CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021164Orig1s000

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research
Office of New Drugs, ODE-IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
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MEMORANDUM TO FILE

Date of Consult Request:	January 23, 2023
From:	The Division of Psychiatry (DP)
To:	Division of Pediatric and Maternal Health (DPMH)
NDA:	021164
Drug:	Gepirone
Applicant:	Fabre-Kramer Pharmaceuticals, Inc.
Indication:	Treatment of Major Depressive Disorder

DP submitted a consult request to DPMH on January 23, 2023: "Pediatric – Review the submitted pediatric study reports draft labeling and provide labeling recommendations."

DPMH attended the labeling meetings. The Agency approved this NDA September 22, 2023; thus, this memorandum will close out the consult request.

DPMH Pediatric MTL:	Shetarra Walker
DPMH Pediatric Reviewer:	Carla Epps
DPMH RPM:	Denise Pica-Branco
DPMH SCSO:	Rosemary Addy

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/s/

DENISE J PICA-BRANCO
09/25/2023 07:45:57 AM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency

Date:	September 18, 2023
Reviewer(s):	Andrew D. Mosholder, MD, MPH Division of Epidemiology I
Team Leader:	Yandong Qiang, MD, PhD, MPH, MHS Division of Epidemiology I
Deputy Director:	Wei Hua, MD, PhD, MHS, MS Division of Epidemiology I
Subject:	ARIA Sufficiency Memo for safety evaluation of gepirone during Pregnancy/Lactation exposure
Drug Name(s):	Gepirone hydrochloride, extended release (ER)
Application Type/Number:	NDA 021164
Applicant/sponsor:	Fabre-Kramer Pharmaceuticals, Inc.
Task Tracking Tool #:	2023-4918

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type	
-Initial	
-Interim	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	
-Yes	
-No	X
If "No", please identify the area(s) of concern.	
-Surveillance or Study Population	
-Exposure	
-Outcome(s) of Interest	X
-Covariate(s) of Interest	X
-Surveillance Design/Analytic Tools	X

1. BACKGROUND INFORMATION

1.1. Medical Product

Gepirone is a selective agonist at 5-hydroxytryptamine (serotonin) 1A 5HT1A receptors that is currently not marketed in any country. It has been developed as an antidepressant. Fabre-Kramer Pharmaceuticals's New Drug Application (NDA) 021164, for EXXUA (gepirone HCl Extended-Release Tablets) for the indication of treatment of major depressive disorder (MDD) is under the review of U.S. Food and Drug Administration (FDA). The regulatory history of this compound spans a number of years and has involved multiple sponsors.[a] The original NDA for MDD was submitted September 30, 1999 but was not filed because FDA determined that there were not two adequate and well-controlled studies demonstrating efficacy. Subsequent resubmissions of the NDA resulted in three Not Approvable actions (March 15, 2002, June 23, 2004, November 2, 2007), all because of deficiencies in the demonstration of efficacy.

Since the time of the 2007 NDA submission,[b] the sponsor reports conducting only additional Phase 1-type clinical trials of gepirone. On June 13, 2014, the sponsor requested a formal dispute resolution regarding the past Not Approvable actions. An Advisory Committee meeting regarding gepirone in the treatment of MDD was held December 1, 2015;[c] the Psychopharmacologic Drugs Advisory Committee voted against approval. However, on March 16, 2016, the Office of New Drugs granted the sponsor's appeal, concluding that there was in fact substantial evidence of efficacy for gepirone in the treatment of depression.[d] This decision resulted in the current resubmission of the NDA, December 23, 2022

According to the sponsor's proposed labeling, the recommended starting dose for the treatment of MDD is 20 mg/day, which may be titrated up to a maximum of 80 mg/day if needed.

The Prescription Drug User Fee Amendment goal date is September 23, 2023.

1.2. Describe the Safety Concern

The sponsor reports a total of 20 pregnancy exposures to gepirone during clinical trials.[e] Of these, there were 9 with unknown outcomes, 6 full-term births with no congenital malformations, 1 preterm birth, 1 elective abortion, 1 spontaneous abortion, and 2 cases of dilation and curettage (one of which involved absent fetal heart tones in a fetus with a cystic hygroma).[f] A literature

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[a] Regulatory History. Prepared by Sarah Seung, Division of Psychiatry, May 23. 2023.

[b] Fabre-Kramer Pharmaceuticals. NDA 21-164. Response to June 23, 2004 Action Letter, submitted May 1, 2007.

[c] Summary Minutes Meeting of the Psychopharmacologic Drugs Advisory Committee December 1, 2015. Available at https://wayback.archive-it.org/7993/20170403224141/https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/ucm461701.htm

[d] Appeal Granted letter, NDA 21164, March 16, 2016.

[e] Fabre-Kramer Pharmaceuticals. NDA 21164. Response to the Division of Pediatric and Maternal Health Information Request dated January 31, 2023.

[f] Jeannie Limpert, Medical Officer, DPHM, personal communication July 31, 2023.

search by the sponsor found no clinical studies of the safety of gepirone use during pregnancy or lactation.[g]

Accordingly, given the small number of pregnancy exposures with known outcomes, a knowledge gap remains regarding the safety of gepirone during pregnancy and lactation. With respect to pregnancy risks of other antidepressants, class pregnancy labeling for selective serotonergic reuptake inhibitors (SSRIs) and serotonergic norepinephrine reuptake inhibitors (SNRIs) notes that their use during pregnancy is associated with an increased risk for neonatal complications.

As described in the class pregnancy labeling for antidepressants, a prospective observational study of women receiving antidepressant therapy who were in remission from depression showed that discontinuing antidepressant treatment during pregnancy increases the risk of relapse. Perhaps reflecting such considerations regarding the risk-benefit balance for antidepressant treatment during pregnancy, antidepressant use during pregnancy is not uncommon. A recent systematic review and meta-analysis of the prevalence of antidepressant use during pregnancy estimated that roughly 5% of pregnant women in North America received a selective serotonin reuptake inhibitor (SSRI) during pregnancy.[h] Accordingly, it is expected that in the postmarketing environment there may be a significant number of women receiving gepirone therapy during pregnancy. This, coupled with the absence of clinical data on use of gepirone during pregnancy and lactation, provides the rationale for requesting that the sponsor conduct postmarketing requirement (PMR) studies of the pregnancy safety of gepirone.

The sponsor's draft labeling for EXXUA includes the following language regarding pregnancy and lactation under Section 8. USE IN SPECIFIC POPULATIONS:

(b) (4)

[redacted]

[g] Fabre-Kramer Pharmaceuticals. NDA 021164 Integrated Summary of Safety addendum, December 23, 2022.

[h] Molenaar NM, Bais B, Lambregtse-van den Berg MP, et al. The international prevalence of antidepressant use before, during, and after pregnancy: A systematic review and meta-analysis of timing, type of prescriptions and geographical variability. Journal of affective disorders. 2020 Mar 1;264:82-9.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected

☐ No approved indication, but practitioners may use product off-label in pregnant women

☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized

☒ No approved indication, but use in women of child-bearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty

☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty. †

☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). †

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☒ Pregnancy registry with internal comparison group

☐ Pregnancy registry with external comparison group

☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)

☒ Electronic database study with chart review

☐ Electronic database study without chart review

☐ Other, please specify:

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☐ Study Population

☐ Exposures

☒ Outcomes

☒ Covariates

☒ Analytical Tools

For any checked boxes above, please describe briefly:

Outcomes
Several of the desired outcomes cannot be reliably assessed in the Sentinel Distributed Database, namely infant outcomes such as postnatal growth and development, which require clinical assessments that may not be reflected in healthcare claims data, but would be reported in a registry. Additionally, spontaneous and elective abortions may not always be ascertainable in health care claims databases such as Sentinel.

ARIA lacks access to medical records. The pregnancy registry being considered requires that an expert clinical geneticist or dysmorphologist review and classify medical records of all major congenital malformations. Also, although in a first stage, the study using
claims or electronic medical data may be algorithm-based, if it shows an imbalance in any of the outcomes being investigated, FDA will require outcome validation in the selected database(s) or a chart-confirmed analysis.

Covariates
The Sentinel system has incomplete information on covariates of importance for pregnancy and infant outcomes, such as maternal smoking, alcohol and drug use, nonprescription drug use, and body mass index.

Analytical tools
The registry study is intended to provide broad-based signal detection. ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been fully tested and implemented in postmarketing surveillance of maternal and fetal outcomes.

2.5. Please include the proposed PMR language in the approval letter.

The proposed PMR language in the approval letter:

1. Collect data from a prospective pregnancy exposure registry, preferably a disease-based multiproduct registry, using a cohort analysis that compares the maternal, fetal, and infant outcomes of women with MDD exposed to Exxua (gepirone) during pregnancy with an unexposed comparator population(s) in a timely manner. Align the study protocol with protocol(s) outside the US to reach the target sample size. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortion, stillbirths, elective

terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes described in the protocol will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

2. Conduct an additional pregnancy study that uses a different design from the pregnancy registry (for example a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, small for gestational age births and preterm births in women exposed to Exxua (gepirone) during pregnancy compared to an unexposed control population.

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/s/

ANDREW D MOSHOLDER
09/19/2023 01:36:10 PM

YANDONG QIANG
09/19/2023 01:54:58 PM

WEI HUA
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ROBERT BALL
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MEMORANDUM

REVIEW OF REVISED LABELS

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 20, 2023
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 021164
Product Name, Dosage Form, and Strength:	Exxua[a] (gepirone) extended-release tablets, 18.2 mg, 36.3mg, 54.5 mg and 72.6 mg
Applicant/Sponsor Name:	Fabre-Kramer Pharmaceuticals, Inc.
TTT ID #:	2023-3251-1
DMEPA 1 Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA 1 Team Leader:	Madhuri R. Patel, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on September 19, 2023 for Exxua. The Division of Psychiatry (DP) requested that we review the revised container labels for Exxua (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous labels and labeling review[b] and additional recommendations communicated to the Applicant via email.

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

[a] This proposed proprietary name was found conditionally acceptable in the following DMEPA 1 Review: Holmes, L. Proprietary Name Review for Exxua (NDA 021164). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 Mar 21. PNR ID No. 2022-1044724916.

[b] Holmes, L. Labels and Labeling Review for Exxua (NDA 021164). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 Aug 15. TTT ID No.: 2023-3251.

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/s/

LORETTA HOLMES
09/20/2023 11:13:49 AM

MADHURI R PATEL
09/20/2023 04:58:33 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: September 15, 2023

To: Sarah Seung, Regulatory Project Manager, Division of Psychiatry (DP)

Michelle Horner, M.D., DP

Kimberly Updegraff, Associate Director for Labeling, (DP)

From: Samuel Fasanmi, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for Exxua (gepirone) extended-release tablets, for oral use

NDA: 021164

Background:
In response to DP's consult request dated February 1, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide, and carton for the NDA submission for Exxua.

PI:
OPDP's review of the proposed PI is based on the draft labeling received by electronic mail from DP on September 8, 2023, and our comments are provided below.

Medication Guide:
A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the Medication Guide and comments will be sent under separate cover.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the regulatory project manager on September 14, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Samuel Fasanmi at (301) 796-5188 or samuel.fasanmi@fda.hhs.gov.

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/s/

SAMUEL A FASANMI
09/15/2023 03:22:19 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	September 15, 2023
To:	Sarah Seung, PharmD, MS Regulatory Project Manager **Division of Psychiatry (DP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Ruth Mayrosh, PharmD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Sam Fasanmi, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	EXXUA (gepirone)
Dosage Form and Route:	extended-release tablets, for oral use
Application Type/Number:	NDA 021164
Applicant:	Fabre-Kramer Pharmaceuticals, Inc.

1 INTRODUCTION

On December 23, 2022, Fabre-Kramer Pharmaceuticals, Inc. submitted for the Agency's review a Class II Resubmission of their original New Drug Application (NDA) 021164 in response to the Agency's Complete Response (CR) letter dated November 2, 2007 and the Agency's Appeal Granted letter dated March 16, 2016. The proposed indication for EXXUA (gepirone) extended-release tablets is for the treatment of major depressive disorder (MDD) in adults.

The Applicant submissions on May 2, 2023, May 12, 2023, May 17, 2023, May 30, 2023, and May 31, 2023 constitute as a major amendment; therefore, the Agency extended the goal date by three months in order to provide time for a full review of the submission.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Psychiatry (DP) on February 1, 2023 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for EXXUA (gepirone HCl) extended-release tablets.

2 MATERIAL REVIEWED

- Draft EXXUA (gepirone) extended-release tablets MG received on December 23, 2022, and received by DMPP and OPDP on September 8, 2023.
- Draft EXXUA (gepirone) extended-release tablets Prescribing Information (PI) received on December 23, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 8, 2023.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

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SAMUEL A FASANMI
09/15/2023 02:44:57 PM

LASHAWN M GRIFFITHS
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
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Division of Pediatrics and Maternal Health Review

Date: August 10, 2023 **Date consulted:** January 23, 2023

From: Jean Limpert, MD, Medical Officer, Maternal Health Team (MHT)
Division of Pediatrics and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, MHT, DPMH

Lynne P. Yao, MD, OND, Division Director, DPMH

To: Division of Psychiatry (DP)

Drug: EXXUA (gepirone) extended-release (ER) tablets

NDA: 021164

Applicant: Fabre-Kramer Pharmaceuticals, Inc.

Subject: Pregnancy and Lactation Labeling

Proposed Indication: Treatment of Major Depressive Disorder

Materials Reviewed:

- DPMH consult request dated January 23, 2023, DARRTS Reference ID 5113639
- Applicant's submitted background package and proposed labeling for NDA 021164
- Applicant's Information Request (IR) response dated February 10, 2023
- Applicant's follow-up IR response, dated March 21, 2023

Consult Question: "Review of the Full Prescribing Information for PLLR compliance and provide any additional labeling recommendations to ensure the safe use of gepirone in patients of childbearing potential."

INTRODUCTION AND BACKGROUND

On December 23, 2023, the Applicant, Fabre-Kramer Pharmaceuticals, Inc, resubmitted a 505(b)1 NDA for Exxua (gepirone) ER tablets, a new molecular entity. On January 23, 2023, DP consulted DPMH to assist with the Pregnancy and Lactation subsections of labeling.

Regulatory History

- Gepirone immediate-release (and later ER tablets) were initially developed by Mead Johnson and Bristol-Myers Company for the treatment of anxiety and depression. In 1993, Fabre-Kramer Pharmaceuticals, Inc, acquired the rights to gepirone ER and submitted the initial NDA in 1999. There is an extensive regulatory history for this submission. Briefly, on June 16, 2014, the Applicant submitted a Formal Dispute Resolution Request appealing the November 2, 2007, decision that the application was Not Approvable, and on March 16, 2016, the Office of New Drugs (OND) issued an Appeal Granted letter.[1] For additional details, the reader is referred to the Unireview for additional details.
- On December 23, 2022, DPMH sent an IR to the applicant to request pharmacovigilance and literature relevant to the PLLR subsections of labeling. On February 8, 2023, the Applicant submitted their response. On March 10, 2023, DPMH sent a follow-up IR to request clarifying information about the pharmacovigilance cases. On March 21, 2023, the applicant submitted their follow-up response.

Drug Characteristics for Gepirone ER tablets[2]

- *Drug class:* will not be assigned a pharmacological class
- *Mechanism of Action:* not fully understood; thought to be related to modulation of serotonergic activity in the central nervous system through agonist activity at 5HT1A receptors
- *Molecular weight:* 396 g/mole
- *Half-life:* 5 hours
- *Protein binding:* 72%
- *Bioavailability:* 14% to 17%
- *Proposed dosing regimen:* 20 mg administered orally once daily with food at approximately the same time each day. If tolerated, the dose may be titrated up to a maximum dose of 80 mg daily.

[2] Draft PI for Gepirone NDA 21164 under review by team, accessed 6/27/23.

REVIEW

PREGNANCY

Major Depressive Disorder and Pregnancy

- The prevalence of MDD during pregnancy in the United States is 7% to 9%.[3] Women with depression who discontinue their antidepressant medications during pregnancy are at risk for relapse of depression.[4]
- A meta-analysis by Jarde et al (2016)[5] that included 23 observational studies found that pregnant patients with untreated depression had a significantly increased risk of preterm birth and low birth weight compared with pregnant patients without depression. A subsequent individual participant data meta-analysis by Vlentrie et al (2021)[6] found that antidepressant use during pregnancy was associated with preterm birth and low Apgar scores, with the highest risks observed for fluoxetine and sertraline.
- The American College of Obstetrics and Gynecology (ACOG) has treatment algorithms for the management of depression during pregnancy which includes psychotherapy for mild-to-moderate depression and pharmacologic therapy. The choice of antidepressant depends on history of treatment response, comorbid conditions (e.g., panic disorder, eating disorder, substance use disorder), and side effects. Selective serotonin reuptake inhibitors (SSRIs) are the most frequently prescribed class during pregnancy.[7]

Nonclinical Experience

The nonclinical data to support the original NDA were reviewed previously by Linda Fossom, PhD (3/8/2002) and the labeling recommendations at that time included Pregnancy Category C and a statement that in animal reproduction studies, gepirone has been shown to have adverse effects on embryo/fetal and postnatal development. A combined repeat dose, neurobehavioral, and fertility study in juvenile rats was submitted and reviewed with the current resubmission.

In animal reproduction studies, gepirone has been shown to have adverse effects on embryofetal and postnatal development. When gepirone was administered during the period of organogenesis, embryofetal growth was decreased in rats and rabbits with a No Observed Adverse Effect Level (NOAEL) of 9 and 12 times the maximum recommended (MRHD) human dose of 80 mg based on body surface area, respectively. Malformations were not observed in these studies at doses up to 36 and 48 times the MRHD. When pregnant rats were treated through gestation and lactation, decreased birth weight was observed in the offspring at twice the

[3] Grigoriadis, S. Unipolar major depression during pregnancy: Epidemiology, clinical features, assessment, and Diagnosis. UpToDate. Accessed 4/19/2023.

[4] Becker, M., Weinberger, T., Chandy, A. et al. Depression During Pregnancy and Postpartum. Curr Psychiatry Rep 18, 32 (2016). https://doi.org/10.1007/s11920-016-0664-7

[5] Jarde A, Morais M, Kingston D, Giallo R, MacQueen GM, Giglia L, Beyene J, Wang Y, McDonald SD. Neonatal Outcomes in Women With Untreated Antenatal Depression Compared With Women Without Depression: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2016 Aug 1;73(8):826-37. doi: 10.1001/jamapsychiatry.2016.0934. PMID: 27276520.

[6] Vlenterie, Richelle et al. "Associations Between Maternal Depression, Antidepressant Use During Pregnancy, and Adverse Pregnancy Outcomes." Obstetrics and gynecology. 138.4 (2021): 633–646.

[7] Yonkers KA, et al. The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. Obstet Gynecol. 2009; 114(3):703-713. (Guidelines reaffirmed 2014, ACOG)

MRHD. Increased mortality during the first 4 days after birth and persistent growth retardation were observed at all doses; the lowest dose was approximately equal to the MRHD. A NOAEL for fetal effects was not identified in this study. When male and female rats were treated throughout mating, gestation, and lactation, decreased birth weight was observed at 3 times the MHRD, increased still births were seen at 8 times the MHRD, and early postnatal mortality was increased at 18 times the MRHD. In addition, decreased pup weight continued to be seen up to 14 weeks after birth with delays in some developmental landmarks in these pups. The NOAEL for these effects observed in this study was below the MRHD.

Reviewer comment: DPMH discussed the nonclinical findings from the rat studies with the Pharmacology/Toxicology team, which include increased offspring mortality at all doses, persistent growth retardation at all doses, and stillbirths at 8 times the MRHD. The Pharmacology/Toxicology team regards these findings as concerning, though similar findings for other serotonergic antidepressants were also noted.[8]

For full details, the reader is referred to the Pharmacology/Toxicology section of the Unireview by Eric Maltbie, PhD, and the March 8, 2002 Pharmacology/Toxicology review Dr. Linda Fossom, PhD.

