Patients will then continue to undergo clinical blood sampling at hours 6, 8, 10 and 12 hours post dose followed by breakfast and sampling at 14, 16 and 20 hours post dose.

Patients will then be released from the clinical site after receiving a final dose of the study medication at 20-2100 (48 hours after confinement).

Patients were to return to the clinic on day 7, 8 and 9 for period 1 and days 18, 19 and 20 for period 2 to receive pre-dose evening blood sample collections in order to assess for bioequivalence at steady state. Patients also received medication at the study site prior to returning home at 21:00.

Subject Selection Criteria:

Key Inclusion Criteria:

- Male and non-pregnant female patients with treated psychotic illnesses, in general good health, who were stabilized for at least three months on multiples of 100mg clozapine once daily in the evening
- Age 18-55 years old
- BMI of 19 but <35
- Alcohol and drug free
- Competent and freely provided informed consent

Key Exclusion Criteria:

- Caffeine intake was greater than 500mg/day
- Patients had significant orthostatic hypotension or syncope
- History of epilepsy or risk of seizures
- Concomitant drug treatment for hypertension that may predispose a patient to orthostatic hypotension
- Concomitant use of drugs known to suppress bone marrow function
- History of granulocytopenia or myeloproliferative disorder
- A total white blood cell count below $4.0 \times 10^9/L$ to an absolute neutrophil count below $2.0 \times 10^9/L$.
- Concurrent primary psychiatric or neurological diagnosis, incl. organic mental disorder, severe tardive dyskinesia or idiopathic Parkinson's disease
- Medical or surgical conditions that would interfere with oral absorption of the product.
- Patients who are HIV positive

Baseline Demographics and other Characteristics:

Thirty patients were enrolled and completed the study: 5 females and 25 males. The mean age was 38 years; the range was 24 to 57 years of age. The mean body weight was 93.5 kg with a range of 57.2 to 136 kg. The mean height was 1.74 m (range 1.61 to 1.97 m). The mean BMI was 30.8, with a range of 22.1 to 42.0

The following table shows that the ethnicities of the patients were primarily European and Maori:

Ethnic Group	N
European	16
Maori	11
African/European	1
Maori/European	1
South African	1

Patient Disposition:

All patients completed the study.

Concomitant Medication Use:

The use of concomitant medications is outlined below:

Patient ID	Concomitant Medication
D01-01	Quetiapine 50 mg /night
	Fluoxetine 20 mg /night
	Temazepam 10 mg as required (once every few weeks)
	Ventolin Inhaler as required
	Flixotide Inhaler as required
	Fish oil capsules
	Evening primrose capsules
D02-02	Methotrimeprazine maleate 25 mg (if required)
	Clonazepam 2mg (if required)
	2 x 25mg Quetiapine 2 x daily
	Loperamide 2 mg (if required)
	Propranolol 40 mg 2 x daily
D04-04	Citalopram 40 mg 1 x in morning
	Simvastatin 10 mg /night
	Clonazepam 0.5mg /day
	Benzatropine 2 mg 1/2 tablet as required
	Methotrimeprazine 100 mg 1 x at night
D05-05	Clonazepam 2mg /day
	Simvastatin 20 mg /night
D06-06	Lithium 5 x 500 mg /night
	Simvastatin 40 mg /night
D07-07	Amitriptyline 25 mg 2 x daily
D08-08	Subutamol sulfate/ipratropium bromide anhydrous Inhaler as required
	Fluticasone propionate Inhaler as required
	Omeprazole 20 mg
	Calcium Carbonate 1.25g
D09-09	Vitamin B 75 mg 1 x daily
	Multivitamin 1 x daily
	Rescue remedy
	Liver/kidney cleanse capsules
	Multivitamin 1 x daily
D15-10	Clonazepam 0.5 mg 3 x week
	Haloperidol 5 mg 5 x week
	Haloperidol Deconate 50 mg /month
	Cilazapril 2.5 mg/ 0.5 tablet morning
	Pantoprazole 40 mg 1 x daily
	Fluticasone propionate 125 mcg Inhaler as required
	Salbutamol Inhaler 100 mcg as required
D11-11	Lamivudine 100 mg 1 x daily
	Pantoprazole 40 mg 1 x daily
D12-12	Levonorgestrel 20 mcg daily

