

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EXXUA™ safely and effectively. See full prescribing information for EXXUA.

EXXUA (gepirone) extended-release tablets, for oral use
Initial U.S. Approval: 2023

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS
See full prescribing information for complete boxed warning.

Increased risk of suicidal thinking and behavior in pediatric and young adult patients taking antidepressants. Closely monitor for worsening and emergence of suicidal thoughts and behaviors (5.1). EXXUA is not approved for use in pediatric patients (8.4).

INDICATIONS AND USAGE
EXXUA is indicated for the treatment of major depressive disorder (MDD) in adults (1).

- DOSAGE AND ADMINISTRATION**
- Correct electrolyte abnormalities and perform electrocardiogram (ECG) prior to initiating treatment with EXXUA. Do not initiate EXXUA if QTc is > 450 msec (2.1).
 - Perform ECGs during dosage titration and periodically during treatment (2.1).
 - The recommended starting dose is 18.2 mg administered orally once daily with food at approximately the same time each day (2.2, 2.3).
 - Depending on clinical response and tolerability, the dosage may be increased to 36.3 mg once daily on Day 4. Dosage may be further titrated to 54.5 mg once daily after Day 7 and to 72.6 mg once daily after an additional week (2.3).
 - Geriatric patients: Recommended starting dosage is 18.2 mg once daily. Dosage may be increased to 36.3 mg after 7 days (2.4).
 - Renal Impairment (creatinine clearance < 50 mL/min): Recommended starting dosage is 18.2 mg once daily. Dosage may be increased to 36.3 mg once daily after 7 days (2.5, 8.6).
 - Moderate Hepatic Impairment (Child-Pugh B): Dosage may be increased to 36.3 mg once daily after 7 days (2.6, 8.7).
 - Adjust EXXUA dose by 50% when a moderate CYP3A4 inhibitor is administered (2.7).

DOSAGE FORMS AND STRENGTHS
Extended-release tablets: 18.2 mg, 36.3 mg, 54.5 mg, and 72.6 mg (3).

- CONTRAINDICATIONS**
- Known hypersensitivity to gepirone or components of EXXUA (4).
 - Prolonged QTc interval > 450 msec at baseline (4).
 - Congenital long QT syndrome (4).
 - Concomitant use of strong CYP3A4 inhibitors (4).
 - Severe hepatic impairment (4).
 - Use with an MAOI or within 14 days of stopping treatment with EXXUA. Do not use EXXUA within 14 days of discontinuing an MAOI (4).

- WARNINGS AND PRECAUTIONS**
- QT Interval Prolongation: EXXUA prolongs the QTc. Correct electrolyte abnormalities. Perform ECGs prior to initiation, during dose titration, and periodically during treatment with EXXUA. Monitor ECGs more frequently when EXXUA is used concomitantly with drugs known to prolong the QT interval, in patients who develop QTc ≥ 450 msec during treatment or are at significant risk of developing torsade de pointes. Do not escalate dosage if QTc > 450 msec (2.1, 5.2, 7).
 - Serotonin Syndrome: Increased risk when co-administered with other serotonergic agents. If serotonin syndrome occurs, discontinue EXXUA and initiate supportive measures (5.3).
 - Activation of Mania/Hypomania: Screen patients for bipolar disorder (5.4).

ADVERSE REACTIONS
Most common adverse reactions (incidence of ≥ 5% and at least twice incidence of placebo) were dizziness, nausea, insomnia, abdominal pain, and dyspepsia (6.1).
To report SUSPECTED ADVERSE REACTIONS, contact Aytu Therapeutics at 1-855-298-8246 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
Strong CYP3A4 inducers: Reduces EXXUA exposure. Avoid concomitant use (7).

USE IN SPECIFIC POPULATIONS
Pregnancy: Third trimester use may increase the risk for persistent pulmonary hypertension and symptoms of poor adaptation (respiratory distress, temperature instability, feeding difficulty, hypotonia, irritability) in the neonate (8.1).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.
Revised: 07/2025

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FULL PRESCRIBING INFORMATION

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adult patients in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors [see Warnings and Precautions (5.1)]. EXXUA is not approved for use in pediatric patients [see Use in Specific Populations (8.4)]

1 INDICATIONS AND USAGE

EXXUA is indicated for the treatment of major depressive disorder (MDD) in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Important Recommendations Prior to Initiating and During Treatment with EXXUA

Electrocardiogram and Electrolyte Monitoring

- Correct electrolyte abnormalities prior to initiating EXXUA. In patients with electrolyte abnormalities, or who are receiving diuretics or glucocorticoids, or who have a history of hypokalemia or hypomagnesemia, also monitor electrolytes during dose titration and periodically during treatment with EXXUA [see Warnings and Precautions (5.2)].
- Perform an electrocardiogram (ECG) prior to initiating EXXUA, during dosage titration, and periodically during treatment.
- Do not initiate EXXUA if QTc is > 450 msec at baseline.
- Monitor ECGs more frequently if EXXUA is used:
 - concomitantly with drugs known to prolong the QT interval
 - in patients who develop QTc ≥ 450 msec during treatment
 - in patients with a significant risk of developing torsade de pointes [see Warnings and Precautions (5.2) and Drug Interactions (7)].
- Do not escalate the EXXUA dosage if the QTcF is > 450 msec [see Warnings and Precautions (5.2)].