Review of Pharmacovigilance Database

During the clinical development program, the studies utilized pregnancy testing and contraception recommendations. Twenty pregnancies were reported in participants treated with gepirone during the clinical development program. The applicant's tabular summary may be found in Appendix A[9] which includes the gepirone formulation and dose for each case. A brief summary of 20 outcomes compiled by this reviewer is as follows:

- 6 full-term births (no congenital malformations reported)
- 1 preterm live birth due to short cervix (no congenital malformations reported)
- 9 unknown outcomes
- 2 cases of dilation and curettage
    - 1 case noted absence of fetal heart tones at 13 weeks; fetus with a cystic hygroma, Turner's syndrome karyotype.
    - 1 case occurred in third month of pregnancy (reason unknown)
- 1 elective abortion (reason unknown)
- 1 spontaneous abortion (gestational age not reported)

Reviewer comment: DPMH requested the information about the timing of gepirone exposure during pregnancy. Despite a follow-up IR to clarify the information, the applicant does not clearly state the timing of gepirone exposure according to the gestational week of pregnancy. It appears exposure primarily occurred in the pre-conception/first trimester period and that gepirone was discontinued at the time of positive pregnancy testing. There are no data about chronic gepirone use throughout pregnancy.

[8] DPMH discussion with Pharmacology/Toxicology on 6/14/23
[9] Applicant's IR response submitted March 21, 2023

Review of Literature

Applicant's Review of Literature

The applicant conducted cumulative literature searches in Medline for publications relevant to gepirone and pregnancy. The reader is referred to the referenced portion of applicant's submission for the search strategies that were used.[10] No publications relevant to pregnancy were identified.

DPMH Review of Literature

DPMH performed a search in PubMed, Embase, Micromedex,[11] TERIS,[12] REPROTOX,[13] and *Drugs in Pregnancy and Lactation* [14] to find relevant articles related to the use of gepirone during pregnancy Search terms included "gepirone" AND "pregnancy," "pregnant women," "birth defects," "congenital malformations," "stillbirth," "spontaneous abortion," "miscarriage," and "fetal loss." Gepirone is not referenced in Micromedex, TERIS, REPROTOX, or *Drugs in Pregnancy and Lactation.* No articles were identified.

LACTATION

Nonclinical Experience

Gepirone is present in rat milk. When pregnant rats were treated through gestation and lactation, decreased birth weight was observed in the offspring at twice the MRHD and increased mortality during the first 4 days after birth and persistent growth retardation were observed at all doses. When male and female rats were treated throughout mating, gestation, and lactation, early postnatal mortality was increased at 18 times the MRHD. In addition, decreased pup weight continued to be seen up to 14 weeks after birth with delays in some developmental landmarks in these pups. The NOAEL for these effects observed in this study was below the MRHD.

Reviewer comment: DPMH discussed the lactation findings with Pharmacology/Toxicology. While it is not clear if the effects were due to in utero exposure or lactational exposure, the Pharmacology/Toxicology team currently considers that the findings should not alter the clinical lactation recommendation.[15]

For full details, the reader is referred to the Pharmacology/Toxicology review by Eric Maltbie, PhD.

Review of Pharmacovigilance Database

The applicant conducted a cumulative search and did not identify cases relevant to lactation.

[10] Integrated Summary of Safety Addendum for NDA 21164, section 5.3.5.3.6.1, dated February 8, 2023
[11] https://www.micromedexsolutions.com, accessed 3/23/23
[12] Truven Health Analytics information. TERIS, accessed 3/23/23
[13] Truven Health Analytics information. REPROTOX, accessed 3/23/23
[14] Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 12th edition. 2022, Philadelphia, PA. online, accessed 3/23/23
[15] DPMH discussion with Pharmacology/Toxicology on 6/14/23

Review of Literature

Applicant's Review of Literature

The applicant conducted cumulative literature searches in Medline for publications relevant to gepirone and lactation. The reader is referred to the referenced portion of applicant's submission for the search strategies that were used.[16] No publications relevant to lactation were identified.

DPMH Review of Literature

This Reviewer performed a search in PubMed, Embase, Micromedex,[17] TERIS,[18] REPROTOX,[19] and *Drugs in Pregnancy and Lactation,*[20] *Medications and Mothers' Milk,*[21] and LactMed[22] to find relevant articles related to the use of gepirone during lactation. Search terms included "gepirone" AND "breastfeeding" or "lactation." Gepirone is not referenced in Micromedex, TERIS, REPROTOX, or *Drugs in Pregnancy and Lactation.* No articles were identified.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Gepirone was not mutagenic or genotoxic. Fertility studies in male and female rats revealed no evidence of impaired fertility in males and females at doses up to 24.5 mg/kg/day (approximately three times the MRHD on a mg/m^2 basis). Higher doses (>58.1 mg/kg/day) were associated with a higher incidence of stillborns, lower implantation and survival indices, and reduced fetal weight and crown-rump distances, and these were associated with maternal findings (reduced weight gain and food intake).

For full details, the reader is referred to the Pharmacology/Toxicology review by Eric Maltbie, PhD.

Review of Pharmacovigilance Database

The applicant conducted a cumulative search and did not identify cases relevant to fertility.

Review of Literature

Applicant's Review of Literature

The applicant conducted cumulative literature searches in Medline for publications relevant to gepirone and fertility. The reader is referred to the referenced portion of applicant's submission for the search strategies that were used.[23] No publications relevant to fertility were identified.

DPMH Review of Literature

This Reviewer performed a search in PubMed, Embase, and REPROTOX to find relevant articles related to the use of gepirone and effects on fertility. Search terms included "gepirone" AND

[16] Integrated Summary of Safety Addendum for NDA 21164, section 5.3.5.3.6.1, dated February 8, 2023
[17] https://www.micromedexsolutions.com, accessed 3/23/23
[18] Truven Health Analytics information. TERIS, accessed 3/23/23
[19] Truven Health Analytics information. REPROTOX, accessed 3/23/23
[20] Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 12th edition. 2022, Philadelphia, PA. online, accessed 3/23/23
[21] https://www.halesmeds.com
[22] https://www.ncbi.nlm.nih.gov/books/NBK501922/
[23] Integrated Summary of Safety Addendum for NDA 21164, section 5.3.5.3.6.1, dated February 8, 2023

"fertility," "infertility," "contraception," and "oral contraceptives." No articles were identified.

DISCUSSION AND CONCLUSIONS

Pregnancy

While gepirone will not be assigned to an established pharmacological class, gepirone is thought to modulate serotonergic activity in the central nervous system through agonist activity at 5HT1A receptors. (b) (5) [redacted]

There were twenty pregnancies that occurred during the clinical development program, though nearly half of them had unknown outcomes. The known outcomes include live births (seven cases), one spontaneous abortion, one elective abortion, and two outcomes of dilatation and curettage. There are insufficient data of gepirone exposure during pregnancy to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes.

The nonclinical studies indicate adverse findings at clinically relevant exposures, which include stillbirths (8x the MRHD), increased offspring mortality (all doses), and persistent growth retardation (all doses). While the Pharmacology/Toxicology team notes these findings as concerning, they do not feel that a Warning and Precaution for embryo-fetal toxicity is warranted since other serotonergic antidepressants do not have Warning and Precaution statements based on the animal data findings.

It is anticipated that gepirone will be used in females of reproductive potential. There is an established disease-based pregnancy registry for antidepressants and the applicant proposes to include contact information for this particular pregnancy registry in labeling. DPMH agrees with the inclusion of relevant pregnancy registry information for gepirone in labeling and the reader is referred to the post-marketing requirement (PMR) language below for additional details.

Lactation

There are no published literature or pharmacovigilance data to inform the clinical aspects of lactation labeling. Gepirone is present in rat milk, but it is not known to what extent gepirone would transfer into human milk. There were adverse effects noted during lactation in the nonclinical studies but it is not clear if the effects were the result of in utero exposure or lactational exposure. The Pharmacology/Toxicology team did not believe that these findings should impact the clinical lactation recommendation. At the time of the August 8, 2023 labeling meeting, the Warnings and Precautions were still being discussed by the DP review team. If the DP review team determines that there are serious adverse reactions that may impact the breastfed infant, additional discussion with DPMH is recommended to modify the lactation labeling recommendation.

Since MDD is prevalent in females of reproductive potential, including lactating individuals, and there are no clinical lactation data, a PMR milk-only lactation study in females of reproductive potential is recommended. This clinical lactation study will be informative in determining the amount of gepirone transfer into human milk and may capture reports of effects on the breastfed infant.

Females and Males of Reproductive Potential

Nonclinical data will be described in Subsection 13.1 of labeling and there are no clinical data to evaluate for an adverse effect on fertility. Subsection 8.3 will be omitted.

PMR RECOMMENDATIONS

DPMH recommends the following:

1. The applicant should conduct a pregnancy exposure registry. The following PMR language is suggested:

   Collect data from a prospective pregnancy exposure registry, preferably a disease-based multiproduct registry, using a cohort analysis that compares the maternal, fetal, and infant outcomes of women with MDD exposed to TRADENAME during pregnancy with an unexposed comparator population(s) in a timely manner. Align the study protocol with protocol(s) outside the US to reach the target sample size. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortion, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes described in the protocol will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

2. The applicant should conduct a complementary pregnancy safety study. The following PMR language is suggested:

   Conduct an additional pregnancy study that uses a different design from the pregnancy registry (for example a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, small for gestational age births and preterm births in women exposed to TRADENAME during pregnancy compared to an unexposed control population.

3. The applicant should conduct a milk only lactation study using a validated assay in order to inform the lactation subsection of labeling. The following PMR language is suggested.

   Perform a lactation study (milk only) in lactating women who have received TRADENAME to assess concentrations of gepirone in breastmilk using a validated assay and to assess the effects on the breastfed infant.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1, 8.2, and section 17 of labeling for compliance with the PLLR (see below). DPMH discussed the labeling recommendations with the DP review team on July 26, 2023 and August 8, 2023. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

(b) (4)

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

APPENDIX A

Applicant's Table: Pregnancies (n=20) Reported in Subjects Receiving Gepirone During the Clinical Development Program[24]

Study	Subject ID	Age	Study Drug	Dosing Regimen and Duration	Pregnancy Date	Exposure to Drug	Pregnancy Outcome	Gestational Age for Pregnancy Outcome
C-1762	(b) (6)	31	Gepirone ER	Up to 40 mg/day for 48 days	(b) (6) (positive test)	• (b) (6), modal dose 40 mg/day	Healthy baby	Unknown
CN105-022	(b) (6)	21	Gepirone IR	Up to 30 mg/day for 67 days	(b) (6) (confirmed)	• (b) (6), 5 mg/day • (b) (6) 10 mg/day • 15 mg/day • 20 mg/day • 20 mg/day • (b) (6), 30 mg/day • (b) (6), 10 mg/day	Healthy baby	39 weeks
CN105-037	(b) (6)	23	Gepirone IR	Up to 4 mg/day for 60 days	(b) (6)	• (b) (6), 2 mg/day • (b) (6), 4 mg/day • (b) (6), 0 mg/day • (b) (6), 4 mg/day	Dilatation and curettage; Congenital anomalies[25]	Approximately 13-weeks
CN105-057	(b) (6) [26]	24	Gepirone ER	Up to 4 mg/day for 56 days	(b) (6) (positive test)	• (b) (6), 2 mg/day • 2 mg/day • (b) (6), 4 mg/day • (b) (6), 4 mg/day • (b) (6), 4 mg/day	Unknown	Unknown

[24] Applicant's DPMH IR response, dated March 21, 2023

[25] Ultrasound interpreted as showing a 13-week fetus with a cystic hygroma. Three days later, the subject's obstetrician determined that there were no fetal heart tones ((b) (6)). Karyotyping revealed a Turner's syndrome karyotype. The subject had taken tetracycline, pseudoephedrine, acetaminophen, pyrilamine, pamabrom, and an unspecified diuretic. Around the time of conception, the subject had vaginal exposure to Monistat® cream, Betadine® douche, and a Today® sponge contraceptive device. The subject had an obstetric history significant for two miscarriages, and the subject's daughter had a history of significant developmental delays. The subject had also reportedly used amphetamines in the past, and had been occupationally exposed to chemicals, as well as embalming chemicals.

[26] Not included in AE listings or summaries, no narrative available.

Study	Subject ID	Age	Study Drug	Dosing Regimen and Duration	Pregnancy Date	Exposure to Drug	Pregnancy Outcome	Gestational Age for Pregnancy Outcome
FKGBE007	(b) (6)	21	Gepirone ER	Up to 60 mg/day for 55 days	(b) (6) (positive test)	• (b) (6) to (b) (6), modal dose 60 mg/day	Unknown	Unknown
FKGBE007	(b) (6)	33	Gepirone ER	up to 80 mg/day for 42 days	(b) (6) (positive test)	• (b) (6) to (b) (6), modal dose 80 mg/day	Unknown	Unknown
FKGBE007	(b) (6)	22	Gepirone ER	Up to 80 mg/day for 54 days	Noted on Day 39 of treatment	• (b) (6) to (b) (6), modal dose 80 mg/day	Spontaneous miscarriage	(b) (6)
FKGBE008	(b) (6) [27]	34	Gepirone ER	Up to 80 mg/day for 59 days	(b) (6) positive result at Visit 6, which was confirmed with a repeat test.	• First day of active treatment, (b) (6) • Last day of investigational product, (b) (6)	Unknown	Unknown

[27] Not included in AE listings or summaries, no narrative available.

Study	Subject ID	Age	Study Drug	Dosing Regimen and Duration	Pregnancy Date	Exposure to Drug	Pregnancy Outcome	Gestational Age for Pregnancy Outcome
03A7A-003	(b) (6)[28]	33	Gepirone ER	Up to 30 mg/day for 42 days	Unknown	• (b) (6) to (b) (6), 10-30 mg/day	Unknown	Unknown
03A7C-001B	(b) (6)	33	Gepirone IR	Up to 60 mg/day for 71 days	Week 10 of treatment (positive test)	• (b) (6) to (b) (6), total daily dose 10 to 60 mg • Had been on high dose for 71 days and was currently taking 40 mg	Healthy baby	37 weeks
28709	(b) (6)	33	Gepirone ER	Up to 60 mg/day for 86 days	(b) (6) (positive test)	• (b) (6) to (b) (6), modal dose 60 mg/day	Dilatation and curettage- reason unknown	3rd month of pregnancy
28709	(b) (6)	30	Gepirone ER	Up to 80 mg/day for 112 days	Noted on (b) (6)	• (b) (6) to (b) (6), 20 mg/day • (b) (6) to (b) (6), 40 mg/day • (b) (6) to (b) (6), 60 mg/day • (b) (6) to (b) (6), 80 mg/day	Healthy baby	(b) (6)
134004/134502	(b) (6)	23	Short-term: Fluoxetine, Extension: Gepirone ER	Gepirone ER, 20 mg/day for 2 days	(b) (6) (positive test)	• (b) (6) to (b) (6), 20 mg/day	Healthy baby	Unknown
134004/134502	(b) (6)	37	Short-term: Gepirone ER, Extension: Fluoxetine	Gepirone ER, up to 80 mg/day for 55 days	Noted on day 104 of Fluoxetine treatment	• (b) (6) to (b) (6) • Fluoxetine was discontinued when the subject was approximately 1 month pregnant	Healthy baby	(b) (6)

[28] Not included in AE listings or summaries.

Study	Subject ID	Age	Study Drug	Dosing Regimen and Duration	Pregnancy Date	Exposure to Drug	Pregnancy Outcome	Gestational Age for Pregnancy Outcome
134006/134503	(b) (6)	37	Gepirone ER	Up to 80 mg/day for 151 days	(b) (6) (diagnosed)	• (b) (6) to (b) (6), 20-80 mg/day	Unknown	Unknown
134023	(b) (6)	25	Gepirone ER	Up to 60 mg/day for 19 days	(b) (6) (diagnosed)	• (b) (6) to (b) (6), 20 mg/day • (b) (6) to (b) (6), 40 mg/day • (b) (6) to (b) (6), 60 mg/day	Unknown	Unknown
134501	(b) (6)	19	Gepirone ER	up to 60 mg/day for 77 days	(b) (6) (informed site)	• (b) (6) to (b) (6), 40 mg/day • (b) (6) to (b) (6) 40 mg/day • to 40 mg/day • to 40 mg/day • to (b) (6), 40 mg/day • to (b) (6), 60 mg/day • to (b) (6), 60 mg/day	Unknown	Unknown
134501	(b) (6)	23	Gepirone ER	Up to 80 mg/day for 78 days	(b) (6) (informed site)	• (b) (6) to (b) (6), 40 mg/day • (b) (6) to (b) (6), 40 mg/day • (b) (6) to (b) (6), 80 mg/day • (b) (6) to (b) (6), 80 mg/day • (b) (6) to (b) (6) 80 mg/day • to 80 mg/day • to (b) (6), 80 mg/day • (b) (6) to (b) (6), 80 mg/day	Elective abortion-reason unknown	(b) (6)

Study	Subject ID	Age	Study Drug	Dosing Regimen and Duration	Pregnancy Date	Exposure to Drug	Pregnancy Outcome	Gestational Age for Pregnancy Outcome
134501	(b) (6)	19	Gepirone ER	60-80 mg/day for 240 days	(b) (6)	• (b) (6) to (b) (6), 60 mg/day • to (b) (6), 60 mg/day • (b) (6) to (b) (6), 80 mg/day • (b) (6) to (b) (6), 80 mg/day • to (b) (6), 80 mg/day • (b) (6) to (b) (6), 80 mg/day • (b) (6) to (b) (6), 80 mg/day • (b) (6) to (b) (6), 80 mg/day • (b) (6) to (b) (6), 80 mg/day • (b) (6) to (b) (6), 80 mg/day • (b) (6) to (b) (6), 80 mg/day	Mild jaundice but healthy baby.	Preterm delivery 1 month early due to short cervix.
134501	(b) (6)	38	Gepirone ER	Up to 80 mg/day for 110 days	(b) (6)	• (b) (6) to (b) (6), 20 mg for 3 days, 40 mg for 4 days, 60 mg for 8 days.	Unknown	Unknown

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/s/

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08/10/2023 04:45:13 PM

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LABELS AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	August 15, 2023
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 021164
Product Name, Dosage Form, and Strengths:	Exxua[a] (gepirone) extended-release tablets, 18.2 mg, 36.3mg, 54.5 mg and 72.6 mg[b]
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Fabre-Kramer Pharmaceuticals, Inc. (Fabre-Kramer)
FDA Received Date:	February 3, 2023 and July 31, 2023
TTT ID #:	2023-3251
DMEPA 1 Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA 1 Acting Team Leader:	Madhuri R. Patel, PharmD

[a] This proposed proprietary name was found conditionally acceptable in the following DMEPA 1 Review: Holmes, L. Proprietary Name Review for Exxua (NDA 021164). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 Mar 21. PNR ID No. 2022-1044724916.

[b] According to the Office of Pharmaceutical Quality (OPQ), the proposed strengths (i.e., 20 mg, 40 mg, 60 mg, and 80 mg) are based on gepirone HCl but will have to be changed to reflect gepirone free base (18.2 mg, 36.3 mg, 54.5 mg, and 72.6 mg, respectively).

1 REASON FOR REVIEW

As part of the approval process for Exxua (gepirone) extended-release tablets, the Division of Psychiatry (DP) requested that we review the proposed Exxua Prescribing Information (PI), Medication Guide (MG), and container labels for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

On February 3, 2023, Fabre-Kramer submitted (b) (4) as well as container labels for 100-count bottles for all strengths. However, in response to the Agency's Chemistry, Manufacturing, and Controls (CMC) Information Request (IR) dated April 28, 2023, Fabre-Kramer stated they are withdrawing the submitted (b) (4).[c] Therefore, DMEPA did not review the (b) (4).

In an Information Request (IR) sent to the Applicant on July 12, 2023, DMEPA requested clarity on why, among the labels submitted on February 3, 2023, there were two 60 mg 100-count container (bottle) labels with different NDC numbers.[d] We asked the Applicant to clarify and specify the bottle configurations they intend to market for the 60 mg strength. They responded by submitting container labels for 30-count and 100-count bottles for all four strengths as well as a container label for a (b) (4)-count bottle. However, the Office of Pharmaceutical Quality informed DMEPA that there is not adequate quality information to support the new packaging configurations (i.e., the 30-count and (b) (4)-count packaging configurations) in the current submission and that the packaging configuration evaluated is only 100-count bottles. Therefore, DMEPA reviewed the 100-count bottle labels only.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B (N/A)
ISMP Newsletters*	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)

[c] The CMC Information Request dated April 28, 2023 and the Applicant's response dated May 9, 2023 are available in the EDR at: \\CDSESUB1\EVSPROD\nda021164\0024\m1\us\111-information-amendment\qual-info-amendment-cmc20230509.pdf.

