CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218637Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	505(b)(2) NDA Resubmission
Application Number(s)	218637
Priority or Standard	Standard
Submit Date(s)	1/27/2024
Received Date(s)	1/29/2024
PDUFA Goal Date	11/29/2024
Division/Office	Division of Psychiatry (DP)/Office of Neuroscience (ON)
Review Completion Date	11/26/2024
Established/Proper Name	Trazodone hydrochloride oral solution
(Proposed) Trade Name	Raldesy
Pharmacologic Class	Antidepressant
Applicant	Kamat Pharmatech, LLC.
Dosage form	Oral solution
Applicant proposed Dosing Regimen	• Starting dose: 150 mg in divided doses daily. May be increased by 50 mg per day every 3 to 4 days. Maximum dose: 400 mg per day in divided doses (Inpatients (i.e., more severely depressed patients) may receive up to 600 mg/day) • Trazodone hydrochloride oral solution should be taken shortly after a meal or light snack. • When discontinued, gradual dose reduction is recommended.
Applicant Proposed Indication(s)/Population(s)	Treatment of major depressive disorder
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	370143000 Major depressive disorder (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Treatment of major depressive disorder in adults
Recommended SNOMED CT Indication Disease Term for each Indication	370143000 Major depressive disorder (disorder)
Recommended Dosing Regimen	Starting dose: 150 mg in divided doses daily. May be increased by 50 mg per day every 3 to 4 days. Maximum dose: 400 mg per day in divided doses (Inpatients (i.e., more severely depressed patients) may receive up to 600 mg/day). • Trazodone hydrochloride oral solution should be taken shortly after a meal or light snack.

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Signatures

See archived signatory memos for each discipline.

Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AUC	area under the curve
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
Cmax	maximum concentration
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
CRF	case report form
CSR	clinical study report
DMC	data monitoring committee
DMEPA1	Division of Medication Error Prevention and Analysis 1
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
GCP	good clinical practice
GMR	geometric mean ratio
ICH	International Conference on Harmonisation
IFU	instructions for use
IND	Investigational New Drug
LD	listed drug
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
OPQ	Office of Pharmaceutical Quality
PD	pharmacodynamics
PK	pharmacokinetics
PMR	postmarketing requirement
PP	per protocol
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
Tmax	time to maximum concentration

1 Executive Summary

1.1. Product Introduction

The Applicant submitted a new drug application (NDA) to support trazodone hydrochloride oral solution (NDA 218637; proposed tradename: Raldesy) for the treatment of major depressive disorder (MDD) in adults. The oral solution formulation may be useful for patients that have difficulty swallowing. The Applicant used the 505(b)(2) regulatory pathway and relied on FDA's previous findings of safety and effectiveness of the listed drug (LD), Desyrel (trazodone hydrochloride oral tablets; NDA 018207); approved in 1981 for the treatment of MDD in adults. Trazodone is thought to exert its pharmacological effect via enhancement of serotonergic activity (selective serotonin reuptake inhibition and serotonin-2 receptor antagonism) in the central nervous system (CNS).

The Applicant plans to supply the drug product as a 10 mg/ml clear and colorless solution with a calibrated oral dosing syringe packaged as 150-mL and 300-mL. The proposed dosage and administration instructions are identical to the LD; the initial daily dosage is 150 mg/day that can be increased gradually (50 mg/day every 3 to 4 days), depending on clinical response and tolerance, to a maximum recommended dosage of 400 mg/day in divided doses (or 600 mg/day in divided doses for patients with severe depression).

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness for the treatment of MDD in adults is provided by the Agency's previous findings of effectiveness for the LD and the establishment of an acceptable scientific bridge between the LD and trazodone oral solution using pharmacokinetic (PK) data.

The pivotal PK bridging study (097-21) demonstrated that an adequate scientific bridge has been established between 100 mg trazodone hydrochloride oral solution (10 mg/mL) and 100 mg of the LD. Therefore, the trazodone hydrochloride oral solution is expected to have the same efficacy and safety profile in the context of treatment of MDD in adults as the approved trazodone hydrochloride tablet.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

This NDA relies on the Agency's previous findings of safety and effectiveness for the listed rug (LD), trazodone hydrochloride oral tablets (trade name: Desyrel; NDA 018207) and the pharmacokinetic (PK) bridge that was established between the LD and the proposed product, trazodone hydrochloride oral solution. Therefore, the safety profile and effectiveness for trazodone oral solution are expected to be similar to the LD. No new safety issues were identified from the Applicant's PK study. The benefit-risk profile of trazodone hydrochloride oral solution does not differ from the LD. This assessment supports the marketing approval trazodone oral solution for the treatment of MDD in adults and provides an additional formulation option for treatment based on patients' needs and preferences.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Major depressive disorder (MDD) is a serious and life-threatening condition with high rates of individual and society-level morbidity. • MDD typically has a chronic course requiring ongoing treatment. • MDD is considered a leading cause of disability worldwide and is associated with increased mortality rates years of life lost.	Effective treatments for MDD are needed to reduce the functional impairment, morbidity, and mortality that are associated with the condition and to mitigate the public health impact.
Current Treatment Options	• First-line treatments for MDD include psychotherapy and oral antidepressants (e.g., selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors) • If patients do not respond to a first-line treatment, they may benefit from switching to a different antidepressant (either in the same or a different class) or receiving adjunctive treatment (e.g., antipsychotic).	Several treatment options for MDD are available. However, efficacy and tolerability for individual patients are difficult to predict. Thus, it is beneficial to have additional antidepressant options available for patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The Applicant submitted a single, randomized, open-label, three-treatment, three-period, crossover, oral comparative bioavailability study (097-21) intended to establish an adequate PK bridge to the LD. • The geometric mean ratios of PK parameters comparing the trazodone oral solution to oral tablets were within the prespecified bioequivalence limits (80% to 120%) under fed conditions. • Although a high-calorie and high-fat diet decreased maximum concentrations (Cmax) by 30% relative to fasted conditions, the geometric mean ratio for overall exposure (area under the curve (AUC)) was within the bioequivalence limits. The extent of reduction in Cmax of oral solution formulation of trazodone under high-fat diet appears to be similar to that reported for the approved trazodone tablets. Therefore, such lower extent of reduction in Cmax is not expected to be clinically meaningful.	The Applicant established an acceptable scientific bridge via demonstrating an adequate PK bridge between the LD and trazodone oral solution under fed conditions. As the LD is administered under fed conditions, the demonstration of PK bridge under fed state is acceptable. The effectiveness of trazodone oral solution is expected to be similar to the LD. Assessment of food effect also suggests that trazodone oral solution can similarly be administered after a meal or light snack.
Risk and Risk Management	• In premarketing studies for the LD, common adverse reactions (i.e., incidence ≥5% and at least twice the incidence relative to placebo) associated with inpatient or outpatient use included: hypertension, dizziness, drowsiness, fatigue, headache, nausea/vomiting, and incoordination, skin edema, blurred vision, dry mouth, syncope, nasal congestion, and weight gain/loss. • Warnings and precautions described in the prescribing information include risks of suicidal ideation and behavior in adolescents and young adults, serotonin syndrome, cardiac arrhythmias, orthostatic hypotension/syncope, increased risk of bleeding, priapism, activation of mania or hypomania, discontinuation syndrome, cognitive impairment, angle closure glaucoma, and hyponatremia • Safety data collected in Study 097-21 did not reveal any new or	Based on the established bridge, trazodone oral solution is expected to have a similar safety profile as the LD for the treatment of MDD in adults. The risks can mitigated via labeling.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	worsened safety signal associated with trazodone oral solution.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

				Section of review where discussed, if applicable
☐	**The patient experience data that were submitted as part of the application include:**			
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
X	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Major depressive disorder is a serious and life-threatening condition with high rates of individual and society-level morbidity. Table 1 lists the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision* diagnostic criteria for MDD (American Psychiatric Association 2022). As severity increases, patients with MDD may be unable to work, maintain relationships, attend to self-care, and in the most severe cases, may become hospitalized, attempt suicide, or die by suicide. The course of MDD is heterogenous, including chronic recurrent major depressive episodes with variable durations. Inter-episode periods may be remissions or include persisting symptoms. An estimated 22.5 million adults (8.8% of the adult population) in the United States had at least one major depressive episode in 2022, with an estimated prevalence of approximately 280 million people worldwide (Substance Abuse and Mental Health Services Administration 2023; GBD 2019 Mental Disorders Collaborators 2022). MDD is considered a leading cause of disability worldwide and is associated with increased mortality rates and a median rate of 10 years of life lost (Walker et al., 2015).