Bipolar Disorder, Mania, and Hypomania Screening

Screen patients for a personal or family history of bipolar disorder, mania, or hypomania prior to initiating treatment with EXXUA [see Warnings and Precautions (5.3)].

2.2 Important Administration Instructions

Take EXXUA orally with food at approximately the same time each day [see Clinical Pharmacology (12.3)]. Swallow tablets whole. Do not split, crush, or chew EXXUA.

2.3 Recommended Dosage

The recommended starting dosage of EXXUA is 18.2 mg once daily. Based on clinical response and tolerability, the dosage may be increased to 36.3 mg orally once daily on Day 4 and further titrated to 54.5 mg orally once daily after Day 7 and to 72.6 mg orally once daily after an additional week. The maximum recommended daily dosage of EXXUA is 72.6 mg once daily.

2.4 Dosage Recommendations in Geriatric Patients

The recommended starting dosage of EXXUA in geriatric patients is 18.2 mg orally once daily. Based on clinical response and tolerability, the dosage may be increased to maximum recommended dosage of 36.3 mg orally once daily after Day 7 [see Use in Specific Populations (8.5) and Clinical Pharmacology (12.3)].

2.5 Recommended Dosage in Patients with Renal Impairment

The recommended starting dosage of EXXUA in patients with creatinine clearance < 50 mL/min is 18.2 mg orally once daily. Based on clinical response and tolerability, the dosage may be increased to the maximum recommended dosage of 36.3 mg orally once daily after Day 7 [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].

The recommended dosage in patients with creatinine clearance ≥ 50 mL/min is the same as in patients with normal renal function [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].

2.6 Recommended Dosage in Patients with Hepatic Impairment

The recommended starting dose of EXXUA in patients with moderate (Child-Pugh B) hepatic impairment is 18.2 mg once daily. Based on clinical response and tolerability, the dosage may be increased to the maximum recommended dosage of 36.3 mg orally once daily after Day 7 [see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)].

EXXUA is contraindicated in patients with severe (Child-Pugh C) hepatic impairment [see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)].

The recommended dosage in patients with mild (Child-Pugh A) hepatic impairment is the same as patients with normal hepatic function.

2.7 Dosage Modifications for Concomitant Use with CYP3A4 Inhibitors

Reduce the EXXUA dose by 50% when used concomitantly with a moderate CYP3A4 inhibitor [see Drug Interactions (7)].

EXXUA is contraindicated in patients receiving strong CYP3A4 inhibitors [see Contraindications (4) and Drug Interactions (7)].

2.8 Switching a Patient to or from a Monoamine Oxidase Inhibitor (MAOI) Antidepressant

At least 14 days must elapse between discontinuation of an MAOI intended to treat depression and initiation of therapy with EXXUA. Conversely, at least 14 days must be allowed after stopping EXXUA before starting an MAOI antidepressant [see Contraindications (4) and Drug Interactions (7)].

3 DOSAGE FORMS AND STRENGTHS

EXXUA is available as extended-release tablets in the following strengths, as gepirone base:

- 18.2 mg: pink, modified rectangular, with “FK” debossed on one side and “1” on the other side.
- 36.3 mg: off-white, modified rectangular, with “FK” debossed on one side and “7” on the other side.
- 54.5 mg: yellow, modified rectangular, with “FK” debossed on one side and “11” on the other side.
- 72.6 mg: red-brown, modified rectangular, with “FK” debossed on one side and “17” on the other side.

4 CONTRAINDICATIONS

EXXUA is contraindicated in patients:

- with known hypersensitivity to gepirone or components of EXXUA [see Adverse Reactions (6.1)].
- with prolonged QTc interval > 450 msec at baseline [see Warnings and Precautions (5.2)].
- with congenital long QT syndrome [see Warnings and Precautions (5.2)].
- receiving concomitant strong CYP3A4 inhibitors [see Warnings and Precautions (5.2) and Drug Interactions (7)].
- with severe hepatic impairment [see Warnings and Precautions (5.2) and Use in Specific Populations (8.7)].
- taking, or within 14 days of stopping, MAOIs due to the risk of serious and possibly fatal drug interactions, including hypertensive crisis and serotonin syndrome [see Warnings and Precautions (5.3) and Drug Interactions (7)]. Starting EXXUA in a patient treated with reversible MAOIs such as linezolid or intravenous methylene blue is also contraindicated.

5 WARNINGS AND PRECAUTIONS

5.1 Suicidal Thoughts and Behaviors in Adolescents and Young Adults

In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients, and 4,500 pediatric patients, the incidence of suicidal thoughts and behaviors in antidepressant-treated patients aged 24 years and younger was greater than in placebo-treated patients.

There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with MDD. The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1000 patients treated are provided in Table 1.

Table 1 Risk Differences of the Number of Patients with Suicidal Thoughts and Behaviors in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric* and Adult Patients

Age Range	Drug-Placebo Difference in Number of Patients with Suicidal Thoughts or Behaviors per 1000 Patients Treated
Increases Compared to Placebo	
< 18 years old	14 additional patients
18-24 years old	5 additional patients
Decreases Compared to Placebo	
25-64 years old	1 fewer patient
≥ 65 years old	6 fewer patients

*EXXUA is not approved for use in pediatric patients.

It is unknown whether the risk of suicidal thoughts and behaviors in children, adolescents, and young adults extends to longer-term use, i.e., beyond four months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with MDD that the use of antidepressants can delay the recurrence of depression and that depression itself is a risk factor for suicidal thoughts and behaviors.

Monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy, and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing EXXUA, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

5.2 QT Prolongation

EXXUA prolongs the QTc interval [see Clinical Pharmacology (12.2)].

EXXUA is contraindicated in patients with congenital long QT syndrome and in patients with severe hepatic impairment or in patients receiving concomitant strong CYP3A4 inhibitors as they increase EXXUA plasma concentrations [see Contraindications (4), Drug Interactions (7), and Use in Specific Populations (8.7)].

Do not initiate EXXUA if QTc is > 450 msec at baseline [see Dosage and Administration (2.1) and Contraindications (4)].

Correct electrolyte abnormalities prior to EXXUA initiation. In patients with electrolyte abnormalities, who are receiving diuretics or glucocorticoids, or have a history of hypokalemia or hypomagnesemia, also monitor electrolytes during dose titration and periodically during treatment with EXXUA.

Perform an ECG prior to EXXUA initiation, during dosage titration, and periodically during treatment.

Monitor patients with ECGs more frequently:

- If EXXUA is used concomitantly with drugs known to prolong the QT interval [see Drug Interactions (7)].
- In patients who develop QTc ≥ 450 msec during treatment with EXXUA. Do not escalate the EXXUA dosage if QTcF is > 450 msec [see Dosage and Administration (2.1)].
- In patients with a significant risk of developing torsade de pointes, including those with uncontrolled or significant cardiac disease, recent myocardial infarction, heart failure, unstable angina, bradyarrhythmias, uncontrolled hypertension, high degree atrioventricular block, severe aortic stenosis, or uncontrolled hypothyroidism.

Reduce the EXXUA dosage when used concomitantly with moderate CYP3A4 inhibitors, as they may increase EXXUA concentrations [see Dosage and Administration (2.7) and Drug Interactions (7)].

5.3 Serotonin Syndrome

Concomitant use of EXXUA with SSRIs or tricyclic antidepressants may cause serotonin syndrome, a potentially life-threatening condition with changes including altered mental status, hypertension, restlessness, myoclonus, hyperthermia, hyperreflexia, diaphoresis, shivering, and tremor [see Drug Interactions (7)].

The concomitant use of EXXUA with MAOIs is contraindicated. In addition, do not initiate EXXUA in a patient being treated with MAOIs such as linezolid or intravenous methylene blue. If it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking EXXUA discontinue EXXUA before initiating treatment with the MAOI [see Contraindications (4) and Drug Interactions (7)].

If concomitant use of EXXUA with other serotonergic drugs is clinically warranted, inform patients of the increased risk for serotonin syndrome and monitor for symptoms. Discontinue EXXUA and/or concomitant serotonergic drug immediately if the above symptoms occur and initiate supportive symptomatic treatment.

5.4 Activation of Mania or Hypomania

Antidepressant treatment can precipitate a manic, mixed, or hypomanic manic episode. The risk appears to be increased in patients with bipolar disorder or who have risk factors for bipolar disorder. Prior to initiating treatment with EXXUA, screen patients for a history of bipolar disorder and the presence of risk factors for bipolar disorder (e.g., family history of bipolar disorder, suicide, or depression) [see Dosage and Administration (2.1)]. EXXUA is not approved for use in treating bipolar depression.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Suicidal Thoughts and Behaviors in Adolescents and Young Adults [see Warnings and Precautions (5.1)]
- QT Prolongation [see Warnings and Precautions (5.2)]
- Serotonin Syndrome [see Warnings and Precautions (5.3)]
- Activation of Mania or Hypomania [see Warnings and Precautions (5.4)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

During premarketing assessment, multiple doses of EXXUA were administered to 1,976 adult patients with major depressive disorder (MDD) in controlled phase 2 and 3 clinical studies, including 1,639 patients in placebo-controlled phase 2 and 3 trials in MDD, with 237 patients exposed for over six months. The population treated with EXXUA in the pooled placebo-controlled studies ranged from 15 to 78 years of age, was 34% male and 66% female, and was 80% Caucasian, 11% Black, and 9% other race.

The adverse reaction data below are based on two placebo-controlled, flexible-dose, clinical studies (Study 1, Study 2) in which either EXXUA 18.2 mg to 72.6 mg (n=226) or placebo (n=230) was administered to adult patients with MDD during an 8-week double-blind treatment period [see Clinical Studies (14)]. Study 1 had a median age of 39 years and were 61% female, 73% Caucasian, 9% Black, 2% Asian, and 16% Other (Hispanic or Native American). Study 2 had a median age of 39 years and were 69% female, 65% Caucasian, 23% Black, 1% Asian, and 11% Hispanic.

In Study 1 and Study 2, 7% (15/226) of patients treated with EXXUA and 3% (6/230) of patients receiving placebo discontinued treatment due to an adverse reaction. The most common reactions leading to discontinuation for patients taking EXXUA were dizziness and nausea.

The most common adverse reactions (≥ 5% and twice the incidence of placebo) in EXXUA-treated patients were dizziness, nausea, insomnia, abdominal pain, and dyspepsia.

Table 2 presents the adverse reactions that occurred at an incidence of ≥ 2% of patients treated with EXXUA and at a higher incidence than in the placebo-treated patients.