Patient ID	Concomitant Medication
D13-13	Chlormazine 100 mg 1 x daily
	Clonazepam 2 mg 1 x daily
	Levothroxine 0.05 mg 1/night
	Valproate 500 mg x 2/night
	Valproate 200 mg 4 x daily
	Lithium Carb 400 mg x 3/night
D16-15	Simvastatin 80 mg 0.5 daily
	Omeprazole 20 mg 0.5 daily
	Sodium 200 mg x 1 per month
	Citalopram 60 mg 1 x nightly
	Amisulpride 100 mg breakfast
D18-16	Omeprazole 20 mg 1 x daily
D19-17	Clonazepam as needed
W02-19	Omeprazole 40 mg /night
	Sodium valproate 700 mg morning and night
	Simvastatin 20 mg night by mouth or orally
W15-20	Omeprazole 20 mg morning by mouth or orally
	Metformin 850 mg morning by mouth or orally twice daily
	Diclofenac 75 mg as needed twice daily by mouth or orally
W01-21	Omeprazole 20 mg /night
	Sodium valproate 800 mg morning and night
W03-22	Amisulpride 400 mg twice daily
W13-23	Venlafaxine 150mg at night
W16-24	Lithium Carbonate 1500mg in the morning
W07-25	Metoprolol succinate 95 mg by mouth or orally in the morning
	Omeprazole 20 mg by mouth or orally in the morning
	Atorvastatin 30 mg by mouth or orally in the morning
W14-26	Amisulpride 600 mg twice daily by mouth or orally
	Lithium Carbonate 1200mg at night
W05-27	Fluoxetine 40 mg in the morning
	Multivitamin 1 x daily
	Omega-3 1 g daily
	Fish oil capsules
W04-29	Risperidone 0.5 /night
	Benzotropine mesylate 2 mg /night
W09-30	Fluoxetine 30 mg in the morning
	Multivitamin 1 x daily

Based on review of the concomitant medications, there appears to be no major pharmacokinetic interactions which would adversely affect the study results.

Important Protocol Violations

Two patients (D-07-07 and D09-09) consumed Echineacea 600mg X1 and 200ml of orange juice, respectively. Both items were prohibited during the study.

Use of prohibited medications

5 patients took ferrous sulfate for iron deficiency anemia; 3 patients took acetaminophen for headache (one dose each); one patient took ibuprofen 400 mg for headache; one patient took flucloxacillin 500 mg QID for an infection; one patient took lactulose 30 ml

TID for constipation; one patient took docusate for constipation: and one patient was prescribed temovate cream for a rash.

It is unlikely that any of these medications or substances interfered with the BE analysis of the study.

Dosing:

For inclusion in the bioequivalence study, all patients must have been previously stabilized on 100-mg multiples of clozapine tablets. Patients were then randomized to one of two sequences. In Sequence 1 (days 1-11), patients continued their current clozapine dose, administered as 100-mg multiples of Clozaril tablets, taken with 240 mL of water. For days 12 to 22, they would cross over to receive their usual dose, administered as 100-mg multiples of Clozapine suspension (50mg/mL), taken with 240 mL of water until.

The other randomization sequence randomized patients to multiples of Clozaril 50mg/ml suspension for days 1-11, followed by cross-over to multiples of Clozaril tablets on days 12-22.

6.2 Bioequivalence Results

Fasting Study:

Based on the log data and geometric mean data for both AUC_{0-t} and C_{max}, the suspension formulation was shown to be bioequivalent based on mean ratio % that fell between 0.8 and 1.25. T_{max} was slightly shorter for the suspension relative to the tablets (Suspension 0.3041 Vs. 0.3629 Clozaril Tablets; Mean Ration 83.82%). However the result was still within the bioequivalence standard of 0.8 to 1.25. The Log Data results are shown below:

	AUC _{0-t} (ng.hr/ml)	C _{max} (ng/ml)	C _{min} (ng/ml)	T _{max} (hr)
<i>Clozapine 50 mg/ml suspension (Douglas, America, B: 7805.005A) (Test)</i>				
Mean	3.4670	2.4151	1.8140	0.3041
S.D	0.1995	0.1445	0.2470	0.1838
Range	2.8582-3.9206	2.0195-2.8590	1.0306-2.2961	0.0000-0.5461
<i>Clozaril® 100 mg tablet (Novartis, USA, B: F0133) (Reference)</i>				
Mean	3.4828	2.4172	1.8088	0.3629
S.D	0.1768	0.1375	0.2580	0.1834
Range	2.9904-3.8810	2.1069-2.8157	0.9593-2.3234	0.0000-0.7782
Mean Ratio %^a	99.55	99.91	100.29	83.82

Using Geometric Mean data, Bioequivalence was still seen:

	AUC_{0-t} (ng.hr/ml)	Cmax (ng/ml)	Cmin (ng/ml)	Tmax (hr)
<i>Clozapine 50 mg/ml suspension (Douglas, America, B: 7805.005A) (Test)</i>				
Geometric Mean	2930.94	260.07	65.16	2.01
S.D^c	1353.56	86.45	37.40	0.86
Range	721.51-8329.98	104.59-722.84	10.73-197.73	1.00-3.52
<i>Clozaril[®] 100 mg tablet (Novartis, USA, B: F0133) (Reference)</i>				
Geometric Mean	3039.18	261.34	64.39	2.31
S.D^c	1239.97	82.56	38.65	0.97
Range	978.22-7602.87	127.92-654.14	9.10-210.56	1.00-6.00
Mean Ratio %^a	96.44	99.51	101.20	87.35
P-Values	0.1611	0.8705	0.5590	-
Sequence	0.7461	0.9445	0.6985	-
Period	0.0520	0.3299	0.0907	-
90% CI^b	(0.924,1.007)*	(0.946,1.047)*	(0.978,1.047)	-

Fed Study:

In similar fashion, bioequivalence was established for testing under fed conditions based on log and geometric mean data for AUC_{0-t} and Cmax. The suspension had a slightly lower rate of absorption in fed state compared to the fasted state. Therefore, there is a small food-effect with the administration of the suspension related to the rate of absorption. When comparing the rate of absorption of the tablet product in the fasting vs. fed state, a food-effect is also noted. However the food effect with the tablet product is larger than compared to the food effect with the suspension product.

When one compares the rate of absorption of the suspension product to the rate of absorption of the Clozaril tablet in the fed state, the suspension product is noted to have a faster rate of absorption.

	AUC_{0-t} (ng.hr/ml)	Cmax (ng/ml)	Cmin (ng/ml)	Tmax (hr)
<i>Clozapine 50 mg/ml suspension (Douglas, America, B: 7805.005A) (Test)</i>				
Mean	3.4482	2.3148	1.8000	0.4013
S.D	0.1921	0.1600	0.2450	0.2856
Range	2.8466-3.8774	1.9187-2.7203	1.0306-2.3413	0.0000-1.0792
<i>Clozaril® 100 mg tablet (Novartis, USA, B: F0133) (Reference)</i>				
Mean	3.4592	2.3215	1.7940	0.6255
S.D	0.1689	0.1393	0.2538	0.2562
Range	2.9859-3.8432	2.0310-2.6688	0.9593-2.2870	0.0000-1.1461
Mean Ratio %^a	99.68	99.72	100.34	64.15

Geometric Mean Data

	AUC_{0-t} (ng.hr/ml)	Cmax (ng/ml)	Cmin (ng/ml)	Tmax (hr)
<i>Clozapine 50 mg/ml suspension (Douglas, America, B: 7805.005A) (Test)</i>				
Geometric Mean	2806.77	206.46	63.10	2.52
S.D^c	1249.80	76.18	35.86	1.65
Range	702.48-7540.92	82.92-525.20	10.73-219.46	1.00-12.00
<i>Clozaril® 100 mg tablet (Novartis, USA, B: F0133) (Reference)</i>				
Geometric Mean	2878.83	209.63	62.22	4.22
S.D^c	1122.17	67.19	36.74	2.50
Range	967.96-6970.06	107.39-466.41	9.10-193.64	1.00-14.00
Mean Ratio %^a	97.50	98.49	101.40	59.68
P-Values	0.3212	0.6037	0.3657	-
Sequence	0.6926	0.7561	0.7277	-
Period	0.0160	0.1004	0.1951	-
90% CI^b	(0.934,1.018)*	(0.937,1.035)*	(0.988,1.041)	-

In summary, the bioequivalence analysis results for the AUC_{0-t} and Cmax demonstrate that the suspension is bioequivalent to the RLD to extent of absorption.