Table 1. Diagnostic Criteria for Major Depressive Disorder.

Criteria for a Major Depressive Episode	A	Five (or more) of the following symptoms present during the same 2-week period and represent a change from previous functioning; at least one of which is either (1) or (2): 1. Depressed mood most of the day, nearly every day[1] 2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day[1] 3. Significant weight loss when not dieting or gain, or decrease or increase in appetite nearly every day 4. Insomnia or hypersomnia nearly every day 5. Psychomotor agitation or retardation nearly every day 6. Fatigue or loss of energy nearly every day 7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick) 8. Diminished ability to think or concentrate, or indecisiveness, nearly every day[1] 9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan; a specific suicide plan; or a suicide attempt
	B	Symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
	C	The episode is not attributable to the physiological effects of a substance or another medical condition
Additional Required Criteria	D	At least one major depressive episode is not better explained by schizoaffective disorder and is not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or other schizophrenia spectrum and other psychotic disorders
	E	There has never been a manic or hypomanic episode

Note: Criteria A to C represent a major depressive episode
[1]As indicated by either subjective report or observation made by others
Source: Clinical reviewer-adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision *(American Psychiatric Association, 2022).*

2.2. Analysis of Current Treatment Options

Typical first-line treatments for MDD include psychotherapy and oral antidepressant medications of several classes (e.g., selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors). Safety and tolerability profiles differ across classes and individual medications; all antidepressants include a Boxed Warning for increased risk of suicidal thoughts and behavior in pediatric and young adult patients taking antidepressants based on data from randomized, placebo-controlled, short-term studies. Antidepressants have demonstrated efficacy in the treatment of MDD, including in patients who are severely depressed (Fournier et al. 2010; Gartlehner et al., 2008). However, approximately 30 to 40% of patients with MDD fail to respond to first-line treatments (Rush et al., 2006). If first-line treatments fail, treatment options include adding or switching psychotherapy; switching to a different antidepressant (either in the same or a different class); adding augmentation treatment to an ongoing antidepressant (typically a drug with a different mechanism of action, such as another antidepressant, certain second-generation antipsychotics, or off-label lithium or thyroid hormone); or referral for a device treatment such as electroconvulsive therapy or transcranial magnetic stimulation (American Psychiatric Association 2010; Brunoni et al., 2017). Esketamine is approved for the treatment of depressive symptoms in patients with MDD with acute suicidal ideation or behavior (and also indicated for treatment-resistant depression). Although many treatment options are available, it is currently not possible to predict which treatment will be effective and tolerable for a particular patient. Therefore, it is beneficial for patients to have a variety of antidepressant treatment options.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

FDA initially approved trazodone oral tablets (trade name: Desyrel) in December 1981 for the treatment of MDD in adults. Currently, trazodone oral solution is not marketed in the United States for any indications. Of note, the original Sponsor for trazodone oral tablets (the proposed LD) has discontinued manufacturing, and as per Federal Registration determination, trazodone oral tablet was not withdrawn or discontinued due to safety or effectiveness reasons. Only generic versions of trazodone hydrochloride oral tablets are available (Abbreviated NDA 071196 is designated as the reference standard in the Orange Book).

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant used the 505(b)(2) regulatory pathway to rely, in part, on the Agency's previous findings of safety and effectiveness for the LD, Desyrel (NDA 018207), as well as published literature. The following list summarizes key milestones for the development of trazodone oral solution for the treatment of MDD in adults under investigational new drug (IND) application 143176:

- May 17, 2019: In an email correspondence with the Applicant, the Division provided informal guidance regarding the need to conduct a comparative bioavailability study in the fed state and a food effect study.

- June 5, 2019: In a follow-up email correspondence, the Applicant inquired whether the chemistry, manufacturing, and controls (CMC) development package submitted under the 505(b)(1) development pathway would be similar to a new oral solution product. The Division clarified that an application submitted under the 505(b)(2) regulatory pathway is subject to the same CMC requirements as an application submitted under the 505(b)(1) pathway.

- January 13, 2022: Type B (Pre-IND) Meeting to obtain Division concurrence on the acceptability of the Applicant's proposed CMC, nonclinical, clinical, and regulatory strategies.

    - The Division indicated that the Applicant's proposal to rely on Desyrel as the LD was reasonable.

    - The Division stated that the Applicant's proposed pivotal three-arm (test product under fasting conditions, test product under fed conditions, LD under fed conditions) comparative bioavailability study was reasonable.

  - Given the potential for [redacted] exposure up to [redacted] mg/day, the Division indicated that the Applicant would need to control the amount of [redacted] in the drug product to levels that will not exceed the permitted daily exposure of [redacted] mg/day.

- July 11, 2022: The Applicant submitted a request for IND exemption, given that their planned pivotal comparative BA study was to be conducted in India. Because the Applicant's planned study was to be performed outside the United States, the Division clarified that an IND was not required.

- July 10, 2023: Type B (Pre-NDA) Meeting to obtain Agency concurrence on the acceptability of the proposed CMC, nonclinical, clinical, and regulatory strategies to support and NDA.

  - Given that the proposed product is a combination product (active drug + oral syringe device), the Division indicated that development of the proposed product would be subject to 21 CFR Part 4 (Current Good Manufacturing Practice Requirements for Combination Products).

  - The Division requested that the Applicant submit a certification that the formulation contacting [redacted] components complies with USP <87> and <88> and a risk assessment for the presence of nitrosamine in the drug product.

  - Given that the proposed product is a new dosage formulation of trazodone, the Division emphasized that the NDA is subject to Pediatric Research and Equity Act (PREA) requirements and an agreed iPSP, with the necessary pediatric assessments, must be submitted with the NDA.

- September 20, 2023: The Applicant submitted their NDA on July 25, 2023. Given that the Applicant failed to address the requirements under PREA (lack of an agreed initial pediatric study plan (iPSP) submitted with the NDA), the Division refused to file the application under 21 CFR 314.101(d). The Division had noted in several previous communications (written responses to the pre-IND meeting and pre-NDA meeting requests) that a pediatric assessment is required for NDA submission for the proposed new trazodone dosage formulation.

- January 8, 2024: The Applicant submitted an agreed iPSP that included pediatric assessments to evaluate children 7 to 12 years of age and adolescents for the treatment of MDD.

- January 27, 2024: The Applicant re-submitted the NDA, which the FDA filed on April 9, 2024.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Study Integrity and Surveillance (OSIS)

The Office of Study Integrity and Surveillance (OSIS) was consulted for an inspection of the clinical (Ecron AcuNova, Ltd., Tamil Nadu, India) and bioanalytical ([(b) (4)] [(b) (4)] sites of the pivotal relative bioavailability study (097-21).

OSIS conducted Remote Regulatory Assessment (RRA) of the bioanalytical site in [(b) (4)] for ANDAs [NON-RESPONSIVE] Following review of the objectionable conditions and written response from the bioanalytical site, OSIS concluded that data from the reviewed study were reliable.

OSIS determined that an inspection of the clinical and bioanalytical sites was not needed for this application because the Office of Regulatory Affairs (ORA) conducted an inspection of the same clinical site in November 2022 for Abbreviated New Drug Applications (ANDAs [NON-RESPONSIVE] and [NON-RESPONSIVE]). After review of inspection findings and responses from the clinical study site, OSIS concluded that data were reliable.

4.2. Product Quality

The Office of Product Quality (OPQ) recommends approval for this application based on drug substance, drug product, process/facilities, biopharmaceutics, and microbiology reviews.

Drug Substance: The Applicant references drug master file (DMF [(b) (4)], along with providing general information, manufacturing process, specification, batch data, reference standards, and container closure information on the drug substance in the NDA. The drug substance CMC information is adequate based upon the adequate status of the referenced DMF and upon the information provided in this NDA. Based upon the available long-term [(b) (4)] stability data, DMF [(b) (4)] holder has a re-test period of [(b) (4)] for the drug substance. The applicant re-tests the drug substance every [(b) (4)]

Drug Product: The drug product has one strength, 10 mg/mL. The drug substance and all excipients in the drug product are of compendial grade, United States Pharmacopoeia (USP)/National Formulary (NF). Four container closure system are proposed: 150 mL and 300 mL HDPE bottles, and 150 mL and 300 mL amber glass bottles. The adequacy of the container closure systems was demonstrated through food grade certifications, extractable/leachable studies, which found a low risk of leachables, and the stability studies. The drug substance review found the risk of [(b) (4)] formation to be negligible, and there is a negligible risk of [(b) (4)] formation in the drug product based on the excipients and impurity profiles.