Table 2 Adverse Reactions that Occurred in ≥ 2% of Patients Treated with EXXUA and Greater than the Incidence in Placebo-Treated Patients in Pooled MDD Studies (Study 1 and Study 2)

Adverse Reaction	Placebo (N=230) (%)	EXXUA (18.2 mg to 76.2 mg) (N=226) (%)
Dizziness*	10	49
Nausea	13	35
Headache*	20	31
Feeling Sleepy or Tired*	14	15
Insomnia*	5	14
Diarrhea	9	10
Upper Respiratory Tract Infection	7	8
Dry Mouth	5	8
Vomiting	4	7
Abdominal Pain*	3	7
Dyspepsia	2	6
Increased Appetite	3	5
Constipation	3	4
Nasopharyngitis	3	4
Nasal Congestion	2	4
Paresthesia	1	4
Hyperhidrosis	0	4
Palpitations	0	4
Weight Increased	1	3
Agitation	0	3
Feeling Jittery	0	3
Heart Rate Increased	0	2
Lethargy	0	2

*The following terms were combined:
Dizziness=Lightheadedness, Dizziness, Dizziness Postural.
Headache=Headache, Sinus Headache, Tension Headache.
Feeling Sleepy or Tired=Fatigue, Sedation, Somnolence.
Insomnia=Initial Insomnia, Insomnia, Middle Insomnia, Terminal Insomnia.
Abdominal Pain=Abdominal Discomfort, Abdominal Pain, Abdominal Pain Upper.

Other Adverse Reactions Observed in Clinical Studies

The following is a list of adverse reactions that occurred at an incidence of < 2% in MDD patients treated with EXXUA and at least greater than placebo in Study 1 and Study 2: breast tenderness, confusional state, dyspnea, edema peripheral energy increased, feeling abnormal, hypoesthesia, poor quality sleep, and thinking abnormal.

Additional Adverse Reactions Observed in Clinical Studies

Hypersensitivity reactions including rash, pruritus, and urticaria were reported in clinical studies with EXXUA.

7 DRUG INTERACTIONS

Table 3 displays clinically important drug interactions with EXXUA.

Table 3 Clinically Important Drug Interactions with EXXUA

CYP3A4 Inhibitors	
Clinical Impact	Strong CYP3A4 Inhibitors Concomitant use of EXXUA with a strong CYP3A4 inhibitor increases EXXUA exposure by ~ 5-fold [see <i>Clinical Pharmacology</i> (12.3)]. Moderate CYP3A4 Inhibitors Concomitant use with a moderate CYP3A4 inhibitor increases EXXUA exposure by ~ 2.6-fold [see <i>Clinical Pharmacology</i> (12.3)].
Intervention	Strong CYP3A4 Inhibitors EXXUA is contraindicated in patients taking strong CYP3A4 inhibitors [see <i>Dosage and Administration</i> (2.7), <i>Contraindications</i> (4), and <i>Warnings and Precautions</i> (5.2)]. Moderate CYP3A4 Inhibitors If EXXUA is used with a moderate CYP3A4 inhibitor, reduce the dosage of EXXUA [see <i>Dosage and Administration</i> (2.7) and <i>Warnings and Precautions</i> (5.2)].
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact	Concomitant use of EXXUA with MAOIs increases the risk of serotonin syndrome.
Intervention	EXXUA is contraindicated in patients taking MAOIs, including MAOIs such as linezolid or intravenous methylene blue or in patients who have taken MAOIs within the preceding 14 days. Allow at least 14 days after stopping EXXUA before starting an MAOI [see <i>Dosage and Administration</i> (2.8), <i>Contraindications</i> (4), and <i>Warnings and Precautions</i> (5.3)].
Drugs that Prolong the QTc Interval	
Clinical Impact	Concomitant use of drugs that prolong the QTc interval may add to the QTc prolonging effects of EXXUA and increase the risk of cardiac arrhythmias.
Intervention	Monitor patients with ECGs more frequently if EXXUA is administered with other drugs known to prolong QT interval [see <i>Warnings and Precautions</i> (5.2)].
CYP3A4 Inducers	
Clinical Impact	Concomitant use of EXXUA with a strong CYP3A4 inducer reduces EXXUA exposure by 20- to 29-fold [see <i>Clinical Pharmacology</i> (12.3)].
Intervention	Avoid concomitant use of EXXUA in patients taking strong CYP3A4 inducers.
Other Serotonergic Drugs	
Clinical Impact	Concomitant use of EXXUA and serotonergic drugs increases the risk of serotonin syndrome.
Intervention	Monitor for symptoms of serotonin syndrome when EXXUA is used concomitantly with other drugs that may affect the serotonergic neurotransmitter systems. If serotonin syndrome occurs, consider discontinuation of EXXUA and/or concomitant serotonergic drug [see <i>Warnings and Precautions</i> (5.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants, including EXXUA, during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Antidepressants at 1-866-961-2388 or visiting online at <https://womensmentalhealth.org/research/pregnancyregistry/antidepressants/>.