Clozapine 50 mg/ml suspension (II) vs Clozaril® 100 mg tablet (I) (fasting)			
	Geometric mean ratio %	Intra-patient CV%	90% confidence interval
AUC_{0-t}	96.44	9.78	(0.924,1.007)
C_{max}	99.51	11.56	(0.946,1.047)
Clozapine 50 mg/ml suspension (II) vs Clozaril® 100 mg tablet (I) (fed)			
	Geometric mean ratio %	Intra-patient CV%	90% confidence interval
AUC_{0-t}	97.50	9.74	(0.934,1.018)
C_{max}	98.49	11.26	(0.937,1.035)

Although a small food effect is noted with the suspension product, the food effect is much smaller with the suspension product when compared to the food effects with the tablet product.

Conclusions

The suspension is bioequivalent to Clozaril based on extent of absorption (AUC and C_{max}). A small food-effect on T_{max} was observed with the suspension product. The presence of food delays absorption for both the suspension and the tablet. However when the food effect of the suspension is compared to the food effect of the tablet product, the suspension appears to have a much smaller food effect. From a clinical standpoint, the extent of absorption is the most clinically useful measure for efficacy of a product, whereas the rate of absorption is useful to determine onset of efficacy for acute acting drugs, as well as the maximum point to experience any adverse reactions associated with the medication. Since the rate of absorption in the fed state for the suspension is very similar to the fasted state, one would not expect any increase in adverse reactions in the fed state. In fact, the smaller-food effect noted with the suspension product may confer an advantage over the tablet product with regards to administration with or without food. However for antipsychotic medications that are being used and labeled for maintenance treatment and not acute treatment of psychosis, the rate of absorption has little clinical significance other than a possible increase in some adverse reactions. Therefore the minimal food effects seen with the suspension product compared to the tablet on the rate of absorption are likely to have little clinical significance.

Thus this reviewer concludes that the product is bioequivalent based on extent of absorption. The minimal food-effects noted on the rate of absorption with the suspension product are likely of little clinical significance, thus no additional labeling changes are recommended to be included in the labeling in the clinical pharmacology section of the label. No additional clinical action or language in Warnings or Precautions is indicated at this time.

7 REVIEW OF SAFETY

Safety Summary

Data obtained from this small, 30 patient bioequivalence study is insufficient to assess the safety of the clozapine suspension product. However, administration of the suspension form of clozapine was associated with adverse events that are similar to what has been reported in labeling for the innovator product. The product was well tolerated, associated with no deaths or serious adverse events or drop-outs. There were no new or unexpected safety findings compared to the known safety and tolerability profile of clozapine.

Therefore this reviewer recommends that no changes to the warnings and precautions section of the RLD label be made based on the safety results of this product.

7.1 Methods

This reviewer reviewed the clinical summary tablets, the clinical study report for the single bioequivalence study and post-marketing reports of clozapine.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The results from ZPS-411 were used to evaluate safety related to the bioequivalence of this product were reviewed by this reviewer.

7.2 Adequacy of Safety Assessments

The primary objective for this study was to demonstrate bioequivalence between the innovator product compared to the RLD. The safety of the active ingredient has been examined and labeled since initial approval in 1989 and is deemed to be adequate.

Therefore the safety assessments conducted by the sponsor for this bioequivalence study are adequate when taken in context with the decades-worth of safety data accumulated since approval of clozapine in 1989.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Dosages for patients ranged from 100 mg to 800 mg/day. The mean calculated dose was 426.67mg/day. The sponsor did not provide any exposure data for this 22 day study. However since 30 patients completed the 22 days of exposure, the patient-days exposure for this study is calculated to be 660 patient-days of exposure to both clozapine suspension and clozapine tablets. Since all patients received clozapine suspension, the total patient-days exposure to the clozapine suspension was 330 patient-days.

