CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021164Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	021164
PDUFA Goal Date	Sept 23, 2023
NEXUS TTT #	2023-3250
Reviewer Name(s)	Somya Dunn, MD
Acting Team Leader	Timothy Bernheimer, Pharm.D.
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	Sept 21, 2023
Established Name	Exxua
Trade Name	Gepirone Extended-Release
Name of Applicant	Fabre-Kramer Pharmaceuticals, Inc.
Therapeutic Class	Antidepressant
Formulation	Oral tablet
Dosing Regimen	Starting dose is 18.2 mg administered once daily initial dose. If tolerated, can increase to 36.3 mg once daily may begin as early as Day 4 of dosing. If the 36.3 mg dose is well tolerated and additional efficacy is desired, the dose may be increased to 54.5 mg after one week and to 72.6 mg after an additional week

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for Exxua (gepirone extended-release) is necessary to ensure the benefits outweigh its risks. Fabre-Kramer Pharmaceuticals, Inc (the Applicant) submitted a New Drug Application (NDA) 021164 for Exxua with the proposed indication for the treatment of major depressive disorder (MDD) in adults.

The clinical review team recommends approval of Exxua on the basis of the efficacy and safety information currently available. The Prescribing Information (PI) for Exxua will contain a boxed warning for the class-wide antidepressant risk of suicidal thinking and behavior in pediatric and young adult patients. The *Warnings and Precautions* of the PI will contain the risk of QTc interval prolongation. Other antidepressant risks addressed in the *Warnings and Precautions* of the PI will be the increased risk of serotonin syndrome, and activation of mania/hypomania.

DRM has determined that a REMS is not necessary to ensure the benefits of Exxua outweigh the risks. The risks will be communicated through PI and further evaluated through Post-Market Requirements (PMRs), the need for REMS and can be re-evaluated if new safety information becomes available.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Exxua (gepirone extended-release (ER)) is necessary to ensure the benefits outweigh its risk. Fabre-Kramer Pharmaceuticals, Inc. (hereafter refer to as the Applicant) submitted New Drug Application (NDA) 021164 with a proposed indication for major depressive disorder (MDD) in adults.

This application is under review in the Division of Psychiatry (DP). The Applicant did not submit a REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Exxua is a 5-HT_{1A} receptor agonist proposed for the treatment of major depressive disorder (MDD) in adults. Exxua is a new molecular entity[a] originally submitted as NDA 021164 on October 1, 1999 and resubmitted most recently on December 23, 2022. Although Exxua is not associated with an established pharmacologic class, the mechanism of action is similar to buspirone, which is approved for the treatment of generalized anxiety disorder (GAD). The primary mechanism of action for Exxua is moderate affinity agonist of the 5-HT_{1A} receptor. The recommended starting dose is 20 mg administered orally once daily with food at approximately the same time each day. If the 20 mg initial dose is adequately tolerated, an increase to 40 mg given once daily may begin as early as day four 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. The dose should be adjusted dose by

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity*

50% when a moderate CYP3A4 inhibitor is administered. This medication would be generally given to patients to self-administer at home for a diagnosis of MDD and is intended for chronic administration.[b] All antidepressant labels include a boxed warning about an increased risk of suicidal thoughts and behaviors in pediatric and young adult patients. Exxua is not currently approved or marketed in any country.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 021164 relevant to this review, for more details see the FDA BLA/NDA 021164 Multi-Disciplinary Review:

- 9/30/1999: Organon submitted the original NDA.
- 11/30/1999: FDA issued a refused to file because the Applicant did not have two positive and well-controlled trials.
- 05/18/2001: Organon resubmitted the NDA and included 2 short-term studies with the ER formulation in subjects with MDD along with 3 efficacy studies using the immediate-release (IR) formulation.
- 3/15/2002: FDA issued a Non-Approvable Letter dated, citing inadequate evidence of effectiveness.
- 12/23/2003: Organon amended the NDA with additional clinical data from a long-term relapse/prevention study.
- 6/23/2004: Second Not-Approvable Letter issued to Organon.
- 6/24/2005 Transfer of ownership for Exxua changed from Organon to Fabre-Kramer Pharmaceuticals.
- 04/03/2007: The Applicant resubmitted the NDA and included a new efficacy study.
- 11/02/2007: The Agency issued a second Not-Approvable letter describing concerns with short and long-term efficacy.
- 12/10/2012: Applicant submitted an amendment based on meetings/discussion with FDA.
- 4/18/2014: FDA responded with an Advice Letter stating ongoing concerns about the efficacy of Exxua.
- 6/13/2014: The Applicant appealed the November 2, 2007 Not-Approvable Letter and the April 18, 2014 General Advice Letter which concluded that the Applicant had not demonstrated substantial evidence of effectiveness.
- 11/12/2014: The Applicant requested reconsideration by FDA Chief Counsel.
- 1/27/2015: FDA accepted the Applicant's request for dispute resolution.
- 12/01/2015: FDA conducted a Psychopharmacological Drug Advisory Committee (PDAC) meeting to discuss the efficacy and safety of Exxua. The panel was generally in agreement that the Applicant the Applicant had not demonstrated substantial evidence of effectiveness.
- 3/16/2016: The FDA OND Director granted the Applicant's appeal and provided guidance to address the remaining CMC issues noted in the 2007 Not-Approvable Letter.
- 12/23/2022: The Applicant resubmitted the NDA.
- 6/05/2023: The Agency issued a Major Amendment Letter to the Applicant due to data received during the review cycle that was not in standard format and that had multiple quality issues. The Applicant required multiple extensions to fulfill information requests regarding the data issues, with some taking over a month to receive. The amount of resubmitted material required additional time for review.