Risk Summary

Based on animal reproduction studies, gepirone has been shown to have adverse effects on embryo/fetal and postnatal development. In rats, increased mortality during the first 4 days after birth and persistent reduction in body weight through lactation and weaning were observed at all doses and increased still births were seen with a no observed adverse effect level (NOAEL) at 3 times the maximum recommended human dose (MRHD) on a mg/m² basis. In embryofetal development studies in rats and rabbits, decreased embryofetal growth, body weights and lengths, with accompanying skeletal variations were seen with a NOAEL at 9 and 12 times the MRHD on a mg/m² basis, respectively (see *Data*). There are insufficient clinical data on gepirone use during pregnancy to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. There are clinical considerations regarding neonates exposed to serotonergic antidepressants during the third trimester of pregnancy (see *Clinical*

Considerations and Data). There are risks associated with untreated depression during pregnancy (see *Clinical Considerations*). Consider if the risks outweigh the benefits of treatment with gepirone during pregnancy.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated Maternal and/or Embryofetal Risk

Women who discontinue antidepressants during pregnancy are more likely to experience a relapse of major depression than women who continue antidepressants. This finding is from a prospective, longitudinal study of 201 pregnant women with a history of major depressive disorder who were euthymic and taking antidepressants at the beginning of pregnancy. Consider the risk of untreated depression when discontinuing or changing treatment with antidepressant medication during pregnancy and postpartum.

Fetal/Neonatal Adverse Reactions

Neonates exposed to other serotonergic antidepressants in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremors, jitteriness, irritability, and constant crying. These findings are consistent with either a direct toxic effect of SSRIs or possibly a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome [See *Warnings and Precautions* (5.3)].

Data

Human Data

Exposure during late pregnancy to serotonergic antidepressants may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1- 2 per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality.

Animal Data

In embryofetal development studies, oral administration of gepirone to pregnant rats (75, 150, and 300 mg/kg) or pregnant rabbits (50, 100, and 200 mg/kg) during the period of organogenesis resulted in decreased embryofetal growth, body weights and lengths, with accompanying skeletal variations at mid and high doses; the mid doses are 18 and 24 times the MRHD on a mg/m² basis in rats and rabbits, respectively. No malformations were seen in these studies. The developmental NOAEL was 9 and 12 times the MRHD on a mg/m² basis in rats and rabbits, respectively.

When pregnant rats were treated with gepirone (10, 20, and 40 mg/kg) from late gestation through weaning, decreased birth weights were seen at mid and high doses; the mid dose is twice the MRHD. Increased offspring mortality during the first 4 days after birth and persistent reduction in body weight were observed at all doses; the lowest dose is approximately equal to the MRHD on a mg/m² basis. The no-effect dose for fetal effects was not determined in this study.

When gepirone was administered orally to male and female rats prior to and throughout mating, gestation, and lactation at doses of 5, 27, 64, and 150 mg/kg/day, increased still births were seen at ≥ 64 mg/kg. Early postnatal mortality was increased at 150 mg/kg (18 times the MRHD on a mg/m² basis). The NOAEL (27 mg/kg) for still births was associated with a maternal dose 3 times the MRHD on a mg/m² basis. Fetal weights were decreased at 27 mg/kg (3 times the MRHD on a mg/m² basis) and fetal lengths were decreased at 64 mg/kg (8 times the MRHD on a mg/m² basis) and above. Pup weights were decreased at birth, throughout lactation and weaning, and until at least 14 weeks of age, with delays of some developmental landmarks, at 64 mg/kg and above. The NOAEL for growth and development (5 mg/kg) was associated with a maternal dose below the MRHD on a mg/m² basis.

8.2 Lactation

Risk Summary

There are no data on the presence of gepirone in human milk, the effects on the breastfed infant, or the effects on milk production. Gepirone is present in rat milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk. There are reports of breastfed infants exposed to other serotonergic antidepressants experiencing irritability, restlessness, excessive somnolence, decreased feeding, and weight loss (see *Clinical Considerations*). The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EXXUA and any adverse effects on the breastfed infant from EXXUA or from the underlying maternal condition.

Clinical Considerations

Monitor breastfeeding infants for adverse reactions, such as irritability, restlessness, excessive somnolence, decreased feeding, and weight loss.

8.4 Pediatric Use

The safety and effectiveness of EXXUA in pediatric patients have not been established for the treatment of MDD.

Efficacy was not demonstrated in two 8-week, randomized, placebo-controlled trials in 426 pediatric patients 7 to 17 years of age with MDD. The primary efficacy endpoint was change from double-blind baseline to Week 8 on the Children's Depression Rating Scale-Revised (CDRS-R) measure. The effect of treatment with EXXUA was not significantly different from placebo. In the pediatric trial patients, there was a higher occurrence of vomiting in pediatric patients (13%) compared to adults (6.6%).

Antidepressants, such as EXXUA, increase the risk of suicidal thoughts and behaviors in pediatric patients [see *Warnings and Precautions* (5.1)].

Juvenile Animal Toxicity Data

In a juvenile animal study, male and female rats were treated with gepirone once daily with oral doses of 0, 10, 40, and 70 mg/kg, from postnatal day 14 to 42. Increased motor activity and impaired performance in the Morris water maze were observed at 40 and 70 mg/kg after a two-week recovery period. The no observed adverse effect level (NOAEL) for the neurobehavioral development effect was 10 mg/kg. When the animals were mated after a 3-week recovery period, increased pre-implantation loss was observed for mated pairs treated with 70 mg/kg. The NOAEL for this finding was 40 mg/kg/day.

8.5 Geriatric Use

Of the 1,639 patients exposed to EXXUA in placebo-controlled clinical studies of MDD, 0.7% (12 patients) were 65 years of age or older and 0.2% (3 patients) were 75 years or older.