7.2.4 Routine Clinical Testing

The study protocol included evaluations of suicidal ideation and suicidal behavior using the C-SSRS at baseline and at study day 7 and at study day 12 for each cross-over period. Complete blood counts and vital signs were obtained at day 1 and day 12 of each cross-over period. Adverse events were assessed on each study day of the visit.

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred in this study.

7.3.2 Nonfatal Serious Adverse Events

No serious adverse events occurred in this trial.

7.3.3 Dropouts and/or Discontinuations

No dropouts occurred in this study.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

During the study, a total of 288 adverse events were experienced by 22 patients. Of the 288 adverse events, 120 were related to administration of the suspension and 168 were related to administration of the tablet, with the remaining 168 adverse events related to administration of the tablet. The sponsor has not provided an analysis of adverse events comparing the tablet and suspension formulations. A list of the adverse events that occurred for both treatments is listed below:

Adverse Event	N
Drowsiness	74
Dizziness	46
Constipation	38
Confusion	34
Blurred Vision	29
Dry mouth	18
Heartburn	9
Headache	7
Low Hemoglobin	5
Urinary problems	4
Weight gain	4
Increased appetite	3

Skin Rash	3
Agitation	2
Nausea	2
Breathing difficulty	1
Dry cough	1
Forearm blister (infection)	1
Insomnia	1
Lightheadedness	1
Salivating	1
Shaking hands	1
Slightly breathless	1
Initial insomnia	1
Tired/lethargic	1

On visual inspection of adverse events between the tablet and suspension formulation, there appears to be no difference in the rates of adverse events between the two formulations. Based on the number of adverse events in patients who were administered suspension (120) v. tablets (168), it appears that the suspension may be slightly better tolerated.

Since the exposure to the suspension is only 330 patient-days, the exposure to the product is insufficient to consider adding the adverse event findings from this study into labeling for the product.

7.4.2 Laboratory Findings

Mean change from baseline parameters were requested by this reviewer and were provided in an amendment to the study. There were very small mean changes from baseline and were clinically not significant. A brief summary of differences in the following parameters is provided below:

Chemistry:

Total bilirubin decreased from baseline at post study. AST decreased from baseline at post study. Total protein decreased from baseline at post study. Serum globulin decreased from baseline at post study.

Hematology:

RBC volume and hemoglobin: there were small decreases from baseline at post study. There were small increases in platelets from baseline to post study. There were small increases in WBC from baseline post study. See table below (b = values deviated from normal deemed to be insignificant; c = values outside normal range not considered clinically significant):

Parameter	Pre Study		Mid Study		Post Study	
	b	c	b	c	b	c
Red Blood Cell Count	3.3% (1/30)	0% (0/30)	3.3% (1/30)	0% (0/30)	6.7% (2/30)	0% (0/30)
Haemoglobin	0% (0/30)	0% (0/30)	6.7% (2/30)	0% (0/30)	20% (6/30)	0% (0/30)
Packed Cell Volume	0% (0/18)	0% (0/18)	11.8% (2/17)	0% (0/17)	11.8% (2/17)	0% (0/17)
Mean Cell Volume	0% (0/30)	0% (0/30)	6.7% (2/30)	0% (0/30)	3.3% (1/30)	0% (0/30)
Mean Cell Haemoglobin	13.3% (4/30)	0% (0/30)	13.3% (4/30)	0% (0/30)	6.7% (2/30)	0% (0/30)
Platelets	3.3% (1/30)	0% (0/30)	6.7% (2/30)	0% (0/30)	3.3% (1/30)	0% (0/30)
Total White Blood Cell Count	10% (3/30)	0% (0/30)	13.3% (4/30)	0% (0/30)	13.3% (4/30)	0% (0/30)
Neutrophils	0% (0/30)	3.3% (1/30)	10% (3/30)	0% (0/30)	10% (3/30)	0% (0/30)
Lymphocytes	6.7% (2/30)	0% (0/30)	0% (0/30)	3.3% (1/30)	3.3% (1/30)	3.3% (1/30)
Monocytes	0% (0/30)	0% (0/30)	0% (0/30)	0% (0/30)	0% (0/30)	0% (0/30)
Eosinophils	0% (0/30)	3.3% (1/30)	0% (0/30)	3.3% (1/30)	0% (0/30)	3.3% (1/30)
Basophils	0% (0/30)	0% (0/30)	0% (0/30)	0% (0/30)	0% (0/30)	0% (0/30)
Erythrocyte Sedimentation Rate	0% (0/27)	14.8% (4/27)	-	-	7.7% (2/26)	26.9% (7/26)