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Major depressive disorder (MDD) is a life-threatening, chronic condition. Over an estimated 17 million people in the United States have a depressive disorder.[1,c] The lifetime prevalence of a major depressive episode in developed countries is estimated at 18 percent and the majority of patients with MDD have comorbid psychiatric or other medical conditions, further complicating treatment.[2] Patients with MDD may be unable to work, maintain relationships, attend to self-care, and in the most severe cases may become hospitalized or attempt or commit suicide. MDD is considered the leading cause of disability worldwide and is associated with increased mortality rates with a median rate of 10 years of life lost.[3,d]

The etiology of MDD involves multiple interacting factors, including biological factors (e.g., genetics, neurobiology), psychological factors (e.g., psychological tendencies and traits), and social factors (e.g., stressful life events, trauma, lack of support). Determination of the diagnosis of MDD is clinical as there are no laboratory tests or biomarkers used in the diagnosis of MDD.

3.2 Description of Current Treatment Options

Treatment for MDD includes psychotherapy and, if needed, prescription medication. There are several FDA-approved antidepressant treatments used for MDD, see Table 1. However, about 30 to 40% of patients with MDD fail to respond to first-line treatments including oral antidepressant medications of all classes, this includes selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and other antidepressants such as mirtazapine and bupropion.[Error! Bookmark not defined.] SSRIs and SNRIs are relatively newer and are generally well-tolerated, with common adverse reactions of nausea/vomiting, weight gain, diarrhea, sleep disturbances, and sexual dysfunction. Uncommon but potentially serious adverse events associated with SSRIs and SNRIs include serotonin syndrome, increased risk of bleeding, activation of mania or hypomania, discontinuation syndrome, seizures, and hyponatremia. All antidepressant labels include a boxed warning about an increased risk of suicidal thoughts and behaviors in children, adolescents, and young adults below age 25. Several of the most commonly prescribed antidepressants have a *Warning and Precaution* in their PI for QT interval prolongation including sertraline, citalopram and fluoxetine.

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[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug*

There are two FDA approved medications for treatment resistant depression (TRD), Spravato (esketamine) and a fixed-combination drug of fluoxetine plus olanzapine (Symbyax). There are also devices used to treat TRD which include electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS).

Table 1: Summary of Treatment Armamentarium for MDD

Drug Name (Trade Name, Approval Year)	Common Adverse Reactions	Serious Adverse Reactions/Cautions
Tricyclic (TCAs) and tetracyclic Antidepressants		
Amitriptyline (Elavil, 1977), Amoxapine (Asendin,1992), Desipramine (Norpramin 1964), Doxepin (Sinequan 1969), Imipramine (Tofranil 1959), Maprotiline* (Ludiomil 1988), Nortriptyline (Pamelor 1964) Protriptyline (Vivactil 1967), Trimipramine (Surmontil 1979)	Dry mouth, constipation, blurred vision, drowsiness, low blood pressure	Urinary retention, confusion, fainting, seizures, arrhythmias. Use with caution with narrow-angle glaucoma
MAOIs		
Isocarboxazid (Marplan 1959), Maprotiline (Mylan 1959), Phenelzine (Nardil 1961), Tranylcypromine (Parnate 1961), Selegiline patch (Emsam 2006)	Nausea, restlessness, problems sleeping, dizziness, drowsiness	Headache, stroke, fainting, heart palpitations, blood pressure changes, drug-drug interactions
SSRIs		
Citalopram (Celexa 1998), Escitalopram (Lexapro 2002)*, Fluoxetine (Prozac 1987)*, Paroxetine (Paxil 1992, Paxil CR 1999, Pexeva 2003), Vortioxetine (Trintellix 2013), Vilazodone (Viibryd 2011), Sertraline (Zoloft 1991)	Nausea, tremor, nervousness, difficulty sleeping, sexual problems, sweating, agitation, fatigue	Seizures, abnormal bleeding or bruising, withdrawal symptoms, and serotonin syndrome.
SNRIs		
Duloxetine (Cymbalta 2004), Venlafaxine (Effexor 1993, Effexor XR 1997), Levomilnacipran (Fetzima 2013), Desvenlafaxine (Pristiq 2008, Khedezla 2013)	Nausea, vomiting, dry mouth, constipation, fatigue, feeling drowsy, dizziness, sweating, sexual problems	Seizures, abnormal bleeding or bruising, withdrawal symptoms, and serotonin syndrome
Atypical Antidepressants		
Trazodone (Desyrel 1981) Nefazodone (Serzone 1994)	Dry mouth, dizziness, blurred vision, drowsiness, constipation	Erection, low blood pressure, fainting, confusion, liver failure
Other Antidepressants		
Mirtazapine (Remeron 1996)	Drowsiness, weight gain, dizziness	Agranulocytosis, elevated cholesterol, liver enzymes increase
Bupropion (Wellbutrin 1989, Wellbutrin SR 1996, Wellbutrin XL 2003)	Dizziness, constipation, nausea, vomiting, blurred vision	Seizures, changes in blood pressure
Dextromethorphan/bupropion (Auvelity, 2022)	Dizziness, headache, diarrhea, somnolence, dry mouth, sexual dysfunction, and hyperhidrosis	Seizures, changes in blood pressure, activation of mania, psychosis, angle-closure glaucoma, serotonin syndrome, embryo-fetal toxicity.