[d] The DMEPA Information Request dated July 12, 2023 and the Applicant's response dated July 14, 2023 are available in the EDR at: \\CDSESUB1\EVSPROD\nda021164\0040\m1\us\111-information-amendment\multi-module-amend-rficontainer20230712.pdf.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Other	E (N/A)
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

We reviewed the proposed Prescribing Information (PI) and Medication Guide (MG) submitted on February 3, 2023, as well as the Division's proposed revisions to the draft PI (as of August 11, 2023). We also reviewed the container labels submitted on July 31, 2023. Overall, we noted that in some areas of the labels and labeling the strength is presented based on gepirone hydrochloride salt and in other areas it is presented based on gepirone free base or both. However, the Division is aware and has addressed this issue based on OPQ's recommendation that the strength should be based on gepirone free base. Therefore, we have no recommendations for the draft PI or the MG from a medication error perspective.

We note that the container labels may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for Fabre-Kramer.

4 RECOMMENDATIONS FOR FABRE-KRAMER PHARMACEUTICALS, INC.

Table 2. Identified Issues and Recommendations for Fabre-Kramer Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels			
1.	The established name is presented as "(gepirone HCl)".	Per updates from the Division, the established name should be presented based on gepirone free base and not gepirone HCl salt.	Revise the established name to "gepirone", [i.e., "EXXUA (gepirone) extended-release tablets"].
2.	As presented, the product strengths (i.e., 20 mg, 40 mg, 60 mg, and 80 mg) are based on gepirone HCl salt.	Per updates from the Division, the strength should be presented based on gepirone free base.	Revise the product strengths from 20 mg, 40 mg, 60 mg, and 80 mg to 18.2 mg, 36.3 mg, 54.5 mg, and 72.6 mg, respectively. Additionally, remove the "(XX mg freebase) statement that is adjacent to the strength.

Table 2. Identified Issues and Recommendations for Fabre-Kramer Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
3.	The "Recommended Dosage" statement is preceded by "(b) (4) ", i.e., "(b) (4) "	The term "(b) (4)" is not consistent with Section 2.1 of the Prescribing Information which states "Recommended Dosage". Additionally, the Boxed Warning does not provide recommended dosage information and, therefore, may lead to confusion.	To ensure consistency with the Prescribing Information, revise the statement, "(b) (4) " to read "Recommended Dosage: See Prescribing Information." Please refer to 21 CFR 201.55.
4.	The strength presentation for all strengths is the same (i.e., (b) (4)).	Although the proposed proprietary name, established name, and dosage form all appear (b) (4) that differs according to the product strength, this may not be sufficient to mitigate potential product selection errors.	Consider the use of a colored font for the strength, a color block, or other means to better differentiate the strengths.
5.	The strength lacks prominence due to its size.	The lack of prominence of the strength may impair its visibility.	Increase the size of the strength.
6.	The net quantity statement is in too close proximity to the strength.	From postmarketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength.	Relocate the net quantity statement away from the product strength, such as to the bottom of the principal display panel.
7.	A linear barcode is not shown on the labels.	The linear barcode is often used as an additional verification before drug dispensing or administration.	Add the product's linear barcode to the labels per 21 CFR 201.25(c)(2).

Table 2. Identified Issues and Recommendations for Fabre-Kramer Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
8.	It is not clear whether the container labels will have a human-readable and machine-readable (2D data matrix barcode) product identifier on the labels.	Human-readable and machine-readable (2D data matrix barcode) product identifiers are used for identification and tracking purposes.	Please clarify whether a 2D data matrix barcode will be on the container labels. If not present, we recommend that you review the *Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers* (June 2021) to determine if the product identifier requirements apply to your product's labels. The guidance is available at: https://www.fda.gov/media/116304/download. If you intend to have a 2D data matrix barcode on the labels, please show its proposed location and format on the labels.
9.	Lot number and expiration date placeholders are not shown on the labels.	It is unclear how the lot number and expiration date will appear on the labels.	Add the lot number and expiration date placeholders to the labels. Additionally, to minimize confusion and reduce the risk for deteriorated drug medication errors, please specify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to

Table 2. Identified Issues and Recommendations for Fabre-Kramer Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a slash or a hyphen be used to separate the portions of the expiration date.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Exxua that Fabre-Kramer Pharmaceuticals, Inc. submitted on February 3, 2023.

Table 3. Relevant Product Information for Exxua	
Initial Approval Date	N/A
Active Ingredient	gepirone
Indication	Treatment of major depressive disorder (MDD) in adults
Route of Administration	Oral
Dosage Form	Extended-release tablets
Strengths	20 mg, 40 mg, 60 mg, and 80 mg[e]
Dose and Frequency	The usual target dose of Exxua is 60 to 80 mg/day. The recommended starting dose is 20 mg administered orally once daily with food at approximately the same time each day. The tablets should not be broken, crushed, chewed, or dissolved. If the 20 mg initial dose is adequately tolerated, an increase to 40 mg given once daily may begin as early as Day 4 of dosing. If the 40 mg dose is well tolerated and additional efficacy is desired, the dose may be increased to 60 mg after one week and to 80 mg after an additional week.
How Supplied	**18.2-mg Tablets** – pink, modified rectangular, with "FK" debossed on one side and "1" on the other side. Bottles of 100 NDC 0173-0762-00 **36.3-mg Tablets** – off-white, modified rectangular, with "FK" debossed on one side and "7" on the other side. Bottles of 100 NDC 0173-0767-00 **54.5-mg Tablets** – yellow, modified rectangular, with "FK" debossed on one side and "11" on the other side. Bottles of 100 NDC 0173-0764-00 **72.6-mg Tablets** – red-brown, modified rectangular, with "FK" debossed on one side and "17" on the other side. Bottles of 100 0173-0765-00
Storage	Store at 25°C (77°F); excursions are permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from high humidity and moisture.
Container Closure	Child-resistant closure

[e] According to the Office of Pharmaceutical Quality (OPQ), the proposed strengths based on gepirone HCl (i.e., 20 mg, 40 mg, 60 mg, and 80 mg) will have to be changed to reflect gepirone free base (18.2 mg, 36.3 mg, 54.5 mg and 72.6 mg, respectively).

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APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[f] along with postmarket medication error data, we reviewed the following Exxua labels and labeling submitted by Fabre-Kramer Pharmaceuticals, Inc.

- Container Labels (100-count bottles), submitted on July 31, 2023, available at: \\Cdsesub1\evsprod\NDA021164\0042\m1\us\114-labeling\draft\carton-and-container
- Medication Guide, image not shown, submitted on February 3, 2023, available at: \\CDSESUB1\EVSPROD\nda021164\0007\m1\us\114-labeling\draft\labeling\draft-labeling-text.docx
- Prescribing Information (image not shown), submitted on February 3, 2023, available at: \\CDSESUB1\EVSPROD\nda021164\0007\m1\us\114-labeling\draft\labeling\draft-labeling-text.docx

  We also reviewed the Division's proposed revisions to the draft PI as of August 11, 2023.

F.2 Labels Images (not to scale)

Container Labels

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

[f] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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LORETTA HOLMES
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M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: August 7, 2023

To: Tiffany Farchione, MD, Director
Division of Psychiatry (DP)

Through: Dominic Chiapperino, PhD, Director
Chad Reissig, PhD, Supervisory Pharmacologist
Controlled Substance Staff

From: Edward Hawkins, PhD, Pharmacologist
Controlled Substance Staff

Subject: **Product name:** EXXUA **(**gepirone HCl)
Dosages, formulations, routes: 18.2 mg, 36.3 mg, 54.5 mg, and 72.6 mg extended-release tablets (weights are free base) for oral administration,
NDA number: 021164
IND Number: 023952
Indication(s): Major depressive disorder
PDUFA Goal Date: September 23, 2023

Materials Reviewed:

- NDA 021164 for EXXUA **(**gepirone)
- IND 033626 for gepirone
- IND 023952 for gepirone
- NDA 021164; Pharm/Tox review; Fossom, Linda; 03/08/2002

Table of Contents

I. SUMMARY

1. Background

This memorandum is in response to a consult request from the Division of Psychiatry (DP) to evaluate abuse-related preclinical and clinical data submitted by Fabre-Kramer Pharmaceuticals, Inc. (Applicant) under NDA 021164 and IND 023952 for EXXUA (gepirone). The Applicant submitted a 505(b)(1) application, and DP consulted CSS to review the abuse-related data submitted as part of the NDA. Gepirone was first submitted to the Agency on October 1, 1999, and has gone through several rounds of review. A consult request was sent to CSS on January 1, 2023, and the current goal date for the NDA is September 23, 2023, for the treatment of major depressive disorder.

CSS first communicated with the Applicant during a Type B meeting held on January 30, 2017, in which the Sponsor was informed of the need to compile and submit the appropriate studies and data outlined in the guidance for industry, Assessment of Abuse Potential of Drugs, 2017 as part of their NDA. The Sponsor has submitted study reports for in vitro binding, animal abuse potential studies, and a summary of adverse events collected in clinical development. This document is a review of those data.

Gepirone is an orally bioavailable moderate affinity selective agonist at serotonin 5-HT_{1A} receptors. How this action produces antidepressant activity is currently unknown, however, buspirone has a similar mechanism of action for the treatment of anxiety and does not have abuse liability.

After evaluating the nonclinical and clinical data in the NDA, CSS recommends that gepirone not be controlled under any schedule of the Controlled Substances Act (CSA). Recommendations for the labeling of gepirone regarding its abuse potential appear below in the Recommendations section.

2. Conclusions

CSS has reviewed the nonclinical and clinical abuse-related data submitted in NDA 021164 for gepirone and concludes that the drug does not have abuse potential and should not be controlled under the CSA. This conclusion is based on the following:

- Gepirone is a new molecular entity whose primary mechanism of action is as a moderate affinity agonist of the 5-HT_{1A} receptor. Receptor binding studies indicated that gepirone did not bind to any receptors, transporters, or ion channels typically associated with drugs having a potential for abuse.

- Gepirone is metabolized into one major circulating metabolite 1-pyrimidinylpiperazine (1-PP). The Sponsor did not conduct receptor binding studies on this metabolite.

- Gepirone did not produce reinforcing effects in an IV self-administration study using rhesus macaques

- In drug discrimination studies, rats did not generalize to the discriminative effects of amphetamine and partially generalized to LSD

- An analysis of CNS-mediated adverse events (AEs) that can be indicative of abuse liability or physical dependence was conducted on the clinical studies provided by the Applicant. This analysis indicated that the most prevalent AEs were dizziness and nausea. There were no concerning reports of AEs that suggest that gepirone has a potential for abuse or physical dependence.

3. Recommendations

Based on the data provided in NDA 021164, CSS recommends that:

- Gepirone not be controlled in any schedule under the CSA

(b) (4)

II. DISCUSSION

1. Chemistry

1.1 Substance and Product Information

Gepirone HCl is the name of the active pharmaceutical ingredient in EXXUA. EXXUA is formulated in four dosage strengths of 20 mg, 40 mg, 60 mg, and 80 mg. These dosage strengths have been adjusted to the gepirone freebase weights of 18.2 mg, 36.3 mg, 54.5 mg, and 72.6 mg respectively. Gepirone, also known by the developmental codes Org 33062, BMY 13805-1, MJ 13805-1, (b) (4), and (b) (4) is the nonproprietary name of 4,4-dimethyl-1-[4-(4-pyrimidin-2-ylpiperazin-1-yl)butyl]piperidine-2,6-dione monohydrochloride. Gepirone HCl has a molecular weight of 395.93 g/mol, a chemical formula of $C_{19}H_{29}N_5O_2 \cdot HCl$, and a CAS # of 83928-66-9. The drug substance is a white to off-white crystalline powder that is freely soluble in water and sparingly soluble in ethanol (

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Table **1**). Gepirone is not currently listed in any schedule of the CSA. Gepirone is manufactured under DMF (b) (4).

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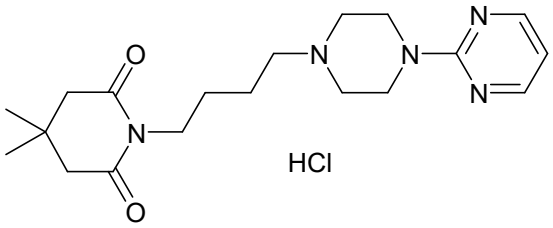
Table 1: General Chemical Properties of Gepirone

Nomenclature	
International Non-proprietary Name (INN)	Gepirone HCl
Chemical Abstract Number (CAS)	83928-66-9; 83928-76-1 (free base)
Chemical Name (IUPAC)	4,4-dimethyl-1-[4-(4-pyrimidin-2-ylpiperazin-1-yl)butyl]piperidine-2,6-dione monohydrochloride
Drug product codes	Org 33062, BMY 13805-1, MJ 13805-1, (b) (4)
Schedule in the CSA	not controlled
Structure	
Molecular Formula	$C_{19}H_{29}N_5O_2 \cdot HCl$
molar weight	395.93 g mol^{-1}
Structure	
General Properties	
Appearance	White to off-white crystalline powder
pKa	7.62
Solubility (25°C)	soluble in water, slightly soluble in ethanol, insoluble in acetone
Chiral form	none

Excipients in the tablet

There are no excipients in the tablets that present concerns from an abuse liability perspective.

1.2 In Vitro Manipulation and Extraction Studies for Products with Abuse-Deterrent Features

The Applicant is not seeking abuse-deterrent labeling and did not conduct manipulation or extraction studies to assess the abuse-deterrent properties of EXXUA.

2. Nonclinical Pharmacology

2.1 Receptor Binding and Functional Assays

The Applicant conducted several in vitro binding studies to assess the primary and secondary pharmacology of gepirone (Data obtained from primary non-clinical review: DARRTS; NDA 021164; Fossom, Linda; 03/08/2002). Study # (b) (4) -11156 determined that gepirone binds with moderate affinity to the 5-HT_{1A} receptor (K_i = 54 nM). Gepirone had little to no affinity at other serotonin receptors and did not bind significantly to dopamine1 (D1) or dopamine2 (D2) receptors. Gepirone did not bind to molecular targets typically associated with having a potential for abuse (e.g., GABAA, opioid receptors, and NMDA receptors).

According to the non-clinical review, the mechanism of action of gepirone as an antidepressant is unknown and this reviewer could not find data indicating that the activity of gepirone had been determined. However, published data indicate that gepirone is a full agonist at 5-HT_{1A} autoreceptors and a partial agonist at postsynaptic 5-HT_{1A} receptors (Blier and Ward, 2003).

Metabolites

Two major circulating metabolites of gepirone were identified in humans, 3′-OH-GEP and 1-PP. Study # (b) (4) -11156 determined that these metabolites had a similar binding profile as gepirone and did not bind to molecular targets typically associated with having a potential for abuse.

Conclusion

Gepirone binds to and functions as an agonist at 5-HT_{1A} receptors as does its major metabolites, 3′-OH-GEP and 1-PP. However, gepirone and its metabolites do not bind to molecular targets typically associated with having a potential for abuse. Notably, gepirone has lower binding affinity to 5-HT_{1A} receptors than buspirone which is approved for medical use and is not controlled in the CSA.

2.3 Animal Behavioral Studies

Toxicity Studies

According to the nonclinical review conducted in 2002 (DARRTS: NDA 021164; Pharm/Tox review; Fossom, Linda; 03/08/2002):

> *"Gepirone was active in animal models that are predictive of antidepressant and anxiolytic activity in humans. Convulsions were occasionally noted in some general toxicology studies, and gepirone lowered seizure thresholds for strychinine and picrotoxin in rats."*

No other studies assessing the neurobehavioral effects gepirone have been submitted since this 2002 review.

Animal Abuse Potential Studies

The Sponsor submitted several study reports that were conducted to assess the abuse potential of gepirone in animals. Gepirone did not demonstrate reinforcing effects in a self-administration study and did not generalize to diazepam, amphetamine, or cocaine in drug discrimination studies. These data indicate that gepirone does not produce effects indicative of having a potential for abuse in animals.

Self-Administration Study

1. Study report # (b) (4)-25095 was a self-administration study conducted in rhesus monkeys trained to self-administer cocaine (IV). Note, the study was conducted in 1987. The objective of the study was to determine if gepirone and its metabolite, 1-pyrimidinylpiperazine (1-PP) produced reinforcing effects. In this study, four rhesus monkeys were trained to self-administer cocaine, two of the animals were drug naïve (ID #sM306 and M315) and the other two had previous drug experience. Animals were kept in chambers that consisted of two levers and three lights. One white light was located over each lever indicating that the lever was active, and a red light was located between the levers and would turn on during a 10 second infusion period. The animals were trained to a fixed ratio 10 (FR10) level of reinforcement using cocaine doses that were determined by the animals' individual weight. The animals were maintained on cocaine and substitution sessions with gepirone or saline occurred following three consecutive sessions in which there was no obvious increase or decrease in cocaine infusions.

   All substitution sessions were preceded by and followed by a cocaine baseline session. Following the initial cocaine session was a saline session which was then followed by a gepirone HCl session (3, 10, 30, 100, or 300 µg/kg/infusion). Following the last dose of gepirone, a dose of 152 µg/kg 1-PP (gepirone metabolite) was tested. The results of the study indicated that each monkey obtainedmore infusions of cocaine compared to saline ranging from an average of 33.9 to 41.9 cocaine infusions compared to 1.0 to 13.8 saline infusions. All monkeys responded with low rates of gepirone infusions and 1-PP infusion upon substitution of these drugs. The number of infusions of both of these drugs was similar to the number of infusions for saline indicating that both gepirone and 1-PP do not serve as positive reinforcers under the doses tested.

Drug Discrimination Study

2. Study report # (b) (4)-10673 was a drug discrimination study conducted to determine the effects of buspirone and gepirone on amphetamine and LSD drug discrimination. Two groups of rats (n = 16 per group) were trained to distinguish drug from saline to an FR 32 schedule of reinforcement. Group 1 was trained to distinguish 1 mg/kg amphetamine sulphate from saline and group 2 was trained to distinguish 0.16 mg/kg of lysergic acid diethylamide (LSD) bitartrate from saline. Substitution tests were performed when the animals attained a group criterion of 90% discrimination accuracy on both drug and saline days and 75% discrimination accuracy on an individual criterion. Two tests were performed: Substitution tests tested the ability of various compounds to mimic the training drug cue (i.e., amphetamine or LSD) and in antagonism testing the drugs were given prior to the training drug in order to determine the degree of attenuation of drug lever responding.

   Gepirone (1, 2.5, 5.75, 5 mg/kg IP) failed to generalize to the discriminative stimulus effects of amphetamine at all doses tested with less than 11% responding on the amphetamine lever.

However, gepirone (1, 2.5, and 5 mg/kg IP) produced partial generalization on the LSD lever with 53% responding on the LSD lever. Doses of 3.75 and 5 mg/kg gepirone also attenuated the the effect produced by 0.16 mg/kg LSD in the antagonism testing paradigm. Overall, these data indicate that gepirone does not generalize to amphetamine or LSD.

2.4 Tolerance and Physical Dependence Studies in Animals

No animal studies were conducted by the applicant to assess the tolerance or physical dependence of gepirone. However, there were recovery arms in the toxicity studies conducted by the Sponsor. According to a previous review (DARRTS: NDA 021164; Pharm/Tox review; Fossom, Linda; 03/08/2002):

> "*Dependence to gepirone was not directly addressed, however, the recovery arms of the chronic toxicology studies could offer some information regarding withdrawal signs, such as weight loss, when dosing was discontinued. In a toxicity study in dogs, the Sponsor concluded that there was no evidence of withdrawal signs during 3 drug-free months after 1-year of daily dosing in dogs. However, there was some evidence of increased incidence of diarrhea in dogs that had received the high dose (16 mg/kg/d). In a study in rats (3-month drug-free recovery after 6 months of daily, dietary dosing), there was no evidence of decreased body weights or food consumption, but the earliest time assessed after termination of dosing was 2 weeks, after withdrawal signs would be expected to be finished*."