Release data for sixteen registration batches is provided, all using the commercial container closure systems (four batches for each container closure system). All certificates of analysis met the acceptance criteria for all tested parameters. The specifications are adequate, and all analytical methods are adequate, with adequate validation reports provided.

Stability data for the registration batches is provided through 12 months at 25°C/60%RH. No out-of-specification results or trends were noted for any tested parameters, including assay and impurities. The requested expiry of 24 months is granted, with the storage conditions of Controlled room temperature: 20° to 25° (68° to 77° F), with excursions permitted to 15°C to 30°C (59°F to 86°F), supported by the results of the long-term and accelerated stability studies.

The proposed product is adequate based on the control strategies, release and stability results of the registration batches, and adequate data supporting the container closure system.

Manufacturing: The proposed drug product trazodone hydrochloride oral solution, 100 mg/10 mL is a drug device combination product with 10 mL oral syringe with adapter. The liquid oral dosage form is desirable for patients that have difficulty in swallowing for various reasons.

Trazodone hydrochloride oral solution, 100 mg/10 mL is a clear, colorless solution, free from any visible foreign and particulate matter, free of precipitation and hazy mass. Trazodone hydrochloride oral solution, 100 mg/10 mL is presented in four packaging configurations (i.e., two fill volumes in two different bottle types (150 ml type (b) (4) amber glass bottle with 28 mm (b) (4) white child resistant cap; 150 cc white high-density polyethylene (HDPE) bottle with 28 mm (b) (4) child resistant cap having (b) (4); 300 ml amber glass bottle with 28 mm (b) (4) white child resistant cap; 300 cc white HDPE bottle with 28 mm (b) (4) child resistant cap having (b) (4)).

The manufacturing process is consisted of (b) (4)

(b) (4)

(b) (4) All facilities are compliant with current good manufacturing practices (cGMP). No pre-approval inspection (PAI) was requested.

See the archived integrated quality assessment review from OPQ for additional information.

4.3. Clinical Microbiology

The drug product is a multi-dose non-sterile, clear, and colorless oral solution that contains 10 mg/mL trazodone hydrochloride. (b) (4). The submission

batches met the microbial limits acceptance criteria. Antimicrobial effectiveness testing (AET) and Burkholderia cepacian Complex (BCC) testing met the acceptance criteria. The stability data is adequate and support the microbiological quality of the drug product through the expiration period of 24 months.

4.4. Devices and Companion Diagnostic Issues

The Applicant submitted a use-related risk analysis (URRA) and threshold analysis to justify not submitting human factors validation study results as part of this NDA. The Division of Medication Error Prevention and Analysis 1 (DMEPA1) did not identify any new, differing, or unique risks for the proposed product as compared to the comparator product, Trileptal (oxcarbazepine) oral suspension. Therefore, DMEPA1 agreed with the Applicant that additional human factors validation study results were not needed. With regards to the product label, DMEPA1 also recommended that the Applicant removing the proposed (b) (4) (b) (4) (b) (4) See DMEPA1's archived review memo (August 6, 2024) for additional information.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The Applicant did not submit any new nonclinical pharmacology/toxicology information. The nonclinical data relied upon to support the original NDA are adequate to support approval of this application.

6 Clinical Pharmacology

6.1. Executive Summary

The LD, Desyrel (trazodone hydrochloride tablets; NDA 018207), is approved for the treatment of MDD. The Applicant is seeking approval of trazodone hydrochloride oral solution for same indication as the LD via the 505(b)(2) pathway. The proposed oral solution formulation of trazodone relies on the Agency's previous findings of safety and efficacy of the LD. Because Desyrel has been discontinued, trazodone hydrochloride 100 mg tablet (ANDA 071196) was used to establish a pharmacokinetic (PK) bridge between the products.

The Applicant submitted a three-treatment, three period, crossover study (Test-Fasting, Test-Fed, and Reference-Fed) to establish a PK bridge between the oral solution formulation of trazodone (100 mg/10 mL) and the LD (100 mg), and to evaluate food effects on the PK of trazodone oral solution.

The Office of Clinical Pharmacology (OCP) reviewed the pivotal relative bioavailability study submitted in this application and finds that exposures of trazodone from the oral solution formulation were within the bioequivalence limits of the LD under fed conditions. As the LD is recommended to be administered under fed conditions, the scientific bridge between the formulations under fed state is acceptable. Therefore, the proposed drug product, trazodone HCL oral solution (100 mg/10 mL) can rely on safety and effectiveness of the LD.

OCP recommends the approval of trazodone hydrochloride oral solution for the treatment of MDD in adults.

6.2. Summary of Clinical Pharmacology Assessment

- In a single-dose relative bioavailability study in healthy adults under fasted and fed conditions, the PK of trazodone was compared between trazodone hydrochloride oral solution (100 mg/10 mL) and the LD (100 mg), under fed conditions, and between trazodone hydrochloride oral solution under fasted and fed conditions. The results showed that the peak plasma concentrations (Cmax) and area under the plasma concentration-time curve (AUCinf) for trazodone hydrochloride oral solution 100 mg/10 mL were similar to the LD and the geometric mean ratio was within the acceptable range of (80% to 125%) of the LD, under fed conditions. The median time to reach Cmax (Tmax) for trazodone oral solution was 1 hour while for the LD was 2.5 hr. As trazodone is intended for the chronic treatment of MDD in adults, the difference in Tmax between trazodone oral solution and the LD is not expected to be clinically significant.

- Compared to fasted conditions, the area under the plasma concentration-time curve (AUCinf) for trazodone hydrochloride oral solution was similar to that under fed conditions,

and peak plasma concentrations (Cmax) was about 30% lower under fed conditions. The magnitude of reduction (i.e., 30%) in Cmax of oral solution formulation of trazodone under high-fat diet appears to be similar to that seen with the approved trazodone tablets. Therefore, such lower extent of reduction in Cmax is deemed clinically not meaningful. The median Tmax was similar between fed and fasted conditions.

- Based on OSIS's recommendation, the clinical and bioanalytical sites for the pivotal relative BA study (097-21) are acceptable.

6.2.1. Pharmacology and Clinical Pharmacokinetics

Absorption
Under fed conditions, trazodone hydrochloride oral solution reaches peak plasma concentrations approximately 1 hour following a single oral dose administration.

Effect of Food
Ingestion of a high-fat meal with trazodone oral solution lowers mean Cmax of trazodone by 31% and increases mean AUC by 8%. Median Tmax was similar between fed and fasted conditions.

Distribution
Trazodone is 89% to 95% bound to human plasma protein in vitro at concentrations attained with therapeutic doses in humans.

Metabolism
In vitro studies in human liver microsomes show that trazodone is metabolized, via oxidative cleavage, to an active metabolite, m- chlorophenylpiperazine (mCPP) by CYP3A4. Other metabolic pathways that may be involved in the metabolism of trazodone have not been well characterized. Trazodone is extensively metabolized; less than 1% of an oral dose is excreted unchanged in the urine.

Elimination
The terminal elimination half-life is 16.9 hr.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing
Since the exposures to trazodone were within the bioequivalence limits of the LD under fed conditions, the information relevant to dosing and therapeutic individualization of trazodone hydrochloride oral solution can rely upon the LD.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. Clinical Pharmacology Questions

Are the exposures of trazodone hydrochloride oral solution 100 mg/10 mL similar to the LD, trazodone hydrochloride tablets, 100 mg under fed conditions?

A randomized, open-label, balanced, three-treatment, three-period, crossover comparative bioavailability study was conducted to evaluate the PK of trazodone hydrochloride oral solution (100 mg/10 mL; test product) and trazodone hydrochloride tablet (100 mg, reference product) in healthy human adult subjects. The study scheme is shown in Table 2:

Table 2. Study Schema for Study 097-21.