Source: Draft FDA NDA Multi-Disciplinary Review and Evaluation NDA 021164 for Exxua, Table 1. Accessed August, 31, 2023.

*Has pediatric indication.

4 Benefit Assessment

The efficacy determination for Exxua was based on results from two Phase 2/3 placebo controlled short-term flexible-dose efficacy studies, 134001 and FK-GBE-007. The primary endpoint for both studies was the change from baseline to 8 weeks in the 17-item Hamilton Depression Rating Scale (HAMD-17) total score for Exxua compared to placebo, when administered to subjects with MDD using a flexible-dose titration for 18.2 mg, 36.3 mg, 54.5 mg, and 72.6 mg. The primary endpoints in both studies were considered statistically significant.[e] The results from these two efficacy trials are displayed in Table 2.

Table 2 Primary Efficacy Results for Change from Baseline in HAMD-17 Total Score at Week 8 in Adult Patients with MDD (Study 1 and Study 2)

Study Number	Treatment Group	Mean Baseline Score (SD)	Week 8/ET LS Mean CFB (SE)	Placebo-subtracted Difference (95% CI)*	p-value
134001	Gepirone ER (N=101)	22.7 (2.45)	-9.04 (0.78)	-2.47 (-4.41, -0.53)	0.013
	Placebo (N=103)	22.8 (2.51)	-6.75 (0.77)		
FK-GBE-007	Gepirone ER (N=116)	23.9 (2.69)	-10.22 (0.75)	-2.45 (-4.47, -0.43)	0.018
	Placebo (N=122)	24.2 (2.93)	-7.96 (0.73)		

Source: Draft FDA NDA Multi-Disciplinary Review and Evaluation NDA 021164 for Exxua, Table 14. Accessed August 31, 2023.
N: sample size; SD: standard deviation; SE: standard error; LS: least-squares; CI: confidence interval
*Difference in baseline-adjusted means from ANCOVA.

Additionally, the Applicant submitted a post-hoc re-analysis of a longer-term study, but the Agency determined the data was not supportive of maintenance of treatment of MDD. Additionally, to fulfill Pediatric Research Equity Act (PREA) requirements, the Applicant submitted results of two pediatric efficacy trials which were both not statistically significant.

5 Risk Assessment & Safe-Use Conditions

A total of 8407 subjects were exposed to Exxua in the Applicant's phase 2 and 3 acute and extension studies. The Agency reviewed the safety of Exxua for adults with MDD during the Applicant's previous NDA submissions and during the PDAC conducted on December 1, 2015; the conclusion was that safety is generally acceptable in adults. Due to this conclusion, the review team focused on newer data submitted with this NDA resubmission and the Applicant's Draft Labeling Text; they also reviewed the older safety data to ensure no signals were missed.

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

5.1 DEATH AND SERIOUS ADVERSE EVENTS

In total, there were four deaths in patients treated with Exxua. Two of them died from suicide, both with a history of previous suicide attempts; another died from aortic dissection, and another died from pulmonary embolism. In terms of suicide, although the clinical team could not conclude that Exxua was not associated with suicide, there is class warning of risks of suicide in antidepressant medications.[f] There were no deaths in the long-term study, Study 28709 or in the pediatric studies.