Overall these data suggest that the physical dependence liability of gepirone is minimal in animals, however, an adequately conducted study would need to be conducted in order to make a final determination.

3. Clinical Studies

3.1 Human Abuse Potential Studies

The Applicant was not required to conduct a human abuse potential study to assess the abuse liability of gepirone.

3.2 Adverse Event Profile Through all Phases of Development

Adverse Events in Clinical Studies Conducted by the Applicant

According to the Sponsor, a total of 5,868 individual subjects were exposed to gepirone ER or IR in 87 clinical studies. These data sets are included in the integrated summary of safety that was put together in 2007. All adverse events (AEs), including abuse-related AEs were coded to a Medical Dictionary for Regulatory Activities (MedDRA) and the MedDRA system organ class (SOC) and preferred term (PT). The following is a description and analysis of abuse-related AEs found during these studies.

The Applicant was initially asked to provide a summary of abuse related AEs on March 1, 2017, as part of a Type B meeting. The Sponsor provided their summary based on the SMQ for drug abuse, dependence, and withdrawal which was deemed insufficient by CSS as this SMQ relates to whether a drug is abused in a highly controlled clinical trial setting. This SMQ does not include PTs that are indicative of the effects produced by a drug that may be sought after by those who abuse drugs. As a result, CSS sent two information requests (one on May 1, 2023, and the second on May 11, 2023) which asked the Applicant to provide an analysis of abuse related adverse events on preferred terms that focus on whether a drug produces effects that will be sought out for abuse purposes. The Applicant provided their response by e-mail on May 24, 2023, and the response was entered into the NDA.

Phase 1 Studies

It is unclear how many abuse related PTs were reported in phase 1 studies. The Sponsor only provided an analysis of the abuse related AEs for the studies used for the safety analysis and labeling (i.e., not the 87 clinical studies mentioned above). This analysis included 26 phase 1 studies. These data are summarized in Table 2 and indicate a minimal number of abuse related AEs from gepirone given to healthy human subjects.

Notably, there are 13 phase 1 studies in the integrated summary of safety from 2007 that are not included in the analysis. These studies are: CN105-026, 28718, CN105-007, CN105-012, CN105-009, 030L1-0002-1869, 59B4A-001-2579, 030L1-0001-1700, 59B4B-001-2587, 03A7D-001, CN105-005, CN105-025, CN105-023. Furthermore, there are three phase 1 studies that were included in the IR response from May 24th, 2023, that are not included in the integrated summary of safety from 2007. These studies are: FK-GBE-011, FK-GBE-012, FK-GBE-014. Because of this discrepancy it is not possible for the Agency to do a complete analysis of the abuse related AEs for all of the phase 1 studies conducted by the Sponsor.

Table 2: Nervous System and Psychiatric Disorder Abuse Related Adverse Events Reported by Preferred Term in Phase 1 Studies (N (%))

Preferred Term	**Gepirone**	**Placebo**
N=	760	72
Nervous System Disorders		
Somnolence	74 (9.74)	4 (5.56)
Disturbance in Attention	7 (0.92)	0 (0)
Feeling abnormal	7 (0.92)	0 (0)
Sensory Disturbance	7 (0.92)	0 (0)
Psychiatric Disorders		
Agitation	3 (0.39)	0 (0)
Euphoric mood	2 (0.26)	0 (0)
Feeling drunk	2 (0.26)	0 (0)

Phase 2/3 Studies

Based on the response of the Applicant to the IR, and using the Integrated Summary of Safety from 2007, CSS generated Tables 3 and 4 as an analysis of the abuse related adverse events that were reported during all phase 2 and 3 studies of clinical development for gepirone. Table 3 contains the abuse related PTs from the SOC of Nervous System Disorders. The majority of the drug related PTs were not significantly different from the placebo group in frequency except for dizziness and balance disorder, both of which are not a significant concern for abuse related effects.

Table 3: Nervous System Disorder-Abuse Related Adverse Events Reported by Preferred Term in Phase 2 and 3 Studies (N (%))

	Treatment (Gepirone formulations + Placebo)			
Preferred Term	**ER**	**IR**	**ER + IR**	**Placebo**
N=	3117	1859	4976	2483
Nervous System Disorders				
Dizziness	969 (31.09)	802 (43.14)	1771 (35.59)	260 (10.47)
Somnolence	210 (6.74)	194 (10.44)	404 (8.12)	158 (6.36)
Disturbance in Attention	35 (1.12)	29 (1.56)	64 (1.29)	29 (1.17)
Amnesia	5 (0.16)	13 (0.7)	18 (0.36)	12 (0.48)
Memory impairment	24 (0.77)	19 (1.02)	43 (0.86)	19 (0.77)
Hypersomnia	13 (0.42)	5 (0.27)	18 (0.36)	9 (0.36)
Balance Disorder	13 (0.42)	9 (0.48)	22 (0.44)	2 (0.08)
Sensory Disturbance	6 (0.19)	6 (0.32)	12 (0.24)	1 (0.04)
Dreamy state	1 (0.03)	0 (0)	1 (0.02)	0 (0)

Table 4 contains the abuse related PTs from the SOC of Psychiatric Disorders. The majority of the drug related PTs were not significantly different from the placebo group in frequency, however, there are a concerning amount of PTs reported. In all, a total of 27 psychiatric PTs were reported in phase 2 and 3 studies resulting in a concerning number of reports of Euphoric Mood (14 (0.28)) and Hallucinations (7 (0.22)). However, the frequency of these events was not significantly different from that of the placebo group: Euphoric Mood (5 (0.2)) and Hallucinations (1 (0.04)). Furthermore, the subject population for the majority of these studies had major depressive disorder who, according to the Diagnostic and Statistical Manual of Mental Disorders -5 (DSM-5), present with many of these PTs as part of the disease state.

Table 4: Psychiatric Disorder-Abuse Related Adverse Events Reported by Preferred Term in Phase 2 and 3 Studies (N (%))

	Treatment			
Preferred Term	**ER**	**IR**	**ER + IR**	**Placebo**
N=	3117	1859	4976	2483
Psychiatric Disorders				
Anxiety	157 (5.04)	86 (4.63)	243 (4.88)	74 (2.98)
Abnormal Dreams	88 (2.82)	36 (1.94)	124 (2.49)	43 (1.73)
Agitation	60 (1.92)	48 (2.58)	108 (2.17)	29 (1.17)
Depression	47 (1.51)	46 (2.47)	93 (1.87)	25 (1.01)
Restlessness	30 (0.96)	26 (1.4)	56 (1.13)	17 (0.68)
Confusional state	15 (0.48)	18 (0.97)	33 (0.66)	10 (0.4)
Disorientation	20 (0.64)	18 (0.97)	38 (0.76)	4 (0.16)
Suicidal ideation	21 (0.67)	6 (0.32)	27 (0.54)	10 (0.4)
Derealization	14 (0.45)	7 (0.38)	21 (0.42)	4 (0.16)
Thinking abnormal	13 (0.42)	5 (0.27)	18 (0.36)	4 (0.16)
Depersonalization	10 (0.32)	7 (0.38)	17 (0.34)	4 (0.16)
Euphoric mood	5 (0.16)	9 (0.48)	14 (0.28)	5 (0.2)
Dissociation	7 (0.22)	3 (0.16)	10 (0.2)	4 (0.16)
Mood swings	8 (0.26)	3 (0.16)	11 (0.22)	1 (0.04)
Affect lability	6 (0.19)	3 (0.16)	9 (0.18)	0 (0)
Dysphoria	2 (0.06)	7 (0.38)	9 (0.18)	0 (0)
Depressed mood	4 (0.13)	1 (0.05)	5 (0.1)	1 (0.04)
Paranoia	4 (0.13)	2 (0.11)	6 (0.12)	0 (0)
Hallucination	2 (0.06)	1 (0.05)	3 (0.06)	0 (0)
Hallucination, auditory	2 (0.06)	0 (0)	2 (0.04)	1 (0.04)
Delusion	2 (0.06)	0 (0)	2 (0.04)	0 (0)
Illusion	2 (0.06)	0 (0)	2 (0.04)	0 (0)
Mania	1 (0.03)	1 (0.05)	2 (0.04)	0 (0)
Mood altered	1 (0.03)	0 (0)	1 (0.02)	1 (0.04)
Delirium	0 (0)	1 (0.05)	1 (0.02)	0 (0)
Hallucination, tactile	1 (0.03)	0 (0)	1 (0.02)	0 (0)
Hallucination, visual	1 (0.03)	0 (0)	1 (0.02)	0 (0)

We note that there were some small individual differences between the frequency of the reported AEs between the ER and the IR formulations of gepirone, however, no significant difference could be seen in the reported AEs between the two formulations.

Overall, this reviewer has determined that gepirone did not produce a concerning number of abuse related AEs to warrant a human abuse potential study.

There were seven documented overdoses of gepirone in the clinical studies. The study #, subject # amount of drug consumed, and AE associated with the overdose are presented in the table below (table obtained from NDA 021164, Module 2.7.4, Summary of clinical studies to evaluate safety 2007, pg. 31). One overdose resulted in an altered level of consciousness; however, it is unknown how much gepirone was consumed.

Table 53 Gepirone Overdoses During the Gepirone Clinical Development Program

ISS Subject ID (Study, Subject ID)	Gepirone Dose Ingested	AEs Associated with Overdose
(b) (6) (134501, (b) (6))	Unknown Gepirone ER	Unknown
(b) (6) (134501, (b) (6))	Unknown Gepirone ER	Altered level of consciousness, seizure
(b) (6) (03A7C-001B, (b) (6))	35 mg Gepirone IR	None noted.
(b) (6) (CN105-053, (b) (6))	200 mg Gepirone ER	Incomplete right bundle branch block
(b) (6) (CN105-053, (b) (6))	500 mg Gepirone ER	None noted.
(b) (6) (CN105-078, (b) (6))	500 mg Gepirone ER	Vomiting
(b) (6) (28709, Subject (b) (6))	Unknown Gepirone ER	None noted

Physical Dependence

The physical dependence liability of gepirone was not directly tested in humans. However, AEs related to a withdrawal syndrome were assessed in several studies. In this regard, two subjects reported the preferred term Drug Withdrawal Syndrome. Based on the 4976 people who received drug, these reports, which are discussed below, are considered insignificant. It is also unclear whether either of the subjects recovered from their symptoms upon discontinuation from the studies or whether their symptoms persisted possibly indicating another issue. Each subject also had a very different timeframe for initiation of the reported withdrawal effect (several hours vs. 10-days) despite taking the same drug formulation, dose, and for a similar amount of time.

1. Subject # (b) (6) (Study # 134501) was a 43-year-old Caucasian female. The subject experienced severe fatigue, shortness of breath, nausea, and couldn't get out of bed in the morning when she didn't take her evening dose of medication. She was taking gepirone ER (80 mg/day) and these symptoms would alleviate when she resumed her treatment.

2. Subject # (b) (6) (Study # 134506) was a 52-year-old Asian female who reportedly experienced a drug withdrawal syndrome 10-days after receiving her last dose of gepirone ER (80 mg/day). No actual AEs were reported that led to the conclusion that the subject was suffering from a drug withdrawal syndrome.

Furthermore, according to the Sponsor, Studies 03A7A-002 and 28709 were conducted to assess relapse of the disease state after gepirone treatment and also contained a discontinuation arm to assess withdrawal syndrome. Subjects received either gepirone IR (Study 03A7A-002) or ER (28709) for a 6- to 12- week period and were assessed for 7-days after drug discontinuation. Although, CSS typically recommends 14-days or longer, there were no clear indications of reported AEs that are indicative of a drug withdrawal syndrome reported in these studies. Overall, we conclude that there is no evidence that gepirone produces physical dependence leading to a distinct withdrawal syndrome.

3.4 Evidence of Abuse, Misuse, and Diversion in Clinical Trials

There were no reports of misuse, abuse, or diversion of gepirone in clinical trials.

4. Regulatory Issues and Assessment

There are no regulatory issues regarding the abuse potential of gepirone. Gepirone does not have abuse liability and will not be required to be controlled under the CSA.

5. References

Blier P and Ward NM (2003) Is there a role for 5-HT1A agonists in the treatment of depression? *Biol Psychiatry* **53**:193-203.

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/s/

EDWARD G HAWKINS
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08/08/2023 03:12:39 PM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: July 28, 2023

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Team Lead, Cardiac Safety IRT, DCN

To: Sarah Seung, PharmD
RPM, DP

Subject: Addendum to QT Consult to NDA 21164 (SDN 71)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo is an addendum to our review dated 4/24/2023, responding to the Division's additional questions through email (Dr. Michelle Horner, dated 07/25/2023) regarding the QT-related sections in the Division's draft of revised label. We reviewed the following materials:

- Previous IRT review for NDA 21164 dated 04/24/2023 in DARRTS; and
- Draft revised label in share point online.

1 Responses for the Division

Question 1. Based on your consult, I added language to Section 2 of the prescribing information. Could you please take a quick look at the QT language in Section 2 of the prescribing information and offer in-text edits and/or comments, as needed?

IRT's response: Please see our response to Question #2.

Question 2. In your review, you mention a variety of missing information or problems with the Sponsor's approach. Therefore, I want to make sure that ECGs are not being suggested for all subjects, just for the mod- to severe renal and higher risk subjects as described in section 2?

IRT's response: After reviewing our previous review and the Division's proposed label revisions, we recommend ECG monitoring in all patients, in addition to more frequent monitoring in patients with renal impairment and at high risk for arrhythmias because mean QTc prolongation exceeded 10 msec at exposure close to clinical exposure of the maximum recommended dose (80 mg QD, ER, with food). The Division's proposed revision of the label also limited the maximum dose to 40 mg QD in patients with severe renal impairment.

Considering these, we proposed changes to the label sections 2.1, 5.2, 7, 8.5, and 12.2 as shown below in section 2.2.

Question 3. In your review, you stated you could not find some of the studies. Do you need any of these studies? Let us know, we can probably get them for you. (e.g., The reviewer could not locate a hERG study, or the reports of the two nonclinical studies mentioned above).

IRT's response: Yes, we would like to see the study reports of hERG study for gepirone and its metabolites if they are available, and reports for the single oral dose telemetry canine study and in vitro cardiac Purkinje fiber study mentioned by the sponsor in "Highlights of Clinical Pharmacology and Cardiac Safety" (link). However, we do not anticipate the nonclinical studies will change our recommendations to the label.

2 BACKGROUND

2.1 Overall

Fabre-Kramer Pharmaceuticals, Inc. (Fabre-Kramer) is developing gepirone hydrochloride (EXXUA) extended-release (ER) tablets for the treatment of major depressive disorder (MDD) in adults.

In our previous review dated 04/24/2023, we reviewed the thorough QT (TQT) study FK-GBE-010 and the sponsor proposed label (referred as "original label"). We recommended ECG and electrolyte monitoring in patients with severe renal impairment or patients at higher risks (patients with QTc ≥ 450 msec or significant risk of developing torsade de pointes). We proposed language modifications in sections 5, 7, 8, and 12.2 in the label.

In the currently proposed label revision (referred to as "revised label"), the Division adopted our language modifications to sections 5, 7, 8, and 12.2, proposed new language in section 2, and recommended maximum dose to be reduced to 40 mg QD in geriatric patients, patients with moderate to severe renal impairment (creatinine clearance <50 mL/min), and patients with moderate hepatic impairment (Child-Pugh B). Unchanged from the original label, gepirone is contraindicated in patients with severe hepatic impairment or in those receiving a strong CYP3A4 inhibitor. Dose adjustment by 50% is suggested when a moderate CYP3A4 inhibitor is administered

Based on the currently recommended dose, the high clinical exposure would be co-administration of gepirone 40 mg QD with moderate CYP3A4 inhibitor (Cmax~35.0 ng/mL, see section 3.3).

In the thorough QT study FK-GBE-010, one dose level of gepirone 100 mg IR formulation, QD, administered with food, was studied. On Day 1, the geomean Cmax was 40.2 ng/mL, providing 1.5-fold coverage of clinical exposure and 1.1-fold high clinical exposure. The largest mean increase in baseline- and placebo-corrected QTc interval (ΔΔQTc) was 18.4 msec (upper 90% confidence interval [CI] = 22.7 ms). On Day 7, the geomean Cmax was 55.3 ng/mL, providing 2.0-fold coverage of clinical exposure and 1.6-fold of high clinical exposure. The largest mean ΔΔQTc was 16.1 msec (upper 90% CI = 20.7 ms).

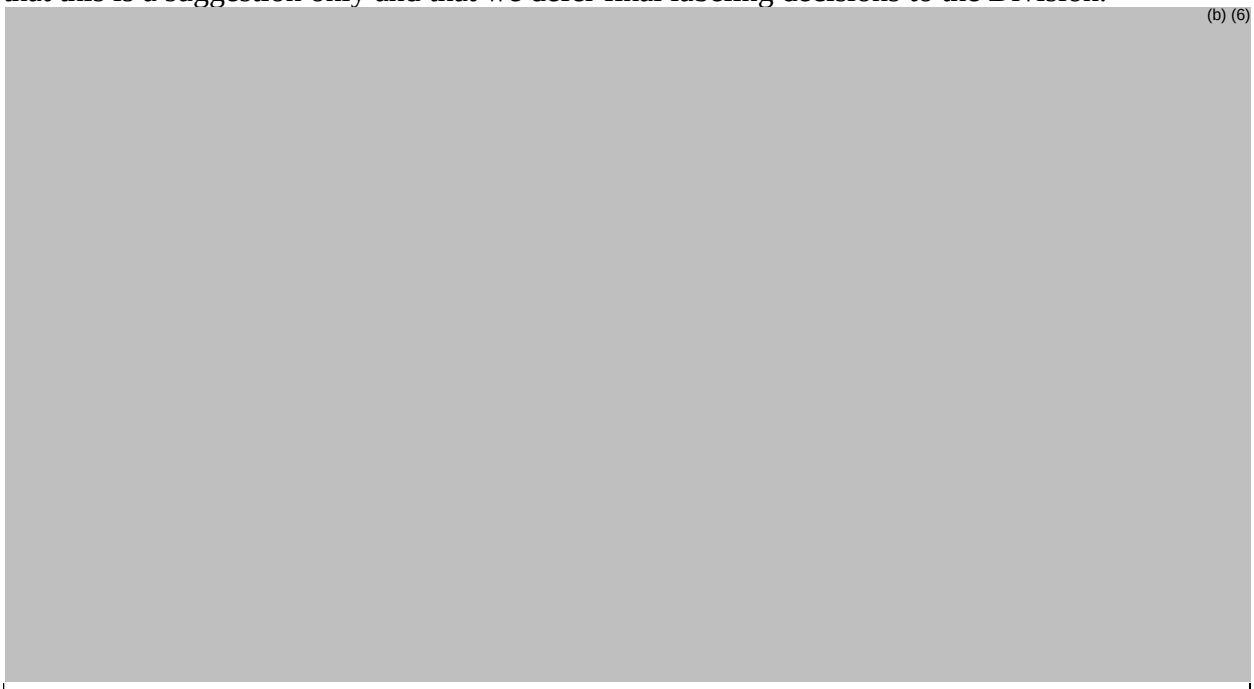
As explained in detail in our last review, we do not recommend using model to predict ΔΔQTc interval at doses not evaluated in the TQT study. Since QTc prolongation exceeding 10 msec was

observed at exposure close to the clinical exposure (Day 1), we recommend ECG and electrolyte monitoring in every patient at baseline, during dose titration, and periodically after that.

2.2 Proposed Label

Below are proposed edits to the revised label (07/26/2023). Our changes are highlighted (addition, ~~deletion~~). Each section is followed by a rationale for the changes made. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

(b) (6)



Reviewer's comment: We recommend ECG and electrolyte monitoring in all patients due to QTc prolongation observed at exposure close to clinical exposure. For patients with QTc > 450 msec or with higher risk for arrhythmias, we recommend more frequent monitoring. We defer to the Division on the monitoring schedule in this patient population.

We also defer to the Division whether dose escalation should be allowed in subjects with QTcF greater than 450 msec, and to withhold the drug until the QTcF drops below 450 msec.

In the revised label, the maximum recommended dose for severe renal impairment is 40 mg QD, which would result in exposure similar to patients with normal renal function. Therefore, for patients with severe renal impairment, we recommend similar monitoring as patients with normal renal function.