Geriatric patients (65 to 81 years of age) had higher EXXUA AUC and C_{max} values than younger adult (18 to 40 years of age) patients [see *Clinical Pharmacology* (12.3)]. The maximum recommended daily dosage of EXXUA in geriatric patients is lower than in younger adult patients [see *Dosage and Administration* (2.4)].

8.6 Renal Impairment

In patients with creatinine clearance < 50 mL/min, the metabolism and excretion of EXXUA and some of its major metabolites were decreased [see *Clinical Pharmacology* (12.3)]. The maximum recommended daily dosage of EXXUA in patients with a creatinine clearance < 50 mL/min is lower than in patients with normal renal function [see *Dosage and Administration* (2.5)]. The recommended dosage in patients with a creatinine clearance $\geq$ 50 mL/min is the same as in patients with normal renal function [see *Dosage and Administration* (2.5)].

8.7 Hepatic Impairment

In patients with mild (Child-Pugh A) hepatic impairment to moderate (Child-Pugh B) hepatic impairment, the metabolism of EXXUA and its major metabolites was decreased [see *Clinical Pharmacology* (12.3)]. The maximum recommended dosage of EXXUA in patients with moderate hepatic impairment is lower than in patients with normal hepatic function [see *Dosage and Administration* (2.6)]. The recommended dosage in patients with mild hepatic impairment is the same as in patients with normal hepatic function.

EXXUA is contraindicated in patients with severe (Child-Pugh C) hepatic impairment [see *Warnings and Precautions* (5.2) and *Clinical Pharmacology* (12.3)].

10 OVERDOSAGE

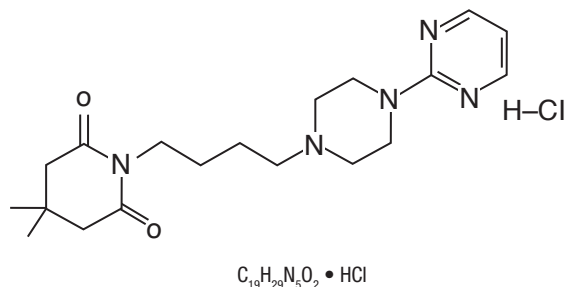
In clinical studies, cases of acute ingestions up to 454 mg (6.25 times the maximum recommended dose) of EXXUA alone or in combination with other drugs, were reported. Signs and symptoms reported with overdose of EXXUA at doses up to 454 mg included vomiting and transient incomplete bundle branch block; an unknown dose of EXXUA produced altered level of consciousness and a 60-second convulsion.

No specific antidotes for EXXUA are known.

Consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdose management recommendations.

11 DESCRIPTION

EXXUA contains gepirone, in the salt form as gepirone hydrochloride (HCl). The chemical name is 2,6-piperidinedione, 4,4-dimethyl-1-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-, monohydrochloride. The molecular weight of gepirone HCl is 395.93 and the structural formula is as follows:



Gepirone HCl is a white to off-white crystalline powder, which is readily soluble in water.

EXXUA is supplied as extended-release tablets for oral administration. Each extended-release tablet contains 18.2 mg, 36.3 mg, 54.5 mg, or 72.6 mg, gepirone equivalent to 20 mg, 40 mg, 60 mg, or 80 mg of gepirone HCl respectively. The extended-release tablets also contain the following inactive ingredients: colloidal silicon dioxide, Hypromellose, iron oxide (red and/or yellow colorants), magnesium stearate, and microcrystalline cellulose.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of the antidepressant effect of EXXUA is not fully understood but is thought to be related to its modulation of serotonergic activity in the CNS through selective agonist activity at 5HT1A receptors.

12.2 Pharmacodynamics

The pharmacological activity of gepirone is attributed to the parent drug and its major metabolites 3'-OH-gepirone and 1-PP. Gepirone and its 3'-OH metabolite bind to 5HT1A receptors (K_i = 38 nM and 58 nM, respectively), where they act as agonists, while the 1-PP metabolite binds to alpha2 receptors (K_i = 42 nM).

Cardiac Electrophysiology

In a thorough QT study, the largest mean increase in baseline- and placebo-corrected QTc interval with administration of 100 mg per day immediate-release formulation of gepirone 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 2-fold the exposure of the maximum recommended dose [see *Dosage and Administration* (2.1) and *Warnings and Precautions* (5.2)].

12.3 Pharmacokinetics

The pharmacokinetics of EXXUA are linear and dose proportional from 18.2 mg to 72.6 mg. Steady-state plasma concentration are typically achieved within two to four days of daily dosing.

Absorption

The absolute bioavailability is 14% to 17%. The maximal plasma EXXUA concentration (C_{max}) after dosing is reached within 6 hours post dose (T_{max}).

Effect of Food

After a high fat meal, T_{max} is reached at 3 hours. A significant effect of food has been observed on the peak plasma concentration (C_{max}) of EXXUA and, to a lesser extent, on the total exposure (AUC0-tlast, AUC0- ∞) to EXXUA. The magnitude of the food-effect was dependent of the fat content of the meal. The systemic exposure of EXXUA and major metabolites was consistently higher under fed conditions as compared to the fasted state. Gepirone C_{max} after intake of low-fat (~ 200 calories) breakfast was 27% higher, after medium-fat (~500 calories) breakfast 55% higher and after a high-fat (~ 850 calories) breakfast 62% higher as compared to the fasted state. The AUC after intake of low-fat breakfast was about 14% higher, after a medium-fat breakfast 22% higher and after a high-fat breakfast 32 to 37% higher as compared to the fasted state. The effect of varying amounts of fat on C_{max} and AUC of the major metabolites 3'-OH-gepirone and 1-PP were similar to that found for gepirone [see *Dosage and Administration* (2.2)].