No. of subjects	Period 1	Period 2	Period 3
14	Treatment 1	Treatment 2	Treatment 3
14	Treatment 2	Treatment 3	Treatment 1
14	Treatment 3	Treatment 1	Treatment 2
Treatment (T1) = TraZODONE Hydrochloride Tablets, USP 100 mg [Reference Product (B)], Manufactured for: Apotex Corp., Weston Florida, 33326 under fed conditions. Treatment (T2) = Trazodone Hydrochloride oral solution 100 mg/ 10 mL [Test Product (A)] of Rubicon Research Pvt. Ltd., India under fed conditions. Treatment (T3) = Trazodone Hydrochloride oral solution 100 mg/ 10 mL [Test Product (A)] of Rubicon Research Pvt. Ltd., India under fasting conditions.			

Source: Clinical study report for Study 097-21, Table-3, p. 29.

The exposures (Cmax and $AUC_{0-\infty}$) of test product administered under fed condition were within the bioequivalence limits (80% to 125%) of reference product administered under fed conditions. Under fed conditions, the median Tmax of trazodone oral solution and the LD was 1 hour and 2.5 hours, respectively. As trazodone is indicated for the chronic treatment of MDD in adults, a smaller difference in Tmax between trazodone oral solution and the LD is not anticipated to be clinically significant.

Given that the reference product is recommended to be administered under fed conditions, the scientific bridge demonstrated between the test and reference products administered under fed conditions are acceptable. The results suggest that trazodone hydrochloride oral solution can rely on safety and efficacy of the LD.

Table 3. Summary of Statistical Comparisons of Plasma Trazodone Pharmacokinetic Parameters after Single Oral Dose Administrations of Trazodone Hydrochloride Oral Solution 100 mg/10 mL (Test Product) and Trazodone Hydrochloride 100 mg (Reference Product) under Fed Conditions.

GeoMean of PK Parameters	Reference	Reference n	Test	Test n	GeoMean Ratio% (90%CI)
AUC_{last} (µg*h/mL)	19201.34	37	20314.60	39	105.80 (101.11, 110.70)
AUC_{inf} (µg*h/mL)	23124.86	37	23860.01	39	103.18 (98.19, 108.43)
C_{max} (µg/mL)	1218.39	37	1308.93	39	107.43 (98.51, 117.16)

AUC=area under the curve; C_{max}=peak plasma concentration; GeoMean=Geometric mean; CI=confidence interval
Source: Reviewer's analysis.

See Section 19.3 Clinical Pharmacology at the Appendices for additional information.

What is the effect of food on the exposures of trazodone hydrochloride oral solution? Does this product require specific dosing instruction regarding food?

In the randomized, open-label, balanced, three-treatment, three-period, crossover, oral comparative bioavailability study, the test product, trazodone hydrochloride oral solution 100 mg/ 10 mL, was administered under fed and fasted conditions. The results showed that the Cmax decreased by 30% under fed conditions, while the $AUC_{0-\infty}$ was similar between fed and fasted states. The median Tmax was similar between fed and fasted conditions. The 30% reduction in Cmax of oral solution formulation of trazodone under high-fat diet appears to be similar to that seen with the approved trazodone tablets. When a single 100-mg oral dose of the reference product was administered under fed and fasted conditions in healthy subjects (b) (4) the Cmax was reduced by approximately 30% under fed conditions, as compared to fasted conditions. The $AUC_{0-\infty}$ remained unchanged. Therefore, approximately 30% reduction in Cmax of oral solution formulation of trazodone is considered clinically not meaningful.

Given that food effect is similar between trazodone hydrochloride oral solution and LD, the proposed drug product, trazodone hydrochloride oral solution, can be administered with food (as similar to the LD).

Comparison of the PK parameters between fed state and fasting state is shown below in Table 4.

Table 4. Summary of Statistical Comparisons of Plasma Trazodone Pharmacokinetic Parameters after Single Oral Dose Administrations of Trazodone Hydrochloride Oral Solution 100 mg/10 mL under Fed State and Trazodone Hydrochloride Oral Solution 100 mg/10 mL under Fasted State.

GeoMean of PK Parameters	Reference	Reference n	Test	Test n	GeoMean Ratio% (90%CI)
AUC_{last} (µg*h/mL)	18824.24	37	20314.60	39	107.92 (103.14, 112.92)
AUC_{inf} (µg*h/mL)	22366.33	37	23860.01	39	106.68 (101.52, 112.10)
C_{max} (µg/mL)	1842.47	37	1308.93	39	71.04 (65.14, 77.48)

AUC=area under the curve; C_{max}=peak plasma concentration; GeoMean=Geometric mean; CI=confidence interval
Source: Reviewer's analysis.

See Section 19.3 Clinical Pharmacology at the Appendices for additional information.

7 Sources of Clinical Data and Review Strategy

7.1. Review Strategy

The Applicant did not conduct any safety and efficacy studies and proposes to rely upon the Agency's previous findings of safety and effectiveness for the LD with a scientific PK bridge to the LD, Desyrel (see Section 6 Clinical Pharmacology). The clinical review will provide a brief overview of the PK trial designs and a review of safety data from the PK trials.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study 097-21

Overview and Objectives

Study 097-21 was titled "A Randomized, Open-label, Balanced, Three Treatment, Three Period, Crossover Oral Comparative Bioavailability Study of Trazodone Hydrochloride Oral Solution 100mg/10 mL Comparing with Trazodone Hydrochloride Tablet in Healthy Adult Subjects." The Applicant's study objectives were:

- Compare the single dose comparative bioavailability of trazodone from trazodone hydrochloride oral solution 100 mg/ 10 mL (test product) with trazodone hydrochloride tablets 100 mg (reference product) under fed conditions.
- Evaluate the food effects of trazodone hydrochloride oral solution 100 mg/ 10 mL.
- Monitor the safety and tolerability of a single dose of the study product.

Trial Design

This was a randomized, open-label, three-treatment, three-period, crossover, oral comparative bioavailability study in 42 healthy adult subjects. Subjects received trazodone oral tablets 100 mg under fed conditions (Treatment 1), trazodone oral solution 100 mg under fed conditions (Treatment 2), or trazodone oral solution 100 mg under fasted conditions (Treatment 3) across three study period. Between Periods 1 and 2 and Periods 2 and 3, all subjects underwent a 7-day and 10-day washout period, respectively. The Applicant planned to conduct the study at a single clinical study center in Chennai, India. All subjects remained in the clinic for at least 11 hours before dosing and for at least 24 hours post-dose in each study period. Subjects returned to the study site for additional assessments 48 hours after dosing. Fasting conditions included 10 hours pre-dose to at least 4 hours post dose; fed conditions included a standardized high-calorie, high-fat breakfast consumed 30 minutes prior to dosing within 30 minutes duration (after overnight fasting of at least 10 hours, with the next standardized meal at least 4 hours post-dose).

Study Eligibility Criteria

The target study population consisted of males or non-pregnant, non-lactating females, 18 to 45 years of age (inclusive), judged to be healthy during screening within 21 days prior to study commencement by psychical examination, clinical laboratory assessments, electrocardiogram results, and chest X-ray. Subjects were also required to have a total body of at least 50 kg and a

body mass index between 18.5 and 29.9 kg/m^2. Females of child-bearing potential must have agreed to use an acceptable method of contraception at least 2 days prior to dosing, during the study, and for at least 7 days following their last dose of study medication; male subjects must have also agreed to use contraception.

The Applicant excluded subjects with current or history of significant diseases or clinically significant abnormal findings during screening. Other pertinent exclusionary criteria consisted of: history or presence of alcohol dependence or drug abuse within the past year; an "every-day" smoker or consumption of tobacco products; history of allergic reactions after taking any medication; hypersensitivity to heparin; surgery anytime during the study period or within 7 days after study completion; history of difficulty in donating blood or unsuitable veins for repeated venipuncture; hospitalization within 28 days prior to study drug administration; systolic blood pressure <90 mmHg or >140 mmHg; or diastolic blood pressure <60 mmHg or >90mmHg.

Subjects could not use tobacco, alcohol, xanthine containing food and beverages, or herbal preparations containing substances known to affect cytochrome enzymes within 48 hours prior to Period 1 and throughout the study. Concomitant administration of antifungals, barbiturates, carbamazepine, central nervous system depressants, digoxin, protease inhibitors, phenothiazines, phenytoin, antidepressants, and warfarin were prohibited. Consumption of any medication (including over-the-counter products and recreational drugs) was not allowed within 14 days of Period 1 and throughout the study.