(b) (6)

Reviewer's comment: See our above comments in section 2 of the label.

(b) (6)

Reviewer's comment: No changes were made in this section.

(b) (6)

Reviewer's comment: See our above comments in section 2 of the label.

(b) (6)

Reviewer's comment: After reducing the maximum dose to 40 mg QD in patients with severe renal impairment, the exposure on Day 1 provided 1.5-fold clinical exposure and 1.1-fold high clinical exposure. The exposure on Day 7 provided 2.0-fold clinical exposure and 1.6-fold high clinical exposure.

2.3 Clinical Pharmacology

The target dose for ER formulation is 60 to 80 mg/day with the starting dose being 20 mg for 3 days followed by 40 mg for 4 days. If additional efficacy is desired and if the 40 mg dose is well tolerated, then the dose may be increased to 60 mg after one week and to 80 mg after an additional week.

Food increases Cmax by 1.6-fold following a high-fat meal compared to the fasted state. Cmax was increased by 1.9-fold in subjects with severe renal impairment compared with healthy subjects and was increased by 2.2-fold in subjects with hepatic impairment compared with healthy subjects. Concomitant administration of gepirone ER with strong CYP3A4 inhibitors (ketoconazole) increased Cmax by 5-fold. Moderate CYP3A4 inhibitors (verapamil) increased gepirone Cmax by 2.6-fold.

In the originally proposed label, gepirone is contraindicated in patients with severe hepatic impairment or in those receiving a strong CYP3A4 inhibitor. Dose adjustment by 50% is suggested when a moderate CYP3A4 inhibitor is administered. (b) (4)

Therefore, severe renal impairment was considered the high clinical exposure scenario (1.9-fold increase in Cmax).

In the currently proposed revision to the label, recommended maximum dose is reduced to 40 mg QD in geriatric patients, patients with moderate to severe renal impairment (creatinine clearance <50 mL/min), and patients with moderate hepatic impairment (Child-Pugh B). Consider linear PK, the high clinical exposure would be administering gepirone 40 mg QD ER with moderate CYP3A4 inhibitors (27.0x0.5x2.6).

Table 2: Summary of dose and exposure assessment

	Mean C_{max}

Highest therapeutic or clinical trial dosing regimen	80 mg QD, ER with food	27.0 ng/mL ($C_{max, ss}$)
Sponsor's High clinical exposure scenario	40 mg QD ER co-administered with moderate CYP3A4 inhibitor	35.0 ng/mL
Highest dose in QT assessment	100 mg QD, IR with food, on Day 7	55.3 ng/mL
C_{max} Ratio	1.6	

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

YANYAN JI
07/28/2023 04:33:49 PM

LARS JOHANNESEN
07/28/2023 04:50:35 PM

CHRISTINE E GARNETT
07/31/2023 08:18:57 AM

Memorandum of Consultation

Date of Consultation:	January 25, 2023
To:	Michelle Horner, DO Sarah Seung, PharmD, RPM Division of Psychiatry (DP)
From:	Linda S. Jaffe, MD Senior Physician Division of Urology, Obstetrics and Gynecology (DUOG) Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM) Office of New Drugs (OND)
Through:	Christina Chang, MD, MPH Director DUOG/ORPURM/OND
Subject:	NDA 021164 (gepirone) re-submission and post hoc analysis of sexual function in females
Applicant:	Fabre-Kramer, Inc.
Drug:	gepirone HCl extended release (ER)
Indication:	Major depressive disorder (MDD)
Dosage Form:	20 mg, 40 mg, 60 mg, and 80 mg, oral

Material Reviewed:
EDR Location: View submission in docuBridge
EDR Folder: \\CDSESUB1\evsprod\NDA021164\0005

Sexual Function Report: \\CDSESUB1\EVSPROD\nda021164\0005\m5\53-clin-stud-rep\535-rep-effic-safety-stud\mdd\5353-rep-analys-data-more-one-stud\sexual-function\sexual-function-study-report-1.pdf

Sexual function report tables, figures and listings:
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Applicant Response to Information Request
(SDN 87)
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1 EXECUTIVE SUMMARY

This consult review documents DUOG reproductive team's response to the consult request from DP that pertains to the assessment of ***female*** sexual function data (b) (4) for gepirone.[1]

Fabre-Kramer, Inc. (the Applicant) is seeking approval for gepirone for the treatment of major depressive disorder (MDD). The current submission constitutes the Applicant's Complete Response to the Office of New Drugs (OND) Appeal Granted letter dated March 16, 2016. In this resubmission, the Applicant has submitted post hoc analysis of clinical trial data and (b) (4) The Division of Psychiatry [(DP), formerly, the Division of Psychiatric Products (DPP)] requests that DUOG reviews the Applicant's sexual dysfunction data and provides feedback and recommendations (b) (4).

The focus of DUOG's review of female sexual dysfunction was on the three studies (134004, 134006 and 134017) described in the Sexual Function Report submitted in this resubmission, the two Phase 3 trials that demonstrated efficacy (134001 and FK-GBE-007) (b) (4)

Based on our review, DUOG has concluded that (b) (4) findings are inadequate (b) (4). We identified multiple concerns, listed below, that would need to be adequately addressed (b) (4).

(b) (4)

[1] See consult review by Dr. Roger Wiederhorn, dated May 19, 2023, for review of male sexual function.

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(b) (4)

6 CONCLUSIONS AND RECOMMENDATIONS

This DUOG Reproductive team concludes that (b) (4) in Studies 134001 and FK-GBE-007, the two Phase 3 placebo-controlled trials that demonstrated effectiveness, are acceptable (b) (4)

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/s/

LINDA S JAFFE
06/26/2023 04:24:13 PM

CHRISTINA Y CHANG
06/26/2023 04:25:00 PM

NDA 21164

Division of Urology, Obstetrics and Gynecology (DUOG) Consultation:
Male Sexual Dysfunction (b) (4)

Date:	May 22, 2023
To:	Sarah Seung, Senior Regulatory Project Manager Division of Psychiatry
From:	Roger Wiederhorn MD, Medical Officer, Division of Urology, Obstetrics and Gynecology (DUOG) Mark S. Hirsch, Medical Team Leader, DUOG Audrey Gassman, Deputy Director, DUOG
Product Name, Route and Dose:	EXXUA (gepirone) oral Tablets, 20 mg - 80 mg once daily
Indication:	Treatment of depressive disorders

1. Executive Summary

On January 25, 2023, DP requested consultation from DUOG, stating *"DP requests that DUOG reviews the Applicant's sexual dysfunction data* (b) (4) *and provides feedback and recommendations*".

In our opinion, (b) (4) are not supported by the sexual dysfunction because (b) (4) was:

- (b) (4)

(b) (4)

For further discussion of these summary points, the reader is referred to Sections 6 and 7 of this consultation.

(b) (4)

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(b) (4)

7. Consultant's Conclusion

DUOG concludes that (b) (4) from the two "pivotal" studies that demonstrated efficacy for gepirone in the treatment of MDD. (b) (4).

We have the following comments and recommendations for DP:

(b) (4)

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/s/

A R WIEDERHORN
05/22/2023 07:48:59 AM

MARK S HIRSCH
05/22/2023 08:41:21 AM
I concur.

AUDREY L GASSMAN
05/22/2023 08:50:21 AM

Clinical Outcome Assessment Review Memorandum

From	Selena Daniels, Pharm.D., Ph.D. COA Team Leader Division of Clinical Outcome Assessment (DCOA) David Reasner, Ph.D. Division Director DCOA
To	Division of Urology, Obstetrics, and Gynecology Division of Psychiatry
COA tracking number	C2023058, C2023059
sNDA# (Drug name)	021164
Drug Sponsor	Fabre-Kramer Pharmaceuticals, Inc.
PDUFA Goal Date:	June 23, 2023
Indication:	Treatment of major depressive disorder (MDD) ☐ Pediatric ☐ Rare Disease/Orphan Designation
Instrument(s) reviewed:	1. Derogatis Interview for Sexual Functioning (DISF) ☒ Patient-reported outcome (PRO)
	2. Changes in Sexual Functioning Questionnaire (CSFQ) ☒ Patient-reported outcome (PRO)
	3. Derogatis Interview for Sexual Function - Self Report (DISF-SR) ☒ Patient-reported outcome (PRO)

In this submission, the applicant is seeking approval of gepirone hydrochloride extended-release tablets for the treatment of major depressive disorder (MDD). The Division of Clinical Outcome Assessment (DCOA) has been consulted regarding the specific clinical outcome assessment (COA) (b) (4) improvement in sexual functioning, which are derived from five[1] short-term (eight-week) randomized, double-blinded, placebo-controlled clinical studies (Studies 134001, 134002, 134004, 134006, and 134017) in adult patients with MDD. The primary objective of this review is to evaluate from a COA perspective if the submitted information supports the COA (b) (4) this concept of interest.

There were no pre-specified COA endpoints that corresponds to the (b) (4).

The applicant purports the following:

- (b) (4)

[1] Three of the studies included an active comparator, either fluoxetine (Studies 134004 and 134017) or paroxetine (Study 134006).

(b) (4)

-
-

Note that there was no formal statistical testing for any of the COAs (not adjusted for multiplicity), as such these are viewed as exploratory endpoints.

From a COA perspective, the DISF, DISF-SR, and CSFQ and its corresponding endpoints (b) (4) for the intended context of use.

Review Conclusions

(b) (4)

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/s/

SELENA R DANIELS
04/24/2023 05:16:23 PM

DAVID S REASNER
04/25/2023 01:08:10 PM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 21164
Submission Number	71
Submission Date	12/23/2022
Date Consult Received	1/19/2023
Drug Name	Gepirone hydrochloride, extended release (ER)
Indication	Major Depressive Disorder (MDD)
Therapeutic Dose	60 to 80 mg/day taken with food
Clinical Division	DP
Protocol Review	Link

Note: Any text in the review with a light background should be considered to be copied from the sponsor's document.

This review responds to your consult dated 1/19/2023 regarding the sponsor's TQT study evaluation. We reviewed the following materials:

- Previous IRT review dated 09/25/2018 and 02/11/2019 in DARRTS;
- Previous Clinical Pharmacology Review for NDA021164 dated 02/19/2002 in DARRTS
- Previous Labelling Review for NDA021164 dated 02/19/2002 in DARRTS
- Sponsor's Cardiac Safety Report (NDA021164/SDN71);
- Sponsor's Clinical Study Report (NDA021164/SDN71);
- Sponsor's proposed Highlights of Prescribing Information (NDA021164/SDN74);
- Summary of Clinical Pharmacology Studies (NDA021164/SDN71);
- Highlights of clinical pharmacology and cardiac safety (NDA021164 / SDN71);
- Integrated Summary of Safety Addendum (NDA021164 / SDN05); and
- Integrated Summary of Safety 2007.

1 SUMMARY

Gepirone prolongs QTcF interval in this thorough QT study – see Table 1 for overall results.

The clinical study FK-GBE-010 is a phase 1, partially double-blind, placebo- and active-controlled, multiple-dose, 3-way crossover study in healthy subjects to evaluate the effect of gepirone 100 mg/day immediate release (IR) on the QTcF interval. The exposure in this study covers the steady state Cmax of 80 mg/day gepirone ER (administered with food) by 2-fold and was similar to the high clinical exposure which is defined as 80 mg/day gepirone ER administered to severely renal impaired patients.

Our primary analysis is the by-time analysis, which showed that gepirone is associated with significant QTc prolongation at exposures close to high clinical exposure. The largest mean increase in ΔΔQTcF interval is 17 msec on day 1 and 15 msec on day 7 (refer to section 4.3). Because the sponsor's concentration-QTc analysis is not appropriate (see below for details), the QTc effect at clinical exposures was not predicted by the model.

Table 1: Summary of findings

<table>
<tr><td>QT assessment pathway</td><td>☒ Thorough QT study
☐ Substitute for thorough QT study (5.1)
☐ Alternative QT study when a thorough QT study is not feasible (6.1)</td></tr>
<tr><td>Clinical QT study findings</td><td>• High clinical exposure scenario is when gepirone-ER is administered with food in patients with severe renal impairment. In these subjects, geometric mean Cmax after 80 mg QD is estimated to be 51 ng/mL (see section 3.1)
• The maximum tested dose in the TQT study was gepirone-IR 100 mg which provided maximum geometric mean Cmax of 55 ng/mL and covers the high clinical Cmax.
<table>
<tr><th>ECG parameter</th><th>Treatment</th><th>Day</th><th>Time (h)</th><th>ΔΔQTcF (msec)</th><th>90% CI (msec)</th></tr>
<tr><td>QTcF</td><td>Gepirone IR 100 mg/day with food</td><td>1</td><td>5.0</td><td>17.4</td><td>(13.2 to 21.6)</td></tr>
<tr><td>QTcF</td><td>Gepirone IR 100 mg/day with food</td><td>7</td><td>3.0</td><td>15.1</td><td>(11.1 to 19.0)</td></tr>
</table></td></tr>
<tr><td>In vitro/in vivo findings</td><td>The sponsor did not conduct a hERG assay for parent or metabolites. Of note, the exposures of 3'-OH metabolite are higher than gepirone.</td></tr>
</table>

Limitations of the concentration-QTc analysis

Drugs that inhibit the hERG channel have a linear response over clinical exposures. However, the sponsor used a nonlinear Emax model to describe the relationship between gepirone concentrations and placebo- and baseline-corrected QTcF (ΔΔQTc) interval. A nonlinear model was used because the exposures to gepirone on day 7 were 40% higher than the exposures on day 1, but without further increases in ΔΔQTc. However, analyzing the data of Day 1 and Day 7 separately showed different concentration-QTc relationships: While Day 1 data indicated that lengthening of QTc interval plateaued after about 10 ng/mL, Day 7 data indicated linear relationship over higher concentrations. It is unclear to us the reason for these differences. It's also unclear to us if the QTc prolongation response is due to gepirone, its two metabolites or a combination of gepirone and metabolites. The sponsor did not conduct any hERG assays to understand the mechanism for QTc prolongation. Given the lack of understanding of the mechanism, the lack of evaluating multiple dose levels in the TQT study, and the possibility of parent and/or metabolites contributing to the QTc response, we do not recommend using the model to predict ΔΔQTc interval at doses not evaluated in the study.

Limitations on Outlier Analysis of QTc Intervals Collected in Patient Studies

We could not find the ECG schedule for the studies included in the sponsor's ISS tables. Therefore, we do not know the adequacy of the outlier analysis results to inform Section 5 of the label. For the two studies used to support efficacy (studies FK-GBE-007 and FK-GBE-008), ECGs were collected only at screening and are not informative for labeling.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

If the Division would like a better characterization of the QTc effect of 80 mg/day gepirone ER on QTc prolongation, we recommend another QT study with multiple dose levels. We do not recommend using the concentration-QTc model to predict ΔΔQTc interval at doses not evaluated in the study due to the limitations with the model.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to SDN 005 (link). Our changes are highlighted (addition, ~~deletion~~). Each section is followed by a rationale for the changes made. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

(b) (4)

Reviewer's comment: *Exposure is increased in subjects with severe renal impairment. Dose titration to 80 mg/day in patients with severe renal impairment will result in increased risk for QTc prolongation. Therefore, we are recommending ECG and*

electrolyte monitoring in this population during dose titration, and periodically during treatment.

See our recommendations in Warnings and Precautions [5] and Use in Specific Populations [8.5].

(b) (4)

Reviewer's comment: We do not agree with the sponsor's proposed language in section 5.2 for the following reasons:

- *We do not agree with the sponsor's conclusion that* (b) (4) *. See our comments below in Pharmacodynamics [12.2].*
- (b) (4) *for renal insufficiency. These patients are at increased risk for QTc prolongation and should be monitored.*
- *We recommend removing* (b) (4)

(b) (4)

(b) (4)

Reviewer's comment: (b) (4)

(b) (4)

Reviewer's comment: Dose titration to 80 mg/day in patients with severe renal impairment will result in increased risk for QTc prolongation. Therefore, we are recommending ECG and electrolyte monitoring in this population during dose titration, and periodically during treatment.

(b) (4)

(b) (4)

Reviewer's comment: We do not agree with sponsor's proposed language for the following reasons:

- *We do agree with* (b) (4) . *Our primary analysis was based on the by-time analysis and the results are consistent with the sponsor's results. Therefore, we included the sponsor's values in the label.*
- *We do not agree with* (b) (4) *. Food increases Cmax by 1.6-fold.*
- *The exposure achieved with 100 mg gepirone IR is similar to plasma concentration at maximum recommended dose in severe renal impairment.*
- *We do not agree with* (b) (4)
- (b) (4)

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

Fabre-Kramer Pharmaceuticals, Inc. (Fabre-Kramer) is developing gepirone hydrochloride (EXXUA) extended-release (ER) tablets for the treatment of major depressive disorder (MDD) in adults. (b) (4) Gepirone is a chemical analog of buspirone (Buspar®) and is considered to be a non-benzodiazepine agent with antidepressant and anxiolytic potential. Gepirone interacts principally with serotonin type-1A receptors and acts as a partial agonist at these sites. It does not strongly interact with brain dopamine receptors. Because gepirone

increases noradrenergic turnover, it is predicted that gepirone should lack benzodiazepine-like liabilities for psychomotor impairment and withdrawal symptoms and should be devoid of benzodiazepine-like abuse potential. Further, as gepirone does not interact potently with ethanol or hexobarbital, it is anticipated that gepirone will be safer than benzodiazepines if inappropriately used with alcohol.

We have previously reviewed the sponsor proposed TQT protocol (in DARRTS 9/25/2018 and 2/11/2019 with links above). The major comments from our first review were to provide dose justification for the supratherapeutic dose. We also recommended the sponsor to provide information on the steady state Cmax for the two major metabolites (3'-OH-gepirone and 1-PP) with 80 mg ER QD and the expected exposures for the parent drug and metabolites with the proposed 100 mg IR QD dosing for 7 days. The sponsor did not provide responses in the last revision of the protocol. We also suggested single dose study design, but it's not clear if this recommendation was delivered to the sponsor.

3.1.1 Clinical Pharmacology

Please refer to the highlight to clinical pharmacology table for more details.

The target dose for ER formulation is 60 to 80 mg/day with the starting dose being 20 mg for 3 days followed by 40 mg for 4 days. If additional efficacy is desired and if the 40 mg dose is well tolerated, then the dose may be increased to 60 mg after one week and to 80 mg after an additional week.

The geometric mean (CV%) Cmax of the ER formulation is 16.9 ng/ml (CV 37.5 %) at steady state of 80 mg QD when given without food. Tmax is ~1 h (IR), ~5 h (ER) and the terminal half-life ~2-3 hours for the IR formulation. The main elimination route is through urine (81%). The two major metabolites are 3'-OH gepirone and 1 PP, both of which have higher concentrations than the parent drug in plasma.

Food increases Cmax by 1.6-fold following a high-fat meal compared to the fasted state. Cmax was increased by 1.9-fold in subjects with severe renal impairment compared with healthy subjects and was increased by 2.2-fold in subjects with hepatic impairment compared with healthy subjects. Concomitant administration of gepirone ER with strong CYP3A4 inhibitors (ketoconazole) increased Cmax by 5-fold. Moderate CYP3A4 inhibitors (verapamil) increased gepirone Cmax by 2.6-fold.

In the proposed label, gepirone is contraindicated in patients with severe hepatic impairment or in those receiving a strong CYP3A4 inhibitor. Dose adjustment by 50% is suggested when a moderate CYP3A4 inhibitor is administered. (b) (4) . No dosage modification is required in patients with mild renal impairment.

The clinical exposure at steady state under 80 mg QD of the ER formulation with food would be 27.0 ng/mL (i.e., 16.9 × 1.6). Since strong CYP3A4 inhibitor and severe hepatic impairment are contraindicated, the high clinical scenario would be administering gepirone with food in patients with severe renal impairment (Cmax ~ 51.4 ng/mL, i.e., 16.9 × 1.6 × 1.9).

In the TQT study, the geometric mean Cmax for gepirone, 3'-OH gepirone, and 1-PP were 55.3 ng/mL, 124 ng/mL, and 39.8 ng/mL, respectively, measured on Day 7. Therefore, geometric mean Cmax of gepirone provided coverage of the high clinical exposure.