Distribution

The apparent volume of distribution of EXXUA is approximately 94.5L. The *in vitro* plasma protein binding in human is 72% and is not concentration dependent. The *in vitro* plasma protein binding for metabolite 3'-OH-gepirone is 59% and 42% for 1-PP.

Elimination

The mean terminal half-life is approximately 5 hours.

Metabolism

EXXUA is extensively metabolized and both major metabolites 1-PP and 3'-OH-gepirone are present in plasma in higher concentrations than the parent compound. CYP3A4 is the primary enzyme catalyzing the metabolism of EXXUA to its major pharmacologically active metabolites.

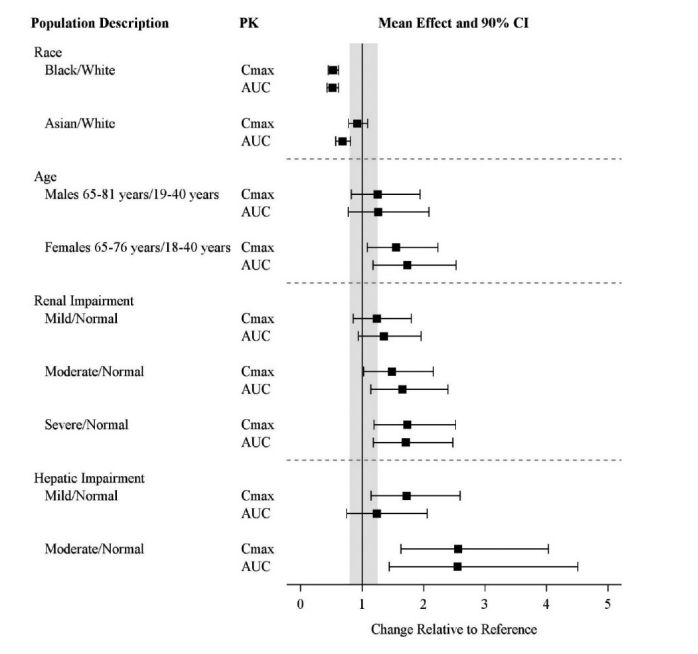
Excretion

Following a single oral dose of [^{14}C]-labeled gepirone, approximately 81% and 13% of the administered radioactivity was recovered in the urine and feces, respectively as metabolites. 60% of the gepirone was eliminated in the urine within the first 24 hours. The presence of hepatic or renal impairment did affect the apparent clearance of EXXUA.

Specific Populations

Exposures of gepirone in specific populations are summarized in Figure 1 [see *Dosage and Administration* (2.3, 2.4, 2.5), *Contraindications* (4), and *Use in Specific Populations* (8.5, 8.6, 8.7)].

Figure 1 Effects of Specific Populations on the Pharmacokinetics of Gepirone



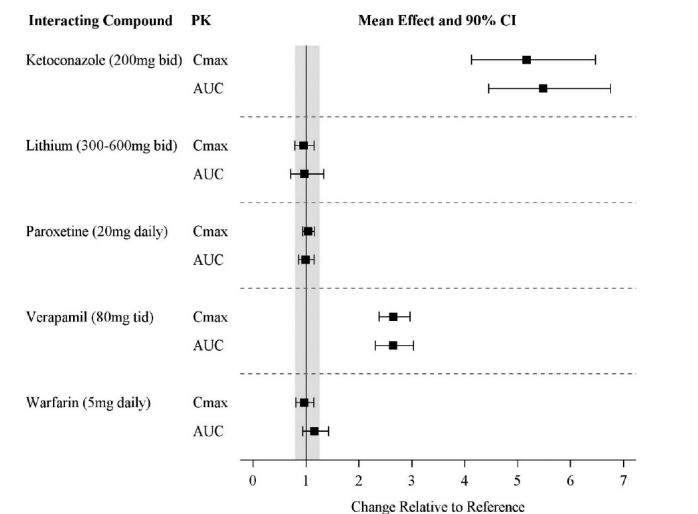
Gepirone dose: 36.3 mg in renal, 18.2 mg in hepatic; steady-state at 18.2 mg for race and 18.2-72.6 mg for age. Data are GMRs and 90% CIs, except for Age groups (arithmetic mean ratios). AUC = area under the plasma concentration-time curve; CI = confidence interval; C_{max} = maximum plasma concentration; GMR = geometric mean ratio.

Drug Interactions Studies

In Vivo Studies

The effect of co-administered drugs on the pharmacokinetics of gepirone is summarized in Figure 2 [see Dosage and Administration (2.6) and Drug Interactions (7)].

Figure 2 Effect of Co-Administered Drugs on the Pharmacokinetics of Gepirone



Gepirone 36.3 mg was administered with interacting drugs at steady-state, except with verapamil (18.2 mg gepirone). Reference = gepirone alone. Data are GMRs and 90% CIs. AUC = area under the plasma concentration-time curve; CI = confidence interval; C_{max} = maximum plasma concentration; GMR = geometric mean ratio.