Overall the changes in both chemistry and hematological parameters were very small and clinically not significant. Since the total exposure to the suspension product in the bioequivalence study was 330 patient-days, the exposure to the suspension product is insufficient to consider small changes to clinical laboratory parameters as conclusive. This reviewer recommends adopting the language from the reference listed product for this NDA product.

7.4.3 Vital Signs

The safety of the active ingredient clozapine has been extensively studied since marketing approval in 1989. This study was not designed to assess changes in vital sign parameters.

The protocol specified that patients vital signs, to include heart rate, blood pressure and temperature, were recorded prior to dosing on days 1, 7, 8, 9, 10 and 11 of period 1 and on days 12, 18, 19, 20, 21, and 22 of period 2. The sponsor has not provided a descriptive analysis of the vital sign data but has provided a line listing of vital signs per patient.

On visual inspection of the data, tachycardia (i.e. heart rates >100bpm) was frequently seen. However the current labeling for clozapine adequately describes the frequent association of tachycardia with clozapine administration, in addition to hypotension-which is labeled as a boxed warning in current labeling. This reviewer recommends adopting the language from the reference listed product for this NDA product.

7.4.4 Electrocardiograms (ECG's)

The safety of the active ingredient clozapine has been extensively studied since marketing approval in 1989. This study was not designed to assess changes in ECG parameters. ECGs were only conducted at screening per the protocol.

Labeling for the reference listed product adequately describes an association of clozapine administration and QTc interval prolongation, as well as ventricular arrhythmias, Torsades des pointes, cardiac arrest and sudden death. This reviewer recommends adopting the language from the reference listed product for this NDA product.

7.5 Deleted

7.6 Additional Safety Evaluations

7.6.2 Human Reproduction and Pregnancy Data

There were no pregnancies that occurred during this trial.

7.6.3 Pediatrics and Assessment of Effects on Growth

There were no pediatric subjects in the study.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no unintentional or intentional overdoses in the bioequivalence study.

7.7 Additional Submissions/Safety Issues

Risk Evaluation and Mitigation Strategy (REMS)

An interim Risk Evaluation and Mitigation Strategy (REMS) review was conducted on 17 August 2012 by Kimberly Lehrfeld, Pharm.D. from the Office of Surveillance and Epidemiology/Division of Risk Management.

After the passage of the Food and Drug Administration Amendments Act (FDAAA) in 2007, all sponsors of clozapine products were required to submit a REMS proposal by 21 Sept 2008. Currently, REMS for all clozapine-approved products are under review. Currently all clozapine products are marketed under approved RiskMAPs.

The sponsor has entered into a business agreement with Jazz Pharmaceuticals, marketers of FazaClo (clozapine orally disintegrating tablet). The proposed REMS submitted by the sponsor is identical to the proposed REMS submitted by Jazz Pharmaceuticals for FazaClo. The proposed REMS includes:

- A communication plan
- Elements to Assure Safe Use
 - Healthcare provider certification
 - Pharmacy certification
 - Monitoring equipment
 - Patient enrollment in a registry
- Implementation plan
- Timetable for submission of assessments.

DRISK provided comments to the sponsor regarding each element of the proposed REMS. At this time, the sponsor is in discussions with (b) (4)

A response to the Agency-requested REMS comments was submitted to the Agency on 1 November 2012 by the sponsor. This REMS submission is currently under review by OMEPRM.