Study Procedures

The Applicant conducted a urine drug screen, pregnancy test, and clinical laboratory assessments prior to check-in for each study period. Vital signs were measured at check-in, 2 hours prior to dosing, at 1, 2, 3, 6, and 13 hours post-dose, and during the ambulatory visit in each study period. Clinical laboratory assessments were also collected at baseline and end of study.

Subjects could withdraw or be withdrawn for several reasons including significant intercurrent illness or surgery, having entered in violation of the study protocol (e.g., noncompliance with diet, alcohol, or drug use), or use of an unacceptable concomitant medication, or post-dose vomiting at or before 2 hours for Treatment 3 or 4 hours for Treatments 1 and 2 (based on median Tmax for trazodone in fed and fasted conditions).

> *Clinical Reviewer Comment: The study design—including the objectives, eligibility criteria, and safety monitoring—is generally acceptable for this comparative bioavailability study.*

Study Endpoints

The primary endpoint of the study was to evaluate the comparative bioavailability of 100 mg

trazodone oral solution with that of 100 mg trazodone oral tablets under fed conditions and the comparative bioavailability of 100 mg trazodone oral solution when administered under fed and fasted conditions.

> *Clinical Reviewer Comment*: *The endpoints appear acceptable for this combined comparative bioavailability and food effect study.*

Statistical Analysis Plan

Primary PK parameters included Cmax, AUC_{0-t}, and $AUC_{0-\infty}$. Secondary PK parameters included Tmax, half-life, and λ_z (terminal elimination rate constant). PK analyses included data from all subjects who successfully completed at least Treatments 1 and 2 (reference and test product under fed conditions) and Treatments 2 and 3 (test product under fed and fasted conditions). The Applicant used Phoenix WinNonlin Version 8.1 to generate PK parameters, which were subject to descriptive statistics (i.e., arithmetic mean, geometric mean, standard deviation, coefficient of variance, median, maximum, and minimum).

The Applicant statistically evaluated ln-transformed data of Cmax, AUC_{0-t}, and $AUC_{0-\infty}$. using PK parameter specific PROC MIXED effect Analysis of Variance (ANOVA) models (SAS version 9.4) with the main effect of treatment, period, and sequence as fixed effects, and subject nested within sequence as a random effect. The Applicant tested the sequence effect at the 0.10 level of significance using the subjects nested within sequence mean square from the ANOVA as the error term. All other main effects were tested at the 0.05 level of significance against the residual error (mean square error) from the ANOVA as the error term.

Based on the 90% confidence intervals for the difference of means of In-transformed Cmax, AUC_{0-t}, and $AUC_{0-\infty}$, the Applicant determined whether the test product is bioequivalent to the reference product under fed condition. The acceptance range for bioequivalence is 80% to 125% for the 90% confidence intervals for the difference of means of In-transformed Cmax, AUC_{0-t}, and $AUC_{0-\infty}$. The Applicant tested the potential for food effects for the test product (trazodone oral solution) based on the ratio of geometric least square means with the corresponding 90% confidence intervals calculated from the exponential of the difference between the data under fed and fasting condition (Treatment 2 and Treatment 3) for the In-transformed parameters Cmax, AUC_{0-t}, and $AUC_{0-\infty}$.

Considering intra-subject variability of approximately 28%, test/reference ratio of 95%, and achieving at least 80% power, the Applicant estimated that 34 subjects were required to establish bioequivalence between two formulations. To account for withdrawals and dropouts due to adverse events or non-compliance or due to personal reasons, the Applicant intended to randomize and dose 42 subjects.

Protocol Amendments

The Applicant issued the original protocol (Version 1) on May 9, 2022. The Applicant did not report any protocol amendments.

> *Clinical Reviewer Comment*: *Refer to the Section 6 regarding the acceptability of the PK analysis from a clinical pharmacology perspective. Of note, the Applicant submitted an IND exemption on July 8, 2022. The Agency granted IND exemption on July 11, 2022, as per 21 CFR 312.120.*

8.1.2. Study Results

Compliance with Good Clinical Practices

In their clinical study report, the Applicant states that the study was conducted in accordance with the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practice (GCP) Guidelines, the Indican Council of Medical Research (ICMR) Ethical guidelines, and all Indian and FDA regulatory requirements. Per 21 CFR 312.120 regarding foreign clinical studies not conducted under an IND, within this NDA submission, the Applicant has submitted: the investigator's qualifications, a description of the research facilities, a detailed protocol, a description of the drug substance, the name and address of the Independent Ethics Committee and statement of approval, a description of informed consent and incentive structure, a description of quality control/assurance auditing, and a statement regarding adherence to GCP.

Financial Disclosure

See Section 19.2 of this review for detailed financial disclosure information. There are no disclosed financial interests or arrangements or missing disclosures that raise questions about the integrity of study data.

Patient Disposition

The Applicant enrolled and dosed 42 subjects (14 subjects per treatment sequence). Only 39 subjects that completed at least two treatment periods (either Treatment 1 and Treatment 2, or Treatment 2 and Treatment 3) were considered for PK and statistical analysis. The Applicant did not use missing values for calculation of PK parameters. Of the three subjects excluded from the analysis, one subject (randomized to Sequence 3) experienced vomiting in Period 3, one subject (randomized to Sequence 2) did not comply with protocol requirements for Periods 2 and 3, and one subject (randomized to Sequence 1) did not report to the study facility on day of check-in in Period 3.

Protocol Violations/Deviations

The Applicant did not note any major protocol deviations; however, there were 20 blood

sample collection deviations that were a result of collecting the blood sample after the prespecified time of collection (subjects did not report to visit on time or difficulty in drawing blood). The Applicant noted that appropriate corrections (i.e., using the actual time of blood sampling) were utilized during PK analysis to estimate parameters for bioequivalence assessment.

Baseline Demographic Characteristics

See Table 2 for a summary of demographic and baseline characteristics among subjects who received treatment.

Table 5. Baseline Demographic Characteristics (Study 097-21).

Demographic Characteristics	Total Treated Subjects (N=42)
Age (years)	
Mean (SD)	33.5 (6.2)
Median (Range)	34 (22, 43)
Sex, n (%)	
Male	34 (81%)
Female	8 (19%)
Weight (kg), mean (SD)	69.0 (11.2)
Height (cm), mean (SD)	165.3 (10.4)
BMI (kg/m^2), mean (SD)	25.3 (3.3)

Abbreviations: BMI = body mass index; SD = standard deviation
Source: Clinical reviewer-created using Applicant's Clinical Study Report Tablet 20 (p 62).

> *Clinical Reviewer Comment*: *Given that the Applicant conducted this study at a single study site in India and the limited sample size, it is expected that the subjects' demographic characteristics will not serve as a representative sample of the general U.S. adult population. However, the product label for the LD does not describe any clinically significant differences in the exposures based on age, [redacted] or race. Therefore, it is unlikely that differences in demographic characteristics will affect the applicability of the study results to a general U.S. study population.*

Other Baseline Characteristics

Subjects were excluded for current significant conditions or use of concomitant medications within various timeframes of dosing, as described above.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

According to the Applicant, all subjects were dosed in the presence of the investigator. No subject required concomitant medications at the discretion of the investigator.

Efficacy Results

The Applicant proposes to rely on the Agency's prior findings of efficacy for the LD with a scientific PK bridge to trazodone hydrochloride tablets; see Section 6 for PK results. Based on the PK and statistical analysis, the Applicant was able to demonstrate that the geometric mean ratios of PK parameters for trazodone oral solution are within the 80% to 125% bioequivalent limit comparable to the LD under fed conditions. The PK bridge between trazodone oral solution and the LD is acceptable. Therefore, the efficacy of trazodone oral solution is expected to be similar to the LD. Trazodone oral solution, similar to the oral tablet formulation, should be administered after a meal or light snack.

The Applicant also determined that the Cmax was lower by approximately 30% under fed state compared to fasting state; however, overall exposure (AUC) was not affected by food intake. The extent of food effect observed with trazodone oral solution is similar to the LD. Therefore, the slight reduction in Cmax under fed state compared to fasted state is deemed clinically not meaningful. See Section 6 for additional information.

Data Quality and Integrity

The reviewers found the quality and integrity of the submitted data satisfactory and acceptable for the review.

8.2. Review of Safety

8.2.1. Safety Review Approach

The Applicant proposes to rely on the Agency's prior findings for safety for the LD with a scientific bridge to trazodone oral trazodone. Given that the application consists of a single PK study (Study 097-21) with a limited sample size, this review will assess whether the collected safety data is consistent with trazodone's known safety profile. See Section 8.1.1 for additional information on Study 097-21. Of note, post-treatment safety assessments included adverse event (AE) monitoring, vital signs, and clinical laboratory tests.