Reviewer's comment*: We could not find steady state Cmax values for the major metabolites (3'-OH gepirone and 1-PP). In the sponsor's cardiac safety report, Cmax at steady state of 80 mg QD when given in fasting state (16.9 ng/mL) was used to predict effect of gepirone on QTc at clinical exposure; however, gepirone is recommended to be taken with food in the label.*

Table 2: Summary of dose and exposure assessment

		Mean C_{max}
Highest therapeutic or clinical trial dosing regimen	80 mg QD, ER with food	27.0 ng/mL ($C_{max, ss}$)
Sponsor's High clinical exposure scenario	1.9-fold increase with severe renal impairment with food	51.4 ng/mL
Highest dose in QT assessment	100 mg IR, Day 7 with food	*55.3 ng/mL
C_{max} Ratio	1.1 (55.3/51.4)	

* Cardiac safety report has slightly different values (52 ng/mL for parent).

3.1.2 Nonclinical Safety Pharmacology Assessments

In a single oral dose telemetry canine study, dogs were administered doses of 4, 8 and 16 mg/kg of Gepirone. At 8 mg/kg and above doses, there was an increase in heart rate. The Fridericia and Sarma correction QT heart rate correction formulas were considered to be the most appropriate algorithms. The results using these formulas showed no consistent findings of gepirone-related QTc prolongation or arrhythmias in the conscious dog receiving the maximum feasible supra-therapeutic dose of up to 16 mg/kg (there was a small (12 ms (~5%)) isolated increase in the QTc interval using the Sarma equation only at 20 hours' post-dose (significantly removed from Cmax) that was not evident using the Fridericia correction method). The study conclusion was that up to the supra-therapeutic dose of 16 mg/kg of Gepirone, that there was no meaningful effect on the QTc interval.

In an *in vitro* cardiac Purkinje fiber study, the action potential duration (ADP) was prolonged at supra-therapeutic concentrations of 1 uM and higher concentrations, but not

at 0.1 uM. At a concentration of Gepirone 1 uM, the APD_{90} was prolonged by 11% at 1 Hz (60 BPM) and 20.5% during marked bradycardia at .33 Hz (20 BPM). Similarly, at a concentration of the 3-OH-gepirone metabolite, the APD_{90} was prolonged by 9.5% at 1 Hz (60 BPM) and 16.3% during marked bradycardia at .33 Hz (20 BPM). At higher exposures, a dose-response relationship was evident.

Reviewer's comment*: The reviewer could not locate a hERG study, or the reports of the two nonclinical studies mentioned above.*

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

The sponsor's primary analysis for gepirone was based on exposure-response analysis, please see section 3.2.3 for additional details.

In the sponsor's by-time analysis, the largest upper bound of 90% CI of ΔΔQTcF were 22.7 msec at 5 hours post dose on Day 1 and 20.7 msec at 3 hours post dose on Day 7.

Reviewer's comment: *The reviewer's primary analysis is by-time analysis. Our results are similar to sponsor's results— the largest one-sided upper bound of 95% confidence interval were above 10 msec on both Day 1 and Day 7. Please see section 4.3 for more details.*

3.2.1.1 Assay Sensitivity

Assay sensitivity was established by the moxifloxacin arm.

Reviewer's comment: *Results from FDA reviewer's analysis are similar to sponsor's results. Please see section 4.3.1.1 for more details.*

3.2.1.1.1 QT Bias Assessment

No QT bias assessment was conducted.

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., >500 msec or >60 msec over baseline), PR (>200 msec and 25% over baseline), and QRS (>120 msec and 25% over baseline). There was one subject of HR >100 beats/min and 25% over baseline.

Reviewer's comment: *Results from FDA reviewer's analysis are similar to sponsor's results with slightly different cutoffs. Please see section 4.4 for more details.*

3.2.3 Exposure-Response Analysis

The sponsor performed concentration-QTc analysis as their primary analysis from data including both Day 1 and Day 7. A full model including gepirone and its metabolites (1-PP and 3'-OH gepirone) was initially fitted and the model with gepirone alone was selected as the final model based on criteria in the model selection procedure. The estimated slope of gepirone plasma concentration in the concentration-QTc relationship was positive and statistically significant (0.21 msec per ng/mL [90% CI: 0.15, 0.27]) with a statistically significant intercept of 4.0 msec possibly due to the observed plateauing of

the increase in QTcF at higher exposures. Even though this model did not provide an ideal fit to the data as it seemed to overestimate the predicted effect in higher gepirone concentration deciles, the effect on ΔΔQTcF was predicted to be 7.5 msec (90% CI: 5.8 to 9.2) at the steady-state concentration of the maximum recommended therapeutic daily dose [80 mg QD] with the ER formulation (16.9 ng/mL) and 14.8 msec (90% CI: 11.8 to 17.8) at the geometric mean steady-state Cmax of 100 mg gepirone IR (52.0 ng/mL, 3.1-fold over steady-state clinical Cmax, and 1-fold over the high clinical Cmax).

The sponsor also fitted the data to an Emax model since a plateauing of gepirone's effect was observed on ΔΔQTcF at higher plasma concentrations. The results of the quantile plot of concentrations versus ΔΔQTcF provided a better fit to the data at high concentrations and confirmed the plateau effect at a maximal value of 15.5 msec. With the Emax model, gepirone's effect on ΔΔQTcF was predicted to be 12.7 msec (90% CI: 10.4 to 15.1) at the geometric mean steady-state Cmax of 100 mg gepirone IR (52.0 ng/mL).

Reviewer's comment: *The sponsor used Cmax at steady state of 80 mg QD when given in fasting state (16.9 ng/mL) to predict effect of gepirone on QTc at clinical exposure; however, gepirone is recommended to be taken with food in the label. Using fasting exposure is inappropriate. In addition, we do not think the concentration-QTc analysis was appropriate for the data from this TQT study for the following reasons:*

- *Day 1 and Day 7 had different time profiles for ΔQTcF, ΔΔQTcF and gepirone concentrations, indicating potential difference in study conduct between the two observation days. For example, ΔQTcF profiles for both placebo and gepirone treatment were lower on Day 7 compared to the corresponding profiles on Day 1. ΔΔQTcF profile for gepirone was also lower on Day 7 compared to Day 1. In addition, despite having short half-life (2.5 hrs), gepirone plasma concentration on Day 7 was observed to be 1.4-fold higher compared to Day 1. Furthermore, hysteresis plots indicate delayed QT prolongation relative to gepirone concentrations on Day 1 but not on Day 7 (Cardiac safety report, Figure 14.2.7.1); ΔΔQTcF profile plateaued between 3 - 8 hours post dose on Day 1 but not on Day 7. Consequently, gepirone concentration-QTc relationship differs between Day 1 and Day 7: While the relationship is non-linear on Day 1, it is linear on Day 7 (See Figure 6 in section 4.5). The reason for this difference is unknown. It is unclear which day represents the true gepirone concentration-QTc relationship.*
- *Contribution of the metabolites to the observed QTc prolongation is not clear. Hysteresis plots for both 1-PP and 3-OH gepirone show clockwise loops on both Days 1 and 7, indicating that QT prolongation preceded exposure of both 1-PP and 3-OH gepirone on Days 1 and 7 (Cardiac safety report, Figure 14.2.7.2 and Figure 14.2.7.3). Due to absence of data from hERG assays, it is not clear whether the metabolites have some contribution to QT-prolongation.*

3.2.4 Safety Analysis

There were no life-threatening TEAEs, SAEs, or deaths reported during study FK-GBE-010.

More subjects experienced TEAEs following gepirone (93.1%) than placebo (32.2%) and moxifloxacin (34.4%). The most common TEAEs overall were nausea (69.7%), dizziness (60.6%), vomiting (42.4%), feeling hot (36.4%), headache (24.2%), medical device site dermatitis (15.2%), somnolence (12.1%), and palpitations (12.1%).

The majority of the reported TEAEs were mild (63.6%) or moderate (24.2%) in severity. There were 2 severe TEAEs (somnolence and mental status changes) reported by 2 subjects following administration of gepirone.

Four subjects (13.8%) following gepirone and two subjects (6.5%) following placebo discontinued from the study due to TEAEs. AEs leading to discontinuation following gepirone were acute mental status changes, vomiting, somnolence, and urinary tract infection.

Reviewer's comment: *None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., seizure, significant ventricular arrhythmias, or sudden cardiac death) occurred in this study in healthy volunteers.*

See section 4.6 for integrated cardiac safety assessment in patients.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., |mean| >10 beats/min) were observed (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall, ECG acquisition and interpretation in this study appear acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY-TIME ANALYSIS

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG.

The statistical reviewer used a linear mixed model to analyze the drug effect by-time for each biomarker (e.g., ΔQTcF, ΔHR) independently. The default model includes treatment, sequence, period, time (as a categorical variable), and treatment-by-time interaction as fixed effects, and baseline as a covariate. The default model also includes subject as a random effect and an unstructured covariance matrix to explain the associations among repeated measures within the period.

The statistical reviewer also performed by-time analysis by period as exploratory analysis. The model is similar to the default model except analyzing each period separately.

4.3.1 QTc

Figure 1 displays the time profile of ΔΔQTcF for different treatment groups. The maximum ΔΔQTcF values by treatment are shown in Table 3. The maximum ΔΔQTcF values by treatment by period are shown in Table 4, in which differences in ΔΔQTcF by treatment by period were noticed.

Figure 1: Mean and 90% CI of ΔΔQTcF Time-course (unadjusted CIs).

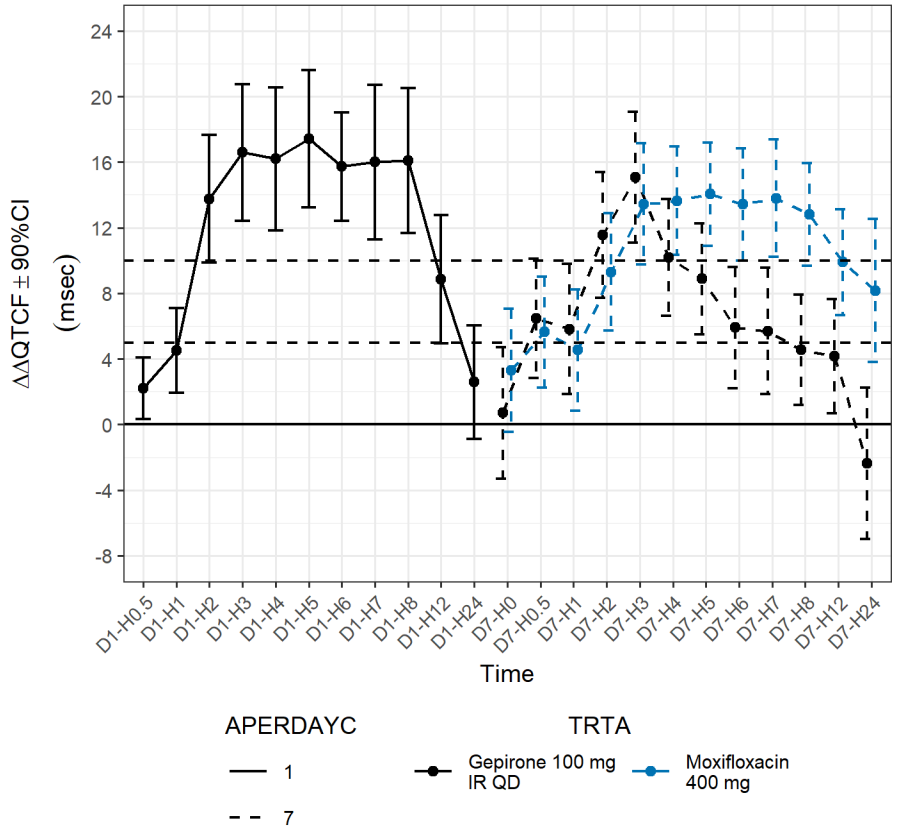


Table 3: Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔΔQTcF

Actual Treatment	Analysis Nominal Period Day (C)	Nact / Npbo	Time (Hour)	ΔΔQTCF (msec)	90.0% CI (msec)
Gepirone 100 mg IR QD	1	24 / 30	5.0	17.4	(13.2 to 21.6)
Gepirone 100 mg IR QD	7	24 / 28	3.0	15.1	(11.1 to 19.0)

Table 4: Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔΔQTcF by Period

Actual Treatment	Analysis Nominal Period Day (C)	Period (C)	Nact / Npbo	Time (Hour)	ΔΔQTCF (msec)	90.0% CI (msec)
Gepirone 100 mg IR QD	1	1	12 / 11	8.0	19.5	(13.3 to 25.6)
Gepirone 100 mg IR QD	1	2	8 / 11	5.0	23.6	(16.3 to 30.9)
Gepirone 100 mg IR QD	1	3	5 / 9	3.0	15.6	(7.5 to 23.7)
Gepirone 100 mg IR QD	7	1	12 / 10	3.0	19.6	(13.4 to 25.9)
Gepirone 100 mg IR QD	7	2	7 / 9	3.0	17.2	(10.1 to 24.2)
Gepirone 100 mg IR QD	7	3	5 / 9	3.0	4.0	(-4.9 to 12.9)

4.3.1.1 Assay Sensitivity

The model used for assay sensitivity is the same as that used for the primary model. The time-course of changes in ΔΔQTcF is shown in Figure 1 and includes the expected time-profile with a mean effect of >5 msec after Bonferroni adjustment for 4 time points (Table 5).

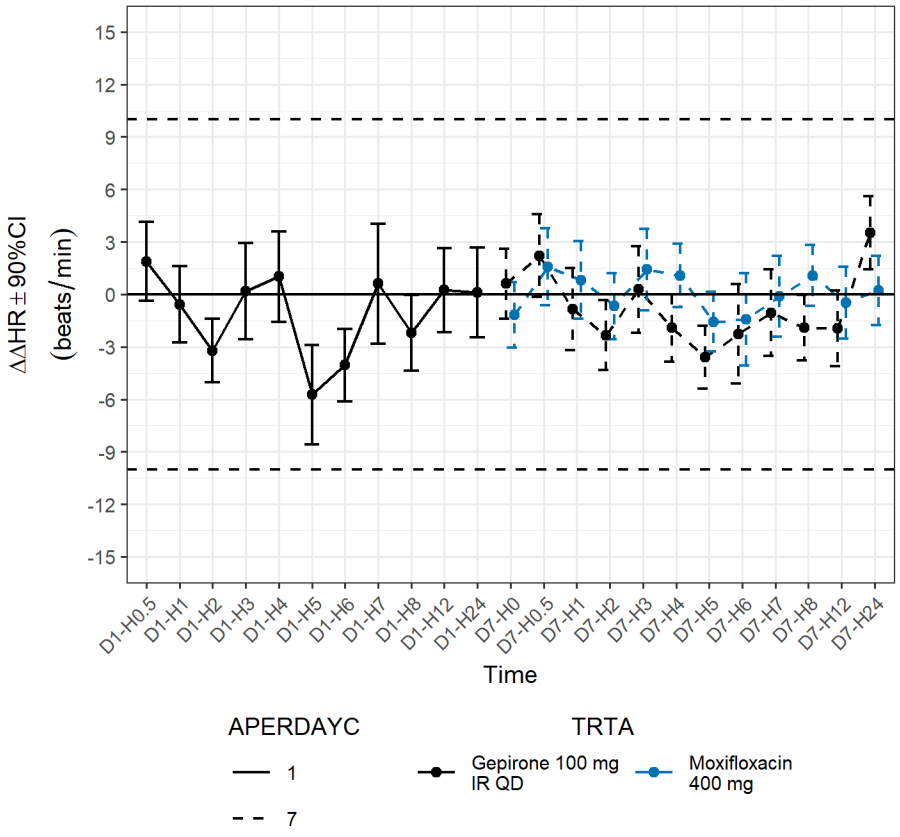
Table 5: The Point Estimates and the 90% CIs Corresponding to the Largest Lower Bounds for ΔΔQTcF

Actual Treatment	Nact / Npbo	Time (Hour)	ΔΔQTCF (msec)	90.0% CI (msec)	97.5% CI (msec)
Moxifloxacin 400 mg	31 / 28	5.0	14.0	(10.9 to 17.2)	(9.6 to 18.5)

4.3.2 HR

Figure 2 displays the time profile of ΔΔHR for different treatment groups.

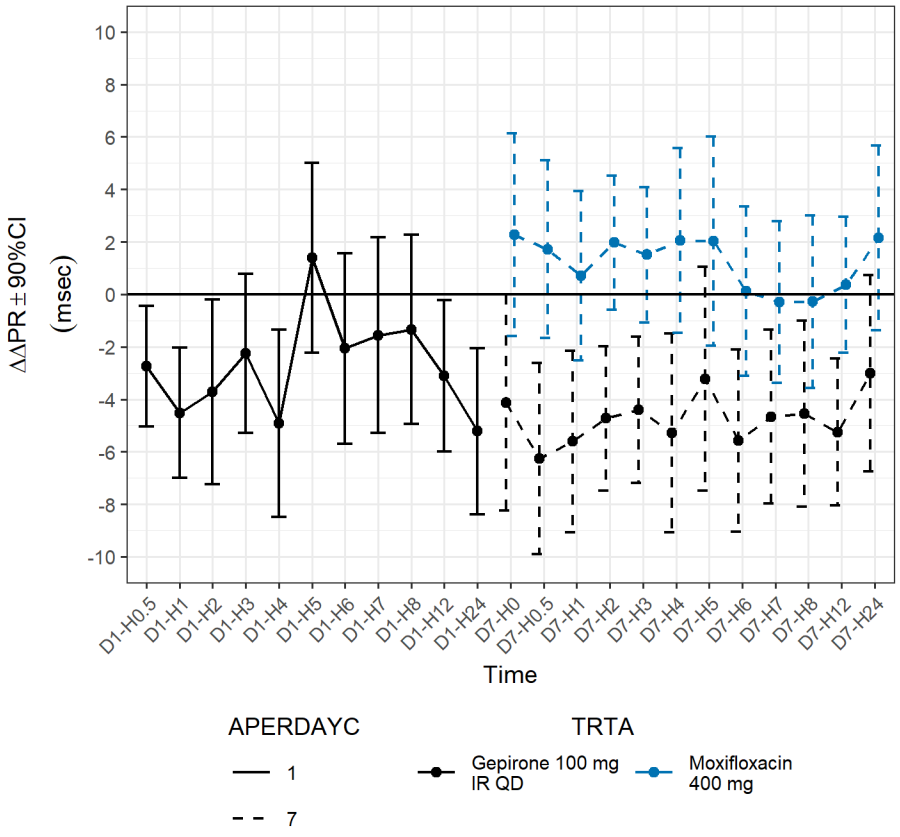
Figure 2: Mean and 90% CI of ΔΔHR Time-course



4.3.3 PR

Figure 3 displays the time profile of ΔΔPR for different treatment groups.

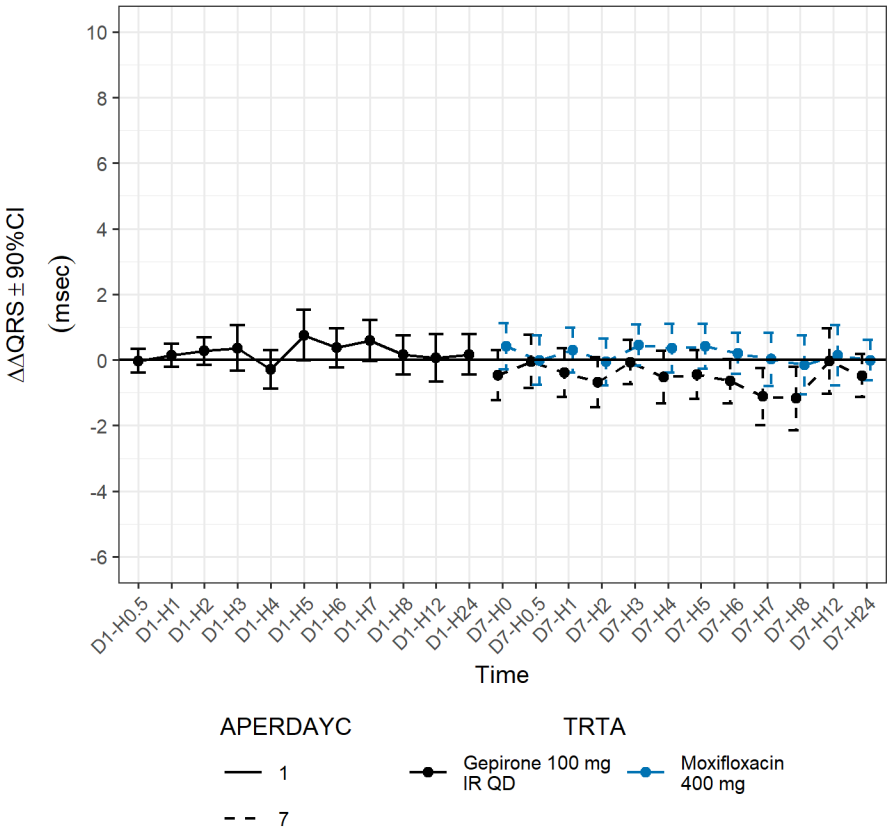
Figure 3: Mean and 90% CI of ΔΔPR Time-course



4.3.4 QRS

Figure 4 displays the time profile of ΔΔQRS for different treatment groups.