Validation Human Factors Study (VHFS)

The sponsor had conducted a Validation of Human Factors Study on 28 November 2011 (submitted to IND 108,466) regarding the oral syringes and instructions for use of the oral syringes with the drug product. After review of the submission, the Division of Medication Errors Prevention Assessment (DMEPA) noted that the submission was a summary study, and the Human Factors Study was conducted after a change in the syringe was accepted. DMEPA provided comments to the sponsor on 21 December 2011,

recommending that the sponsor submit a new Human Factors Study protocol for the revised syringes for comment prior to initiation of the study.

(b) (4)
The Division also recommended that the sponsor conduct the study in the United States. (b) (4)

(b) (4)
(the recommendation to conduct the revised ‘Validation Human Factors Study’ in the United States and (b) (4)).” At that time, the sponsor found it difficult to understand the Agency’s position on conducting the study in the USA (b) (4)
. The sponsor also noted that (b) (4) if conducted in the United States, the study would begin recruiting in (b) (4) and be completed by (b) (4).

Since both scenarios posited by the sponsor would push the completion of the Human Factors study past the PUDFA goal date, the division met to consider the options available to it. During a meeting with DMEPA and the division, it was agreed upon that the usability study was not a mandatory requirement for the sponsor to conduct that would prevent approval of the drug product. Instead the Agency has recommended that the sponsor will be required to provide expedited reporting of adverse events associated with use of the packaging and oral syringes, and reports of overdosing and underdosing. It was further recommended by the Agency that the VHFS would be considered a post-marketing commitment after approval of the drug product.

8. Pediatric Development

The sponsor had requested a full waiver of required pediatric studies with supportive data, citing the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and that the product would be unsafe in pediatric patients. On 14 Feb 2012 during the division filing meeting, the Division of Psychiatry Products stated that a full waiver of required PREA studies would be granted since studies in pediatric patients would be impossible or highly impracticable to conduct due to the small number of pediatric patients that would use the drug. On 29 March, 2012, the sponsor submitted a revised full pediatric waiver requesting that such pediatric studies would be impracticable and the product does not represent a meaningful therapeutic benefit over existing therapies.

On 31 August, 2012, the Agency granted a full waiver to perform pediatric studies. Thus there will be no PREA requirements to fulfill for this product.

9 POSTMARKET EXPERIENCE

This particular clozapine suspension is not currently marketed in any other country. The sponsor has marketed a similar clozapine suspension product in Australia and New Zealand. In addition, the sponsor has contracted manufacturers from (b) (4) to formulate a similar suspension product. Since the sponsor does not own the intellectual property rights to the formulations found in (b) (4), there is no obligation for these countries to submit post marketing adverse events to the sponsor and thus no information is available from these (b) (4) countries. There have been three (3) adverse event reports from Australia with regard to a similar, but not identical, formulation. Each of these three reports was a reduction in clozapine plasma levels when switched from Clozaril tablets to the suspension. No clinical sequelae were reported with these post market reports.

Clozapine tablets have extensive post-marketing use. As a result, final approved labeling will include the most recent adverse reactions associated with post-market use of Clozaril tablets.

10 Labeling Recommendations

Labeling revision are currently ongoing as part of a review of recent recommendations regarding agranulocytosis and hematological monitoring. Therefore a review of the hematological parameters for the clozapine class labeling changes will not be performed at this time. However once the final version of clozapine-class labeling changes have been approved, the sponsor will be required to adopt the new language.

However, since this product is the first suspension formulation of clozapine, specific instructions for use (IFU) have been proposed. As stated above, the sponsor is not able to complete a Validation of Human Factors study which would test the patient-usability of the proposed instructions for use section. Nevertheless the IFU appears to be clear and concise for a caregiver to understand or for a self-medicating patient to understand who is competent to administer the medication to themselves.

Labeling discussions between the sponsor and Agency have taken place and no additional recommendations for labeling changes are recommended by this reviewer at this time.

11 Advisory Committee Meeting

Because there were no controversial bioequivalence, safety, or efficacy issues with this NDA application, we did not hold an advisory committee meeting.

APPEARS THIS WAY ON THE ORIGINAL

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/s/

MARK A RITTER
01/16/2013

ROBERT L LEVIN
01/16/2013
See Cross-Discipline Team Leader review memo to follow.