8.2.2. Review of the Safety Database

Overall Exposure

A total of 42 subjects were enrolled in the study and treated with at least one dose of trazodone 100 mg (either as an oral tablet or solution). Therefore, all subjects contributed to the safety analysis population.

> *<u>Clinical Reviewer Comment</u>: Trazodone is recommended to be administered as titration-based regimen. The doses are escalated based on clinical response and tolerability. Due to safety concerns associated with the use of trazodone, a single dose comparative*

bioavailability study was conducted with a 100 mg dose in healthy subjects as per the product specific guidance for trazodone hydrochloride oral tablet. Although trazodone exhibits linear PK characteristics (i.e., establishment of a scientific bridge would extrapolate to the approved trazodone range), the observed safety profile in this study maybe an underestimation of the safety profile observed in patients using a maximum daily dosage of 400 to 600 mg/day.

Adequacy of the Safety Database

Given the limited sample size of subjects receiving trazodone in this program, the evaluation of safety is purely descriptive.

Clinical Reviewer Comment: As noted above in Section 8.1.2, the demographic characteristics of enrolled subjects do not reflect the general U.S. population. However, significant PK differences between age, [redacted] and ethnic groups are not expected according to the LD label.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

From a safety perspective, there are no issues regarding data integrity and submission quality.

Categorization of Adverse Events

The Applicant categorized AEs by system organ class and preferred terms using the Medical Dictionary for Regulatory Activities Version 25.1. The Applicant collected AEs throughout each study period. The Applicant defined treatment-emergent adverse events (TEAEs) as "any untoward medical occurrence (including a symptom or disease or an abnormal laboratory finding) during treatment with an investigational drug," regardless of causality. The Applicant also appropriately defined severity of AEs and serious AEs. Investigators followed up on all unresolved AEs until the events were resolved, the subject was lost to follow-up, or the AE is otherwise unexplained. The Applicants protocol also including appropriate guidelines for reporting serious AEs; however, there were no specified AEs of special interest. Any subject with an abnormal laboratory test will be monitored until repeat tests return to normal or acceptable levels.

Routine Clinical Tests

Investigators assessed vital signs at check-in, prior to dosing on the day of dosing (within 2 hours prior to dosing), and at 1, 2, 3, 6, and 13 hours post dosing, during check-out at each study period, and at ambulatory visits. Clinical safety laboratory tests (i.e., chemistry and hematology) were collected at baseline and end-of-study. An electrocardiogram (ECG) was performed at baseline.

Clinical Reviewer Comment: The Applicant adequately described their AE monitoring approach, AE severity determinations, and clinical laboratory testing procedures. However, the Applicant did not describe how clinical significance was determined for vital signs or abnormal laboratory tests.

8.2.4. Safety Results

Deaths

The Applicant did not report any deaths.

Serious Adverse Events

The Applicant did not report any serious AEs.

Dropouts and/or Discontinuations Due to Adverse Effects

One subject (1/42; 2.3%) discontinued from the study while participating in Sequence 3, Period 3 after experiencing vomiting.

Treatment Emergent Adverse Events and Adverse Reactions

In Study 097-21, a total of 14 AEs were reported in 13 (31%) subjects. All AEs, including laboratory abnormalities, were considered mild and all were resolved by the end of the observation period. Two subjects (4.8%) reported vomiting; one event in a subject receiving trazodone oral solution under fed conditions, and one event in a subject receiving trazodone oral solution under fasted conditions (one subject discontinued from the study due to vomiting as noted above). AEs related to abnormal laboratory findings are described in Table 3. All subjects who reported decreased hemoglobin also had values below the normal reference range at screening. Both subject with elevated alanine aminotransferase (58 U/L and 62 U/L) after the study period, also had elevated alanine aminotransferase at screening (50 U/L and 56 U/L).

Table 6. Incidence of AEs Related to Laboratory Abnormalities (Study 097-21).

Adverse Events Related to Abnormal Laboratory Values	Safety Population (N=42)
Decreased hemoglobin	5 (12%)
Increased alanine aminotransferase	2 (4.8%)
Increased eosinophils	1 (2.4%)
Increased random blood glucose	1 (2.4%)
Increased erythrocyte sedimentation rate	2 (4.8%)
Increased total white blood cell count	1 (2.4%)

Source: Clinical reviewer-created using Applicant's Clinical Study Report.

Clinical Reviewer Comment: AEs captured in Study 097-21 do not appear to indicate a new or worsened safety signal for trazodone oral solution. As noted, per the LD label, vomiting is one of the most common adverse reactions for the LD. It is important to note that the collection of the clinical laboratory assessments at baseline and end of study confounds a causality assessment given that the majority of subjects received all three treatments. Given that the Applicant was able to establish a scientific bridge to the LD, the safety profile for trazodone oral solution is expected to be consistent with the LD.

Laboratory Findings

Other than the AEs related to laboratory assessments described above, there were no other clinically significant laboratory assessment abnormalities. The Applicant did not report any worsening shifts from normal to abnormal laboratory assessments.

Vital Signs

Vital signs generally fell within the normal range, and none of the pre- or post-dose individual vital sign abnormalities were considered clinically significant. The Applicant did not report any worsening shifts from normal to abnormal vital sign measurements.

Electrocardiograms (ECGs)

ECGs performed at screening were within normal limits. ECGs were not conducted at the end of the study.

Immunogenicity

The Applicant did not report any potentially immunogenicity-related AEs.

8.2.5. Safety Analyses by Demographic Subgroups

Given the limited sample size and the lack of demographic differences (e.g., age, race, sex, region), the Applicant did not report (nor did the Division conduct) any subgroup safety analyses.

8.2.6. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The study drug labeling will include postmarketing experience of adverse reactions for the LD (as described in Section 6.2 of labeling):

- Blood and lymphatic system disorders: hemolytic anemia, leukocytosis
- Cardiac disorders: cardiospasm, congestive heart failure, conduction block, orthostatic

hypotension and syncope, palpitations, bradycardia, atrial fibrillation, myocardial infarction, cardiac arrest, arrhythmia, ventricular ectopic activity, including ventricular tachycardia and QT prolongation.

- Endocrine disorders: inappropriate ADH syndrome
- Eye disorders: diplopia
- Gastrointestinal disorders: increased salivation, nausea/vomiting
- General disorders and administration site conditions: chills, edema, unexplained death, weakness
- Hepatobiliary disorders: cholestasis, jaundice, hyperbilirubinemia, liver enzyme alterations
- Investigations: increased amylase
- Metabolism and nutrition disorders: methemoglobinemia
- Nervous system disorders: aphasia, ataxia, cerebrovascular accident, extrapyramidal symptoms, grand mal seizures, paresthesia, tardive dyskinesia, vertigo
- Psychiatric disorders: abnormal dreams, agitation, anxiety, hallucinations, insomnia, paranoid reaction, psychosis, stupor
- Renal and urinary disorders: urinary incontinence, urinary retention Reproductive system and breast disorders: breast enlargement or engorgement, clitorism, lactation, priapism
- Respiratory, thoracic, and mediastinal disorders: apnea
- Skin and subcutaneous tissue disorders: alopecia, hirsutism, leukonychia, pruritus, psoriasis, rash, urticaria
- Vascular disorders: vasodilation

Expectations on Safety in the Postmarket Setting

Given that the Applicant has demonstrated that the geometric mean ratios of PK parameters for trazodone oral solution are within the 80% to 125% bioequivalent limit comparable to the LD when administered under fed conditions, trazodone oral solution is expected to have a similar safety profile in the postmarketing setting as the LD.

8.3. Conclusions and Recommendations

The Applicant demonstrated an adequate scientific bridge between their test product, trazodone oral solution and the LD, trazodone oral tablets under fed conditions. Therefore, the Applicant can rely on the Agency's previous findings of safety and efficacy of the LD. Trazodone oral solution is expected to have a similar safety profile as the LD when administered after a meal or light snack.

9 Advisory Committee Meeting and Other External Consultations

An Advisory Committee meeting was not convened for this submission. This 505(b)(2) application relies on the findings of safety and efficacy of the LD. There were no questions for an Advisory Committee.