Figure 4: Mean and 90% CI of ΔΔQRS Time-course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs. In the following categorical tables, an omitted category means that no subjects had values in that category.

4.4.1 QTc

There were no subjects who experienced QTcF values of >480 msec or ΔQTcF >60 msec.

4.4.2 HR

Table 6 lists the categorical analysis results for maximum HR (≤100 beats/min and >100 beats/min). There was one subject who had HR values of >100 beats/min in the gepirone group.

Table 6: Categorical Analysis for HR (maximum)

Actual Treatment	Total (N)		Value <=100 beats/min		Value >100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Gepirone 100 mg IR QD	29	567	28 (96.6%)	566 (99.8%)	1 (3.4%)	1 (0.2%)
Placebo	31	675	30 (96.8%)	674 (99.9%)	1 (3.2%)	1 (0.1%)

4.4.3 PR

There were no subjects who experienced PR values of >220 msec and 25% increase over baseline.

4.4.4 QRS

There were no subjects who experienced QRS values of >120 msec and 25% increase over baseline.

4.5 EXPOSURE-RESPONSE ANALYSIS

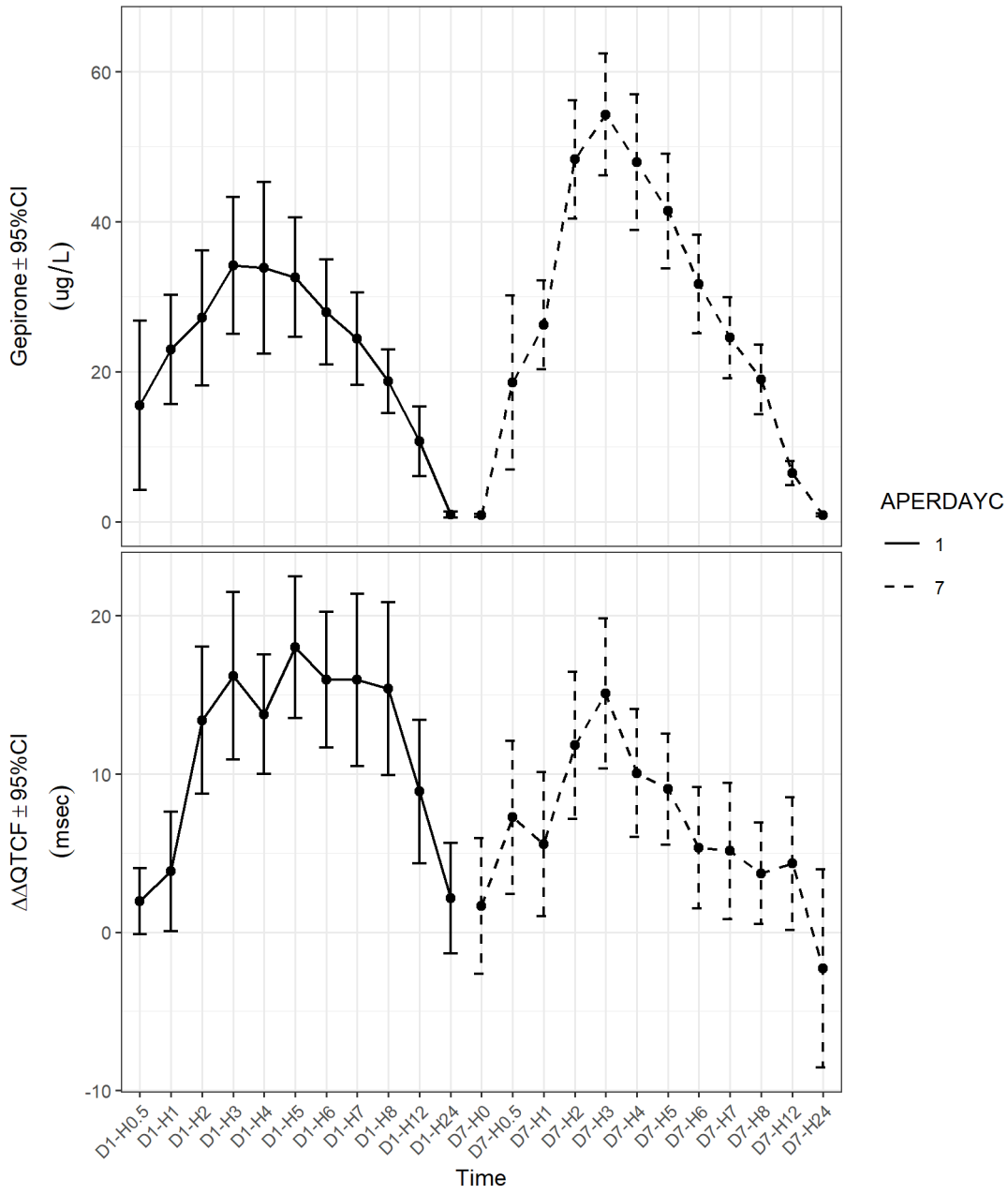
Figure 5 presents temporal relationship between time-course of drug concentration and ΔΔQTcF.

Given its short half-life, gepirone is not expected to accumulate after once daily dosing. However, as indicated in Figure 5, gepirone Cmax on Day 7 was ~1.4-fold higher than that on Day 1, probably due to differences in how food was co-administered between the two days. While gepirone was administered 15 minutes after meals on Day 7, it was administered 75 minutes after meals on Day 1. Food co-administration increases bioavailability of gepirone, and it is likely the reason why Day 7 exposure is higher than Day 1. On the other hand, food consumption shortens the QT interval. ΔQTcF profiles for both placebo and gepirone treatment were lower on Day 7 compared to the corresponding profiles on Day 1.

ΔΔQTcF profile differs on Day 1 and Day 7. While ΔΔQTcF plateaued between 3 - 8 hours post dose on Day 1, it declined sharply after attaining peak at 3 hours on Day 7. QTc prolongation was also delayed relative to gepirone concentration on Day 1 but not on Day 7. This is further demonstrated by examining the relationship between ΔΔQTcF and gepirone concentration on Day 1 and Day 7, separately (Figure 6). While the Day 1 quantile plot indicates that QT prolongation plateau after about 10 ng/mL, the Day 7 quantile plot indicates linear relationship at higher concentrations. The reason for these differences is not clear. It is not clear which day presents the true concentration-QTc relationship.

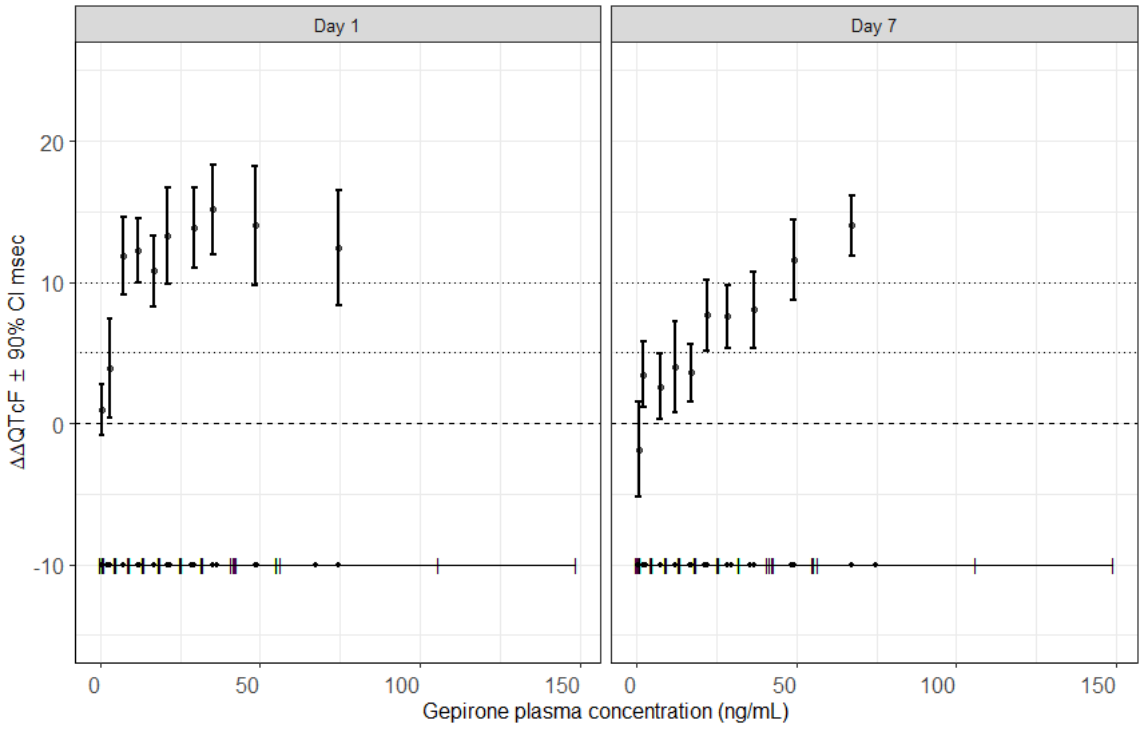
Based on the discrepancy in QT effects between Day 1 and 7, the reviewers find the concentration-QTc analysis uninterpretable and therefore did not perform independent C-QTc analysis.

Figure 5: Time-course of Drug Concentration (top) and QTcF (bottom)[1]



[1] ΔΔQTcF shown were obtained via descriptive statistics and might differ from Figure 1

Figure 6. Quantile plots of ΔΔQTcF versus gepirone plasma concentration



4.6 SAFETY ASSESSMENTS

The sponsor's 2007 integrated summary of safety (ISS) included 87 completed studies in adults, of which 53 were phase II/II studies (42 controlled and 11 open labeled). Since the 2007 ISS report, 4 new studies were conducted with 206 subjects in total (143 subjects receiving gepirone ER or IR). All four studies were phase I studies. One was the TQT study assessed in this report, and the other three were single-dose bioequivalent studies. This section focused on gepirone ER controlled phase II/III studies in depression.

In gepirone ER controlled Phase II/III studies in depression, according to the sponsor, 1976 subjects received gepirone ER, 1275 received placebo, 945 received active control (fluoxetine, paroxetine, imipramine). There were 9 deaths in subjects who participated in Phase II/III studies; 8 were treatment emergent; 4 received gepirone ER. Cause of death in subjects receiving gepirone ER were suicide (n = 2), pulmonary embolus, and coronary heart disease. None of the deaths were related to cardiac arrhythmias. There were no AEs from the narrow SMQ of Torsade de pointes/QT prolongation (MedDRA v25.1) in the gepirone ER group according to the sponsor's analysis. Broad SMQ of Torsade de pointes/QT prolongation (FDA reviewer's analysis) showed that more subjects in the gepirone ER group had syncope and loss of consciousness than placebo (Table 7). Note the reviewer's analysis had different subject count from the sponsor. According to the sponsor, dizziness-related AEs have been known to occur during treatment with antidepressant drugs.

Table 7. Broad SMQ of Torsade de pointes/QT prolongation.

	Gepirone N=1868 n(%)	Placebo N=1275 n(%)	Absolute Risk Difference (95.0% CI)
AE Grouping Related to AESI	10 (0.5%)	2 (0.2%)	0.4 (-0.0, 0.8)
SYNCOPE	6 (0.3%)	1 (0.1%)	0.2 (-0.1, 0.5)
LOSS OF CONSCIOUSNESS	4 (0.2%)	1 (0.1%)	0.1 (-0.1, 0.4)
Serious	3 (0.2%)	0 (0.0%)	0.2 (-0.0, 0.3)
Resulting in discontinuation	2 (0.1%)	0 (0.0%)	0.1 (-0.0, 0.3)
Maximum severity			
Mild	0 (0.0%)	0 (0.0%)	0.0 (0.0, 0.0)
Moderate	4 (0.2%)	0 (0.0%)	0.2 (0.0, 0.4)
Severe	5 (0.3%)	2 (0.2%)	0.1 (-0.2, 0.4)
Unknown	0 (0.0%)	0 (0.0%)	0.0 (0.0, 0.0)

According to the sponsor's analysis, no subjects in the gepirone ER group had QTc ≥ 500 msec and baseline ≤ 500 msec or missing. However, it is unclear how sufficient the ECG timings are for these studies. For example, in the two pivotal efficacy studies FK-GBE-007 and FK-GBE-008, no ECGs were collected other than at screening.

Table 90 Incidence of Clinically Significant QTc Results – All Subjects Treated in Gepirone ER Controlled Phase II/III Studies in Depression – Site Read Results

			Antidepressants	
QTc Interval (msec)	Gepirone ER N=434	Placebo N=228	Fluoxetine N=28	Imipramine N=59
≥450 msec and baseline <450 msec or missing	10 (2.3%)	6 (2.6%)	2 (7.1%)	2 (3.4%)
≥480 msec and baseline <480 msec or missing	1 (0.2%)	1 (0.4%)	1 (3.6%)	0
≥500 msec and baseline <500 msec or missing	0	1 (0.4%)	0	0
Increase of ≥30 msec from baseline	46 (10.6%)	29 (12.7%)	2 (7.1%)	10 (16.9%)
Increase of >60 msec from baseline	4 (0.9%)	9 (3.9%)	1 (3.6%)	4 (6.8%)
Increase of ≥30 msec from baseline and <60 msec from baseline	43 (9.9%)	21 (9.2%)	1 (3.6%)	8 (13.6%)

Source: Statistical Table 19.1.2.

Table 93 Incidence of Clinically Significant QTc Results – All Subjects Treated in Gepirone ER Controlled Phase II/III Studies in Depression – Central Read Results

			Antidepressants	
QTc Interval (msec)	Gepirone ER N=866	Placebo N=668	Fluoxetine N=303	Paroxetine N=234
≥450 msec and baseline <450 msec or missing	29 (3.3%)	4 (0.6%)	13 (4.3%)	20 (8.5%)
≥480 msec and baseline <480 msec or missing	0	0	1 (0.3%)	5 (2.1%)
≥500 msec and baseline <500 msec or missing	0	0	0	0
Increase of ≥30 msec from baseline	53 (6.1%)	12 (1.8%)	11 (3.6%)	35 (15.0%)
Increase of >60 msec from baseline	3 (0.3%)	0	1 (0.3%)	3 (1.3%)
Increase of ≥30 msec from baseline and <60 msec from baseline	53 (6.1%)	12 (1.8%)	11 (3.6%)	35 (15.0%)

Source: Statistical Table 19.2.2.

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 2/9/2023

TO: Division of Psychiatry (DP)
Office of Neuroscience (ON)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct on-site inspections**

RE: NDA 021164

The Office of Study Integrity and Surveillance (OSIS) determined that inspections are not needed for the sites listed below. The rationale for this decision is noted below.

Rationale

BioPharma Services, Inc., St. Louis: The Office of Regulatory Affairs (ORA) conducted an inspection for the clinical site in October 2022. The inspection was conducted under the following submission: ANDA NON-RESPONSIVE .

OSIS concluded that data from the reviewed studies were reliable.

(b) (4) **:** OSIS conducted an inspection for the analytical site in (b) (4) . The inspection was conducted under the following submissions: ANDAs NON-RESPONSIVE .

OSIS concluded that data from the reviewed studies were reliable.

Sites

Facility Type	Facility Name	Facility Address
Clinical	BioPharma Services, Inc.	10330 Old Olive Street Road, Creve Coeur, St. Louis, MO
Analytical	(b) (4)	

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: September 19, 2007

TO: Renmeet Grewal, Pharm.D., Regulatory Project Manager
Earl Hearst, M.D., Clinical Reviewer
Division of Psychiatry Products, HFD-130

THROUGH: Joseph P. Salewski
Acting Branch Chief
Good Clinical Practice Branch 2, HFD-47
Division of Scientific Investigations

FROM: Dianne Tesch, Consumer Safety Officer

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-164

NME: Yes

APPLICANT: Fabre Kramer

DRUG: Gepirone

THERAPEUTIC CLASSIFICATION: 1S

INDICATION: Treatment of moderate to severe major depressive disorder

CONSULTATION REQUEST DATE: June 5, 2007

DIVISION ACTION GOAL DATE: September 24, 2007

PDUFA DATE: November 3, 2007

I. BACKGROUND:

The study was a flexible/fixed-dose study in adults with moderate to severe major depressive disorder (MDD). The purpose was to demonstrate the safety and efficacy of Org 33062 extended release (ER) treatment over placebo in this population of subjects.

The primary objective was to evaluate the therapeutic efficacy of Org 33062 ER in comparison with placebo at the endpoint of an 8-week treatment period in subjects with major depressive disorder (diagnosed according to DSM-IV criteria). The primary efficacy variable evaluated in this study is the HAMD-17.

The secondary objectives were: (1) to describe the safety profile of eight weeks treatment with Org 33062 ER in comparison with placebo in subjects with major depression; and (2) to evaluate the therapeutic efficacy of Org 33062 ER in patients with atypical depression. Secondary variables include the HAMD-21and -28, Montgomery-Åsberg Depression Rating Scale (MADRS), and the Clinical Global Impression (CGI).

Summary Report of U.S. (and/or Foreign) Inspections

II. RESULTS (by protocol/site):

Name of CI and site #, if known	City, State*	Protocol #	Insp. Date	EIR Received Date	Final Classification
Robert J. Bielski, M.D. site 701	Okemos, MI	FKGBE007	7/23/07-8/2/07	8/31/07	NAI
Kenneth Weiss, M.D. site 706	Bala Cynwyd, PA	FKGBE007	8/27/07-8/29/07	9/18/07	NAI

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability
OAI = Significant deviations for regulations. Data unreliable.

A. Protocol # FKGBE007

1. Robert J. Bielski, M.D., Okemos, MI, site 701:

   a. There were forty-four subjects enrolled at the site, and thirty-nine who completed the study. Twenty of the records were reviewed for the data audit.

   b. There were no limitations to the inspection.

   c. There were no regulatory deficiencies..

   d. The data are acceptable for consideration in the NDA review decision.

2. Kenneth Weiss, M.D., Bala Cynwyd, PA, site 706:

   a. There were 20 subjects enrolled at the site. Twenty of the records were reviewed for the data audit.

   b. The original CRFs were put into storage when the CI moved to a new office. They were badly damaged by flooding, and had to be destroyed, The source documents were undamaged. The sponsor supplied copies of the CRFs for the inspection.

   c. There were no regulatory deficiencies.

   d. The data are acceptable for consideration in the NDA review decision.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication. No follow up other than routine surveillance is recommended.

{See appended electronic signature page}

GCPB Reviewer Name
Title

CONCURRENCE:

Supervisory comments

{See appended electronic signature page}

Joseph P. Salewski
Acting Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

Dianne Tesch
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CSO

Joseph Salewski
9/21/2007 11:09:32 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20855

CLINICAL INSPECTION SUMMARY

DATE: May 20, 2004

TO: Paul David, R.Ph., Senior Regulatory Project Manager
Earl Hearst, M.D., Medical Officer
Division of Neuropharmacological Drug Products, HFD-120

THROUGH: Khin Maung U, M.D., Branch Chief
Good Clinical Practice Branch I, HFD-46

FROM: Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspection

NDA: NDA 21-164

APPLICANT: Organon, Inc.