The most commonly reported serious adverse events (SAEs) in in patients treated with Exxua reported more frequently than in placebo subjects were depression (approximately 0.2%), suicidal ideation (approximately 0.2%), suicide attempt (approximately 0.2%), pneumonia (approximately 0.2%), and pregnancy (approximately 0.3%).

The review team did not note any new safety concerns while reviewing the most recent submission and overall determined that the deaths were likely not related to Exxua and that SAEs in general were rare.

5.2 ADDITIONAL SAFETY CONCERNS

During the updated review the review team identified additional significant safety concerns the Applicant had not adequately described, including: 1) clinically meaningful QT prolongation, 2) lower maximum dosing requirements for geriatric patients and patients with renal or hepatic impairment; and 3) potential embryo-toxicity and reproductive toxicity concerns.

5.2.1 QTc Prolongation

The Applicant submitted an Agency requested QT study during this review cycle. The data supports that Exxua prolongs the QTc interval as the largest mean increase in baseline- and placebo-corrected QTc interval with administration of 100 mg per day was 18.4 msec (upper 90% confidence interval [CI] = 22.7 ms) on Day 1 and 16.1 msec (upper 90% CI = 20.7 ms) on Day 7. The exposure in this study was two-fold the exposure of the maximum recommended dose.

6 Expected Post Market Use

If approved, Exxua would be indicated to treat MDD in adult patients and prescribed most often in the outpatient setting. These patients are often managed by psychiatrists, however, MDD is very common and treated by other medical specialties, including primary care providers. These providers will be familiar with the common risks associated with antidepressants and will likely have experience with mitigation and management of these risks.

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The clinical review team recommends approval of Exxua on the basis of the efficacy and safety information currently available. Most of the safety concerns associated with Exxua are known risks associated with other approved antidepressants and include the risks of suicidal thinking and behavior in pediatric and young adult patients, serotonin syndrome, and activation of mania/hypomania. Healthcare providers that typically prescribe antidepressants should be familiar with these risks. These risks will be communicated in product labeling which will include the class-wide antidepressant boxed warning for suicidal thinking and behavior in pediatric and young adult patients. As discussed in Section 5, the risk of QTc prolongation was also identified during the review of this application. Although the Agency is currently working to finalize the PI, at this time, the draft PI has *Warning and Precaution* for QTc prolongation. Although other antidepressants can cause QT prolongation, the review team determined that the risks of QT prolongation observed with Exxua was more concerning in that it was more meaningful and also dose related. They noted that the other common MDD treatments that prolong the QT interval discussed in Section 3.2 did not prolong it to the extent of Exxua. The review team determined that detailed guidance regarding these concerns about QT interval prolongation for Exxua will be included in *Warning and Precaution* of labeling, including recommendations to monitor patients with ECGs with coadministration of drugs known to prolong the QTc interval or in patients with QTc $\geq$ 450 msec. Labeling will also include that patients with significant risk of developing torsade de pointes, including those with (b) (4) uncontrolled or significant cardiac disease, recent myocardial infarction, heart failure, unstable angina, bradyarrhythmia, uncontrolled hypertension, high degree atrioventricular block, severe aortic stenosis, or uncontrolled hypothyroidism should also be monitored. The PI Section 4 *Contraindications* is being edited to contain language for CYP34A inhibitors, hepatic impairment and patients with history of QTc related medical problems. Section 8 *Use in Special Populations* is being edited to include pregnancy stating that data suggest that Exxua may cause fetal harm. There is also a statement for (b) (4) . The Section 17 *Patient Counseling* and will have more recommendations for prescriber to counsel patients about the risks and the Medication Guide will include information for patients on the risks of suicidal thoughts, activation of mania/hypomania and having a history of congenital prolonged QT syndrome.

At this time, the review team is considering post-marketing requirement (PMR) studies to better understand risks in pregnancy and lactation, QT-prolongation, risk of bleeding and long-term treatment with Exxua.

The risks associated with Exxua will be addressed in the PI and with PMRs. These will be sufficient to mitigate the risks and a REMS is not necessary at this time.

9 Conclusion and Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for Exxua to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

Should the Division of Psychiatry have any concerns or questions, or if new safety information becomes available, please send a consult to DRM.

10 References

[1] World Health Organization. Depression and other common mental disorders. Global health estimates. (Geneva:World Health Organization; 2017.)

[2] Kessler, R. C., J. Ormel, M. Petukhova, K. A. McLaughlin, J. G. Green, L. J. Russo, D. J. Stein, A. M. Zaslavsky, S. Aguilar-Gaxiola and J. Alonso. "Development of lifetime comorbidity in the World Health Organization world mental health surveys." *Archives of general psychiatry*. 2011;68(1): 90-100.

[3] Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. *JAMA Psychiatry*. 2015;72:334-341.

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