10 Pediatrics

As noted in Section 3.2, the Applicant failed to address the requirements under PREA (lack of an agreed initial pediatric study plan (iPSP) submitted with the NDA within 210 days), the Division refused to file the original NDA under 21 CFR 314.101(d). The Division had noted in several previous communications (e.g., written responses to the pre-IND meeting and pre-NDA meeting requests) that a pediatric assessment is required for their new trazodone dosage formulation.

On January 8, 2024, the Applicant submitted an agreed iPSP that included pediatric assessments to evaluate children 7 to 12 years of age and adolescents for the treatment of MDD. The Agency agreed with a partial waiver for studies in children younger than 7 years of age because studies would be impossible or highly impractical due to the rarity of the diagnosis of MDD. The Agency also agreed to a deferral for studies in children aged 7 to 12 years and adolescents 13 to 17 years of age.

In alignment with the agreed iPSP and to fulfill the requirements of PREA, the Agency communicated the following postmarketing study requirements (PMR) in the 8-week PMR Communication Letter:

1. Conduct a juvenile animal study to assess the safety of Raldesy in animals of an age range and stage of development that are comparable to the population of children 7 to 12 years.

2. Conduct a randomized, double-blind, placebo-controlled study to assess the safety, efficacy, and pharmacokinetics of Raldesy for the treatment of major depressive disorder in adolescents 13 through 17 years of age.

3. Conduct a randomized, double-blind, placebo-controlled study to assess the safety, efficacy, and pharmacokinetics of Raldesy for the treatment of major depressive disorder in a mixed child and adolescent population 7 through 17 years of age.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information

The Applicant submitted draft labeling that generally aligned with approved labeling for the LD. The label was revised to use product-specific language where appropriate and to include the following:

- Section 12.3 (Clinical Pharmacology: Pharmacokinetics): Pharmacokinetics was revised to include relevant PK measures and parameters that are important for the safe and effective use of trazodone hydrochloride oral solution, as per current labeling guidance.

- Section 14 (Clinical Studies): Clarified that the efficacy of trazodone oral solution for the treatment of MDD is based on prior studies of the immediate-release trazodone hydrochloride oral tablets.

Of note, Section 3 (Dosage Forms and Strengths), Section 11 (Description), and Section 16 (How Supplied/Storage and Handling) are specific to the new dosage formulation (oral solution) relative to the LD (oral tablets) product label.

Medication Guide
The Medication Guide was reformatted to current standards per recommendations from Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP).

Instructions for Use
The LD does not have an Instructions for Use (IFU). The Applicant's submitted IFU included descriptions for use of the medication dispensing system, bottle preparation, medication measurement, and administration. The IFU was revised for ease of readability per recommendations from DMPP and OPDP.

12 Risk Evaluation and Mitigation Strategies (REMS)

No specific risk evaluation and mitigation strategies are recommended as the safety profile trazodone oral solution is not expected to differ from the LD.

13 Postmarketing Requirements and Commitment

Other than the PREA PMRS listed in Section 10, there are no additional PMRs or postmarketing commitments recommended.

14 Clinical Deputy Division Director (Signatory) Comments

This review reflects my edits and feedback. I agree with the findings as described by the review team and concur with the approval decision.

15 Appendices

15.1. References

American Psychiatric Association, 2010, Practice Guideline for the Treatment of Patients with Major Depressive Disorder, Third Edition, Arlington (VA): American Psychiatric Association.

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Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D Report. *Am J Psychiatry*. 2006;163(11):1905-17.

Substance Abuse and Mental Health Services Administration, 2023, Key Substance Use and Mental Health Indicators in the United States: Results From the 2022 National Survey on Drug Use and Health (HHS Publication No. PEP23-07-01-006, NSDUH Series H-58), Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration, accessed January 5, 2024, https://www.samhsa.gov/data/report/2022-nsduhannual-national-report.

Walker ER, McGee RE, and Druss BG. Mortality in mental disorders and global disease burden implications: A systematic review and meta-analysis. *JAMA Psychiatry*. 2015;72:334-41.

15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): 97-21

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 7		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Not applicable Significant payments of other sorts: Not applicable Proprietary interest in the product tested held by investigator: Not applicable Significant equity interest held by investigator in Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. Clinical Pharmacology

Bioanalysis

Plasma concentrations of trazodone were quantified using validated liquid chromatography with tandem mass spectrometry (LC/MS/MS) using trazodone-D6 as the internal standard.

Table 7: Bioanalytical Method Validation Summary.

Analyte		Trazodone Hydrochloride
Internal Standard (IS)		Trazodone D6 Hydrochloride
Matrix		Human plasma
Transition Monitored, Multiple Reaction Monitoring (MRM) (m/z)		Trazodone: 372.167 -> 176.050 Trazodone D6: 378.205 -> 182.090
Retention Time (min)		Trazodone: 3.40 min Trazodone D6: 3.34
Calibration	Range (ng/mL)	1.999 to 3997.000 ng/mL
	#Conc. points	1.999, 3.997, 199.850, 399.700, 799.400, 1598.800, 2398.200, 3197.600, 3997.000 ng/mL
	%CV (precision)	<15 %
	%RE (bias)	-4.97 to 4.70 %
Quality Control	Concentrations (µg/mL)	LLOQ: 2.004 ng/mL LQC: 5.010 ng/mL MQC: 2004.000 ng/mL HQC: 3406.800 ng/mL
	%CV	<15 %
	%Bias	- 5.49 to - 1.50 %
	Dilution Factor	4-fold
Long-term Stability in Matrix Validated		92 days at -20±5°C & -70±10°C
Short-term Stability in Matrix Validated		LQC and HQC in ice-cold water bath and room temperature after 08 hrs and 03 mins, and 21 hrs and 49 mins, respectively.
Longest storage period		61 days at -70±10°C
Date Range of Bioanalytical Assays		32 days (22 December 2022 to 22nd January 2023)

Abbreviations: CV- Coefficient of Variation; HQC- High Quality Control; LLOQ- Lower Limit of Quantification; LQC- Low Quality Control; RE: Relative Error
Source: Adapted from the bioanalytical report for Study (b) (4)

Out of 3079 samples, 263 samples were selected for incurred sample reanalysis (ISR), in which 100% of ISR concentrations were found to be within 20% of the mean of initial and incurred concentrations. Carryover of trazodone peaks was less than 20% of lower limit of quantitation (LLOQ) and is acceptable. Freeze-thaw stability was established with five cycles of freeze at -70°C ± 10°C.

Reviewer's comments: The bioanalytical methods satisfy the criteria for "method validation" and "application to routine analysis" set by the guidance for industry, Bioanalytical Method Development *(May 2018), and are acceptable.*

Individual Study Report

Title

A randomized, open label, balanced, three-treatment, three-period, crossover, oral comparative bioavailability study of trazodone hydrochloride oral solution 100 mg/ 10 mL of Rubicon Research Pvt. Ltd., India comparing with trazodone hydrochloride tablet, USP 100 mg, manufactured for: Apotex Corp., Weston, Florida, 33326, in healthy human adult subjects.

Primary Objectives

- Compare the single dose comparative bioavailability of trazodone from trazodone hydrochloride oral solution 100 mg/ 10 mL (Test Product (A)) of Rubicon Research Pvt. Ltd., India with tradozone hydrochloride tablets, USP 100 mg (Reference Product), manufactured for Apotex Corp., Weston Florida, 33326 in healthy human adult subjects under fed conditions.

- Evaluate the effects of food on the PK of trazodone hydrochloride oral solution 100 mg/ 10 mL (Test Product) of Rubicon Research Pvt. Ltd., India in healthy human adult subjects.

Study Design

- A randomized, open-label, balanced, three-treatment, three-period, crossover, oral comparative bioavailability study in 42 healthy human (8 female, 34 male) subjects.

Study Scheme

No. of subjects	Period 1	Period 2	Period 3
14	Treatment 1	Treatment 2	Treatment 3
14	Treatment 2	Treatment 3	Treatment 1
14	Treatment 3	Treatment 1	Treatment 2
Treatment (T1) = TraZODONE Hydrochloride Tablets, USP 100 mg [Reference Product (B)], Manufactured for: Apotex Corp., Weston Florida, 33326 under fed conditions. Treatment (T2) = Trazodone Hydrochloride oral solution 100 mg/ 10 mL [Test Product (A)] of Rubicon Research Pvt. Ltd., India under fed conditions. Treatment (T3) = Trazodone Hydrochloride oral solution 100 mg/ 10 mL [Test Product (A)] of Rubicon Research Pvt. Ltd., India under fasting conditions.			