DRUG: Gepirone Extended Release Tablets (Org 33062)

THERAPEUTIC CLASSIFICATION: Type S

PROPOSED INDICATION: Major Depressive Disorder (MDD)

CONSULTATION REQUEST DATE: February 10, 2004

ACTION GOAL DATE: June 23, 2004

I. BACKGROUND:

Gepirone (Org 33062) is a serotonin receptor 5-HT_{1A} agonist. The sponsor has requested the use of gepirone in treatment of Major Depressive Disorder (MDD). In response to the deficiencies listed (including inadequate efficacy data) in the non-approvable letter sent by the Agency in May 2001, the sponsor has resubmitted the NDA application in December 2003. This application included the results from protocol 28709 entitled "A Multicenter, Placebo-Controlled Study of Relapse Prevention during Long-Term Treatment with Org 33062 in Outpatients with Major Depressive Disorder" conducted in all non-U.S. sites.
According to the Diagnostic and Statistical Manual-IV (DSM-IV), a major depressive episode

implies a prominent and relatively persistent (nearly everyday for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning and includes at least 5 of the following 9 symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

The protocol 28709 was a multicenter study to assess the safety and efficacy of gepirone in maintaining a treatment response in outpatients with major depressive disorder for up to 44 weeks following 8-12 weeks of initial open-label treatment. The primary objective of this trial was to compare the relapse rates of depression during the continuation phase between the subjects receiving gepirone at the final titrated dose and subjects receiving placebo. All subjects would undergo a single-blind, placebo wash-out period of 3-14 days. Subjects who met the eligibility criteria were enrolled in 8 to 12 weeks of the open-label phase. The starting dose was gepirone ER 20 mg/day with a forced titration up to 40 mg/day on day 4. At the clinical investigator's discretion, the dose could be increased to 60 mg/day on day 8 and 80 mg/day on day 15. The protocol specified that every patient must follow this regime during the first 8-12 weeks of acute treatment phase. Subjects who were in remission (HAMD-17 total score $\leq$8) after the acute treatment phase were randomized to placebo or gepirone for 40-44 weeks of double-blind continuation treatment. In the double-blind continuation phase, active treatment should be given at the final titrated dose. Although the investigator should strive to titrate as close to 80 mg/day as possible, for safety reasons, it was allowed to adjust the dose within the range of 40-80 mg/day.

The primary efficacy parameter was the number of subjects that would have a relapse during the continuation phase. Relapse was defined as having a HAMD-17 score >16 or discontinuation due to lack of efficacy. In addition to these criteria, the investigator must have the opinion that the subject met the criteria of major depressive episode.

An inspection assignment of Drs. Jokinen and Araszkiewicz was issued in February 2004 per the Review Division's request (HFD-120) to investigate their conduct in the protocol 28709. Both investigators were the high enrollers. There was no prior inspection history of these investigators.

II. RESULTS (by site):

NAME	Center #	Location	ASSIGNED DATE	DATE EIR RECEIVED	CLASSIFICATION
Riitta Jokinen, M.D.	SF 093	Turku, Finland	2/19/2004	5/17/2004	VAI
Aleksander Araszkiewicz, M.D.	PL 065	Bydgoszcz, Poland	2/19/2004	5/17/2004	NAI

1. Riitta Jokinen, M.D. (Center SF 093)

a. What was inspected:

For protocol 28709, 45 subjects signed the informed consent at this site. 43 subjects were screened and enrolled in the open label phase and 21 subjects were randomized into the double blind phase. Nine subjects were discontinued and 12 subjects completed the study. An audit of nine subjects' records was conducted.

b. Limitations of inspection: the source documents were recorded in Finnish language.

c. General observations/commentary:

Following a limited review of the source documents, the CRF and data listing (primary efficacy and safety), a Form FDA-483 was issued based on three study subjects who were allowed to remain in the clinical trial after relapse based on HAMD-17 score $\geq$16:

- Subject (b) (6) had a HAMD-17 score of 16 at week 20. This subject's HAM-D 17 was 20 at weeks 24 and 28, but the subject was not discontinued from the clinical trial until after the week 28 visit. The end of trial for continuation phase CRF documented relapse at week 28.
- Subject (b) (6) had a HAMD-17 score of 18 at week 44. This subject's HAM-D 17 was 22 at week 48 and 23 at week 52. This subject remained in the clinical trial through week 52. The end of trial for continuation phase CRF did not document relapse.
- Subject (b) (6) had a HAMD-17 score of 16 at week 24. This subject's HAM-D 17 was 18 at week 28, and the subject was discontinued from the clinical trial after the week 28 visit. The end of trial for continuation phase CRF documents relapse at week 28.

According to the protocol, relapse was defined as having a HAMD-17 score $\geq$16 or discontinuation due to lack of efficacy plus the investigator's opinion that the subject met the criteria of major depressive episode. Based on this definition, the lack of documentation that these three subjects met the criteria for major depressive episode despite their HAMD scores were above 16 at prior visits suggest that the FDA field investigator's determination of the above findings as relapse may not be accurate.

The protocol specified that subjects who comply with all selection criteria could be enrolled in the trial and would be given a subject code number. Code numbers would be assigned to subjects in the order of their enrollment in the clinical trial. The investigator would keep a record relating the names of the subject to their code numbers, to allow easy checking of data in subject files, when required. The record would also include date of subject enrollment and completion (Master Subject Log). The subject ID code list showed the subjects were not enrolled in the numerical sequence and the list was incomplete in that the dates of subject enrollment, randomization and completion were not recorded.

d. Recommendation: DSI suggests the review division to note that protocol defined relapse did occur in subjects (b) (6) and (b) (6) at week 28; and also note that subject (b) (6) had a relapse at week 44 only based on HAMD-17 scores. Overall, data appear acceptable.

2. Professor Aleksander Araszkiewicz, M.D. (Center PL 065)

a. What was inspected:

For protocol 28709, 30 subjects were screened at this site. There were no screen failures. Twenty-six subjects completed the open label phase (three subjects due to worsened depression and one subject due to problem absorbing the study medication) and 15 subjects were randomized into the double blind phase. 4 subjects were discontinued three subjects due to relapse and one subject by the sponsor) and 11 subjects completed the study. An audit of nine subjects' records was conducted.

b. Limitations of inspection: the source documents were written in Polish.

c. General observations/commentary: No Form FDA-483 was issued. All subjects signed the informed consent. No major objectionable conditions noted following the review of the source documents, the CRF and data listing (primary efficacy and safety).

d. Recommendation: Data appear acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

For the two study sites that were inspected, there was sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, that all enrolled subjects received the assigned study medication, and had their safety data captured.

As stated above, the inspection of Dr. Jokinen's site revealed three subjects met the HAMD-17 scores for relapse at visits specified above. The clinical investigator did not document whether the subjects met criteria for major depressive episode during these visits when the HAMD scores reached $\geq$16. The site did not report in the CRFs for actual visit dates when the relapse occurred for subjects (b) (6) and (b) (6); and the site did not report relapse of subject (b) (6) based on HAMD-17 scores. The relapse defined in protocol included the fact that in addition to having a HAMD-17 score $\geq$16 or discontinuation due to lack of efficacy, the investigator must have the opinion that the subject met the criteria of major depressive episode. In such case, one could argue that these subjects did not meet the criteria of MDD episode despite meeting the HAMD scores for relapse.

DSI suggests the Review Division should note the actual visits that relapse occurred in these three subjects based on total HAMD-17 scores. Overall, data from these centers that had been inspected appear acceptable for use in support of this NDA.

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Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

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Khin Maung U, M.D, Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

Key to Classifications
NAI = No deviation from regulations. Data acceptable
VAI = Minor deviations(s) from regulations. Data acceptable
VAI-RR= Deviation(s) form regulations, response received and reviewed. Data acceptable
OAI = Significant deviations for regulations. Data unreliable
Pending = Inspection not completed

cc:
NDA 21-164
HFD-45/Division File / Reading File
HFD-45/Program Management Staff (electronic copy)
HFD-46/Khin
HFD-46/George GCPB1 Files

rd:NK:5/20/04

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/s/

Ni Aye Khin
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MEDICAL OFFICER

Khin U
5/21/04 09:13:58 AM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 17, 2002

FROM: Michael F. Skelly, Ph.D.
Sriram Subramaniam, Ph.D.

THROUGH: C. T. Viswanathan, Ph.D. CTV Jan 17, 02
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering NDA 21-164, Gepirone Hydrochloride Extended-Release Tablets (Ariza®), Sponsored by Organon, Inc.

TO: Russell G. Katz, M.D.
Director, Division of Neuropharmacological Drug Products (HFD-120)

At the request of HFD-120, the Division of Scientific Investigations conducted an audit of the following bioequivalence study:

> **Study # 28718**: "An open label, randomized, four way cross-over, single dose, dosage strength equivalence study to determine the bioequivalence of Org 33062 (Gepirone HCl) 40 or 80 mg ER tablets versus multiple 20 mg ER tablets in healthy young, extensive metabolizers for dextromethorphan, male volunteers."

The clinical portion of the above study was conducted at SGS Biopharma, Antwerp, Belgium. The analytical portion of the study was conducted at (b) (4).

Following the inspections at SGS Biopharma (1/7-1/11/02) and (b) (4), Form FDA-483 was issued at each site. The objectionable findings and our evaluation follow.

Clinical Site: SBG Biopharma, Antwerp, Belgium

> **1. Subject (b) (6) vomited at post-dose time of 1 hr 34 min (Period I, 80 mg). Also, Subjects (b) (6) and (b) (6) vomited at post-dose time of 3 hr 39 min and 3 hr 29 min (Period IV, 80 mg), respectively.**

In addition to the four subjects ([redacted]) who were discontinued from the study after vomiting (Table 1), Subjects [redacted] and [redacted] (1 x 80 mg) vomited within five hours of dosing (subjects in **bold** in Table 2).

Table 1

Subject #	Date	Period	Treatment	Post-Dose Time
[redacted]	[redacted]	I	1 x 80 mg	4 hr 09 min
		I	4 x 20 mg	2 hr 57 min
		I	1 x 80 mg	2 hr 02 min
		I	4 x 20 mg	3 hr 11 min

Table 2

Subject #	Date	Period	Treatment	Post-Dose Time
[redacted]	[redacted]	**IV**	**1 x 80 mg**	**3 hr 39 min**
		IV	**1 x 80 mg**	**3 hr 29 min**
		I	**1 x 80 mg**	**1 hr 34 min**
		III	1 x 80 mg	5 hr 02 min
		III	1 x 80 mg	7 hr 22 min
		II	1 x 80 mg	10 hr 37 min
		III	4 x 20 mg	7 hr 52 min
		II	1 x 80 mg	14 hr 04 min

The data from Subjects [redacted], [redacted], and [redacted] should also be excluded, as vomiting occurred earlier than the mean T_{max} for this study; so gastrointestinal absorption from the gepirone extended release tablets was incomplete at the time of vomiting. It cannot be assured that no unabsorbed drug was expelled and lost.

Five other subjects vomited, but more than five hours after dosing, when absorption was likely complete (Table 2).

2. Failure to record the Dosage Form administered to individual subjects at the time of dosing (Randomization Scheme is not a substitute)

Only the randomization sheets for planned dosing schedules were maintained. Nonetheless, verification of the unit dose packages of drugs administered in the study indicates that randomization scheme was followed.

3. No shipping records were available for receipt of dosing medications.

The firm failed to maintain delivery receipts of drug supplies from the packaging site at [redacted] to the clinical site at Antwerp. Only scraps of paper and taxi receipts were

available. There were no records to confirm drug accountability and custody throughout the study. However, the reserve drugs for the study and the packages of the dose units used in the study were retained at the study site.

4. Failure to record and document the presence of study participant in the facility during the study.

No sign-in log or other record to indicate that subjects were actually present in the study unit for dosing and blood sampling.

5. Failure to preserve certain source data, e.g. data written on posted notes, paper towels etc.

Scraps of paper used to record certain physical examination data and other observations were discarded after the data were transcribed onto CRFs. The source data should have been maintained to verify the accuracy of the CRFs.

6. Original container of study medication from the sponsor was destroyed.

The firm should correct the objectionable practices listed Items 1 to 6 for future studies.

Analytical Site: (b) (4)

(b) (4)

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Conclusions:

The data from subjects # (b) (6), (b) (6), and (b) (6) should be excluded from pharmacokinetic and statistical evaluations (Item 1).

The accuracy and precision of the assays for gepirone and its metabolites are known only approximately, due to incomplete validation and conduct during the study (Items 7 and 8). Post-study validation data are unavailable at the time of this review. Pending availability of such data, we recommend that the study data be accepted for review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Sriram Subramaniam, Ph.D.

Michael F. Skelly, Ph.D.

Final Classifications:
VAI - SGS Biopharma, Antwerp, Belgium
VAI - (b) (4)

cc:
HFA-224
HFD-45 RF
HFD-48 Skelly/CF
HFD-120 David
HFD-860 Fetterly
Draft: MFS 1/10/02, SS 1/14/02
Final: CTV
DSI: (b) (4) ;O:\BE\EIRCOVER\21164gep.org.doc
FACTS (b) (4)

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/s/

Paul David

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DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20857

CLINICAL INSPECTION SUMMARY

DATE: January 18, 2002

TO: Paul A David, R. Ph., Senior Regulatory Project Manager
Earl D. Hearst, M.D., Medical Officer
Division of Neuropharmacological Drug Products, HFD-120

THROUGH: Antoine El-Hage, Ph.D., Chief
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

FROM: Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspection

NDA: NDA 21-164

APPLICANT: Organon

DRUG: Gepiron HCl Extended Release Tablets

THERAPEUTIC CLASSIFICATION: Type S, Standard Review

CHEMICAL CLASSIFICATION: 1S

INDICATION: Major Depressive Disorder

CONSULTATION REQUEST DATE: July 9, 2001

ACTION GOAL DATE: March 18, 2002

I. BACKGROUND:

Gepirone hydrochloride (ORG 33062) is a member of the azapirone class of compounds which has been shown to have preferential binding affinity for serotonin receptors. Specifically, gepirone is a direct 5-HT_{1A} receptor partial agonist, although its mechanism of action for antidepressant effect has not been fully elucidated. In this NDA, the sponsor has requested the use of gepirone in Treatment of Major Depressive Disorder (MDD).

DSI has received a consult request from the Review Division (HFD-120) in July, 2001. Inspection assignment was issued on September 18, 2001 for 3 domestic sites, Drs. Feiger, Haggerty and Quitkin. The studies were carried out using extended release tablets for protocol #134001 (Feiger) and immediate release capsules for protocols #03A7C-001-B (Haggerty) and #03A7A-003 (Quitkin).

II. RESULTS (by site):

NAME	CITY	STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION
Dr. Feiger	Wheat Ridge	CO	9-18-2001	11-07-2001	VAI
Dr. Haggerty	Chapel Hill	NC	9-18-2001	12-19-2002	NAI
Dr. Quitkin	New York	NY	9-18-2001	01-16-2002	VAI

A. Dr. Feiger

The study (protocol #134001), a double-blind, multi-center, randomized, placebo-controlled, efficacy and safety study of Org 33062 ER in subjects with MDD, was conducted between June, 1999 and December, 2000. Dr. Feiger took part in this study as one of the major sites enrolling a total of 69 subjects. Of these 69 subjects, 52 subjects completed the study. There was no death reported. One subject experienced serious adverse event (SAE), listed as accidental injury. Seventeen (17) subjects discontinued from the study. Reasons for discontinuation included lack of efficacy, adverse events and others not mentioned above.

An audit of 54 records was conducted. Inspection findings included protocol deviations and inadequate record, i.e., not signing off drug dosage change or inclusion/exclusion checklist in timely manner and not recording adverse events in CRF of certain subjects. Signed informed consents were present in all participants. Overall, data appear acceptable.

B. Dr. Haggerty

At this site, the study (protocol #03A7C-001-B) using gepirone IR capsules (placebo, gepirone titrated 5-45 mg, 10-90 mg) in treatment of depressed outpatients was conducted between 1987 and 1990. A total of 92 subjects were enrolled, of which 37 subjects discontinued from short-term (8-week treatment) phase of the study. Reasons for discontinuation included adverse events (15 subjects), lack of efficacy (12 subjects), lost to follow up (3), withdrawal of consent (3), data-handling (2) and others. Three cases of SAE's (Angina Pectoris, hospitalized for psychiatric reason and suicidality) were reported at this site. All of these subjects were in gepirone treatment group.

An audit of 12 records was conducted. No major deficiencies were found with the site's conduct of the study or their records.

However, we note that there were some discrepancies between CRF and the data listing of

subjects who discontinued from the study. For example, 6 subjects (# (b) (6) from Gep 5-45 group and # (b) (6) from placebo group) who completed 8-week short-term dosing phase as per CRF were recorded on data listing of subjects discontinued from the short-term phase of study for lack of efficacy. There were also discrepancies in disposition of number of subjects continued into the long-term extension phase: 36 subjects as per data listing versus 20 subjects' records reported by the site. We also note that different dates were listed for Hamilton Depression score of one subject (# (b) (6)) and also one point discrepancy in CGI-severity score on CRF versus data table listing.

As stated before, there were no major deficiencies found with the conduct of the study at this site. However, it should be noted that there were some discrepancies between CRF and the data listing submitted by the sponsor in the NDA application. The veracity of data entry is questionable and requires further verification. For the purpose of assurance in data quality and integrity, it was suggested that comparisons should be made between data listings, tables, CRF, narratives and/or information provided in efficacy/safety summary sections of study report in this NDA application. The findings were also discussed with the Review Division Medical Officer and we have expanded our inspection to include sponsor investigation in regards to data handling.

C. Dr. Quitkin

Under the protocol #03A7A-003, the study entitled "a double blind trial of gepirone versus placebo in the treatment of outpatients with atypical depression" was conducted in the period between 1988-1990 using gepirone IR capsules. At this site, a total of 60 subjects were randomized; of which 24 subjects discontinued from the study. Reasons for discontinuation included 12 subjects who experienced adverse events (8 in gepirone and 4 in placebo group), 7 subjects due to lack of efficacy (1 in gepirone and 6 in placebo group), 2 subjects receiving gepirone withdrew consent, 2 lost to follow up and 1 randomization error (subject # (b) (6)).

An audit of 16 records was conducted. Inspection findings included protocol deviations in that the PI enrolled two subjects who did not meet all the inclusion/entrance criteria. Specifically, subject # (b) (6) and (b) (6) with their Hamilton Depression Score of 8 were enrolled despite the minimum score of 10 required as per protocol.

The inspection also revealed inadequate record keeping in that there were missing two subjects' source documents (subject # (b) (6) and # (b) (6)); and failure to list two physicians who enrolled and prescribed study medications to certain subjects on the FDA-1572 as sub-investigators, and also, minor deficiencies in drug accountability records.

Signed informed consents were present in all participants except for one subject (# (b) (6)) whose informed consent could not be found. We note that there were one to two point discrepancies between the Hamilton Depression total score (subjects # (b) (6) and (b) (6)) on the case report forms and their respective data listing provided by the sponsor. Overall, data seem acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Although some deficiencies were noted in the areas of protocol violations and inadequate record keeping, the data from these sites appear acceptable for use in support of this NDA supplement.

Limitation to this inspection was that the investigators' source documents including informed consents, were missing in certain subjects, as stated above.

This summary was based on Clinical Investigators' audits of these three sites. Because of some discrepancies between the CRF and the data listing provided by the sponsor, we have expanded our inspection to include sponsor investigation in regards to data handling and is currently ongoing. Should the findings of the sponsor's audit when received, contain additional information that would significantly effect the classification or have an impact on the acceptability of the data, we will inform the review division accordingly.

Key to Classifications
NAI = No deviation from regulations. Data acceptable
VAI = Minor deviations(s) from regulations. Data acceptable
VAIr= Deviation(s) form regulations, response requested. Data acceptable
OAI = Significant deviations for regulations. Data unreliable
Pending = Inspection not completed

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Ni A. Khin, M.D., Medical Officer
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CONCURRENCE:

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cc:
NDA 21-164
Division File
HFD-45/Program Management Staff (electronic copy)
HFD-47/c/r/s

HFD-47/Khin
HFD-47/Hajarian/Friend
HFD-45/RF

rd:NK:01/17/02; 01/18/02

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/s/

Michele Balser
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TECHNICAL
Original summary signed by Drs. El-Hage and Khin on 1/18/02.