Source: Clinical study report for Study 097-21, Table-3, p. 29.

Treatments Administered

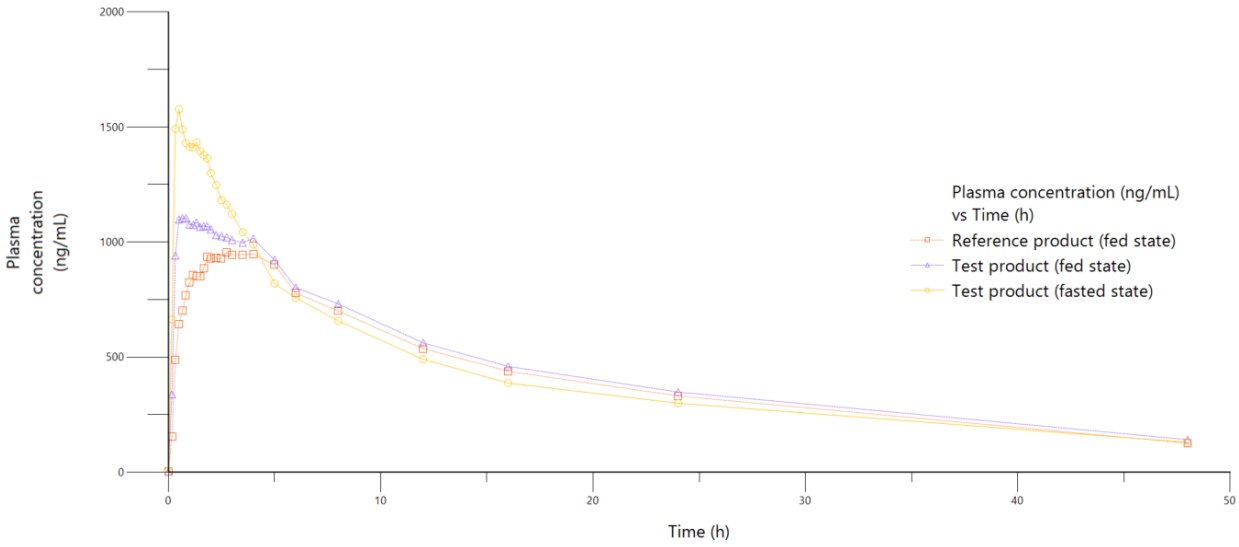
- Reference Product: Tradozone hydrochloride tablets, USP 100 mg, Manufactured for: Apotex Corp., Weston Florida, 33326.

- Test Product: Trazodone hydrochloride oral solution 100 mg/ 10 mL of Rubicon Research Pvt. Ltd., India.

Pharmacokinetic Sampling: Blood samples were collected at pre-dose and post-dose at 00.17, 00.33, 00.50, 00.67, 00.83, 01.00, 01.17, 01.33, 01.50, 01.67, 01.83, 02.00, 02.25, 02.50, 02.75, 03.00, 03.50, 04.00, 05.00, 06.00, 08.00, 12.00, 16.00, 24.00, and 48.00 hours after each treatment period.

The mean plasma concentration-time profile and the PK parameters following a single oral dose administration of the reference product (fed condition) and test product (fed and fasted condition) is shown below in Figure 1 and in Table 8, Table 9, and Table 10, respectively.

Figure 1. Mean Plasma Trazodone Concentration-Time Profiles after Single Oral Dose Administrations of 100 mg Trazodone Hydrochloride Tablet 100 mg (Reference Product) under Fed State and 10 mL of Trazodone Hydrochloride Oral Solution 100 mg/10 mL (Test Product) under Fed and Fasted Conditions.



Source: Reviewer's analysis.

Table 8. Plasma Pharmacokinetic Parameters of Trazodone in Plasma after Single Oral Dose Administrations of Trazodone Hydrochloride 100 mg (Reference Product) under Fed Conditions.

Pharmacokinetic Parameters of Trazodone (ng/mL) for Reference Under Fed (T1)						
Parameter	**t_{half} (hr)**	**K_{el} (1/hr)**	**t_{max} (hr)**	**C_{max} (ng/mL)**	**AUC_{0-t} (hr*ng/mL)**	**AUC_{0-inf} (hr*ng/mL)**
N	37	37	37	37	37	37
Mean	17.7429	0.0425	2.6289	1257.3961	19221.5830	23385.4314
Standard Deviation	5.14430	0.01298	1.80098	395.01560	4587.45789	7615.61604
Minimum	8.711	0.025	0.170	767.608	10935.036	11582.733
Median	16.220	0.043	2.500	1165.284	17995.201	22863.144
Maximum	28.138	0.080	8.000	2445.146	28772.750	46791.027
CV%	28.99	30.51	68.51	31.42	23.87	32.57
Geometric Mean	17.014	0.041	1.897	1204.874	18676.891	22236.836

Source: Applicant's synopsis of study report for Study 097-21, p. 6.

Table 9. Plasma Pharmacokinetic Parameters of Trazodone in Plasma after Single Oral Dose Administrations of Trazodone Hydrochloride Oral Solution 100mg/10mL (Test Product) under Fed Conditions.

Pharmacokinetic Parameters of Trazodone (ng/mL) for Test Under Fed (T2)						
Parameter	**t_{half} (hr)**	**K_{el} (1/hr)**	**t_{max} (hr)**	**C_{max} (ng/mL)**	**AUC_{0-t} (hr*ng/mL)**	**AUC_{0-inf} (hr*ng/mL)**
N	39	39	39	39	39	39
Mean	17.9291	0.0428	1.7923	1348.0613	20984.7615	25465.6832
Standard Deviation	6.76573	0.01293	1.56069	327.94103	5891.73223	11248.03447
Minimum	9.369	0.014	0.330	796.458	11255.239	11560.774
Median	15.955	0.043	1.000	1305.862	20109.726	23758.238
Maximum	48.185	0.074	5.000	2032.266	41386.779	79271.633
CV%	37.74	30.20	87.08	24.33	28.08	44.17
Geometric Mean	16.980	0.041	1.203	1308.930	20247.547	23801.103

Source: Applicant's synopsis of study report for Study 097-21, p. 6.

Table 10. Plasma Pharmacokinetic Parameters of Trazodone in Plasma after Single Oral Dose Administrations of Trazodone Hydrochloride Oral Solution 100mg/10mL (Test Product) under Fasted Conditions.

Pharmacokinetic Parameters of Trazodone (ng/mL) for Test Under Fasting (T3)						
Parameter	**t_{half} (hr)**	**K_{el} (1/hr)**	**t_{max} (hr)**	**C_{max} (ng/mL)**	**AUC_{0-t} (hr*ng/mL)**	**AUC_{0-inf} (hr*ng/mL)**
N	37	37	37	37	37	37
Mean	19.1093	0.0405	1.1073	1935.7503	19665.0333	24308.7893
Standard Deviation	6.61926	0.01345	0.88773	611.74421	6740.16140	12019.94947
Minimum	9.533	0.018	0.170	1024.705	11048.938	11276.004
Median	18.427	0.038	0.850	1800.281	17831.801	23576.005
Maximum	39.406	0.073	4.000	3870.976	49077.683	82111.398
CV%	34.64	33.24	80.17	31.60	34.27	49.45
Geometric Mean	18.079	0.038	0.790	1849.283	18822.463	22448.190

AUC=area under the curve; C_{max}=peak plasma concentration; T_{max}=time post dose to reach peak plasma concentration; K_{el}=elimination rate constant; $t1_{/2}$=half life
Subjects (b) (6) did not complete the study and were excluded from PK analysis. The reason(s) for not completing the study are as follows:
- *Subject (b) (6) experience Adverse event - Vomiting in period 3.*
- *Subject is not complying to the protocol requirements in period 2 and period 3.*
- *Subject did not report to the study facility on the day of check-in in period 3.*

Source: Applicant's synopsis of study report for Study 097-21, p. 6.

Clinical Pharmacology Reviewer Comment: The reviewer's analysis produced results that are consistent with the Applicant's results. The scientific bridge between trazodone hydrochloride oral solution 100 mg/ 10 mL and trazodone hydrochloride tablet (100 mg) is adequate. Therefore, trazodone hydrochloride oral solution can rely on the Agency's previous findings of safety and efficacy of the LD, trazodone hydrochloride tablet.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BERNARD A FISCHER
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