Rifampin

The effect of multiple oral dosing of potent cytochrome P450 3A4 inducer rifampin on the steady-state pharmacokinetics of EXXUA and its major metabolites 1-PP and 3'-OH-gepirone was investigated in 24 subjects. Combined therapy with rifampin (600 mg daily) and EXXUA (20 mg for two days, then 40 mg daily) decreased C_{max} and AUC0-24 of EXXUA 20 times (EXXUA C_{max} alone 9.63 ng/mL, with rifampin 0.491 ng/mL) and 29 times (EXXUA AUC0-24 alone 123 ng-hr/mL, with rifampin 4.19 ng-hr/mL), respectively. The C_{max} and AUC0-24 of 3'-OH gepirone were decreased 2.5 times (3'-OH gepirone C_{max} alone 23.0 ng/mL, with rifampin 9.30 ng/mL) and three times (3'-OH gepirone AUC0-24 alone 371 ng-hr/mL, with rifampin 126 ng-hr/mL), respectively. There was no effect on

the pharmacokinetics of 1-PP (1-PP C_{max} alone 6.37 ng/mL, with rifampin 6.02 ng/mL; 1-PP AUC0-24 alone 92.5 ng-hr/mL, with rifampin 81.1 ng-hr/mL).

Glyburide

Under steady-state conditions for glyburide, the addition of 36.3 mg daily of EXXUA for six days in 16 patients with stable Type II diabetes resulted in statistically significantly lower AUC (glyburide AUC0-12 alone 574.8 ng-h/mL, with EXXUA 483.0 ng-h/mL) and C_{max} (glyburide C_{max} alone 121.0 ng/mL, with EXXUA 96.6 ng/mL) values for glyburide.

Drugs that Interfere with Hemostasis

Following coadministration of stable dose of warfarin (INR 1.4 to 2.0) with multiple daily doses of EXXUA, no significant effect was observed in INR, prothrombin values, or total warfarin (protein bound plus free drug) pharmacokinetics for warfarin.

Drugs that Interfere with Protein Binding

Gepirone is not highly bound to plasma protein and is not likely to be involved in interactions due to altered protein binding. In a clinical study with coadministration of EXXUA (18.2 mg) and warfarin, a highly protein-bound drug, no significant change in international normalized ratio (INR) was observed.

In Vitro Studies

Gepirone at concentrations of 0.5, 5, and 50 ng/mL was shown to have no significant impact on the plasma protein binding of chlorpromazine, desipramine, diazepam, phenytoin, prazosin, propranolol, verapamil, or warfarin. The binding of digoxin and haloperidol were decreased (at maximum) by 5% and 9%, respectively. The plasma protein binding of lidocaine appeared to be increased by 4.9% in the presence of gepirone.

Alcohol: An *in vitro* study showed dissolution rate for both 18.2 mg and 72.6 mg gepirone ER tablets decreased slightly as ethanol concentration increased in 0.01N HCl and 0.1N HCl at 0%, 5%, 10%, 20% and 40% alcohol. At 20 hours and 40% alcohol, approximately (mean) 76.8% and 80.7% were dissolved for the 18.2 mg and 72.6 mg gepirone ER tablets, respectively.

Transporter Systems: EXXUA and its metabolites are unlikely to cause clinically significant inhibition of the following transporters based on *in vitro* data: P-gp, BCRP, BSEP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, and MATE2-K. As such, no clinically relevant interactions with drugs metabolized/transported by these CYP enzymes or transporters would be expected.

Enzyme systems: In addition, EXXUA has not been shown to be an inhibitor or inducer of any of the cytochrome P450 enzymes [see Clinical Pharmacology (12.3)]. Chronic administration of EXXUA is unlikely to induce the metabolism of drugs metabolized by these CYP isoforms.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No evidence of carcinogenic potential was observed in lifetime carcinogenicity studies performed in rats and mice at doses up to 43.6 and 317.8 mg/kg/day, respectively. These doses are approximately 6 and 18 times the maximum recommended human dose (MRHD), respectively, on a mg/m² basis.

Mutagenicity

Gepirone showed no mutagenicity in three different *in vitro* genotoxicity assays (bacterial gene mutation, mammalian gene mutation, or DNA repair). No clastogenicity was observed in a rat micronucleus assay.

Impairment of Fertility

When gepirone was administered orally to male and female rats prior to and throughout mating at daily doses of 5, 27, 64, and 150 mg/kg, the latency to mating was increased at doses of 64 mg/kg (8 times the MRHD on a mg/m² basis) and above.

14 CLINICAL STUDIES

The efficacy of EXXUA for the treatment for major depressive disorder (MDD) in adults was evaluated in two eight-week randomized, double-blind, placebo-controlled, flexible-dose studies in adults (age 18 to 69 years) meeting Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for MDD.

In Study 1, adult patients (18 to 69 years) who met DSM-IV diagnostic criteria for MDD were included in the trial. Patients in Study 1 had a median age of 39 years and were 61% female, 73% Caucasian, 9% Black, 2% Asian, and 16% Other (Hispanic or Native American). After an initial dosage of 18.2 mg once daily, the dosage was titrated to 36.3 mg once daily on Day 4 of treatment. The dosage could then be increased to 54.5 mg once daily after Day 7, and to 72.6 mg once daily after an additional 7 days. In patients that received EXXUA, the final daily dose of EXXUA was 72.6 mg in 64% of patients, 54.5 mg in 20% of patients, and 36.3 mg in 17% of patients.

In Study 2, adult patients (18 to 64 years) who met DSM-IV diagnostic criteria for MDD were included in the trial. Patients in Study 2 had a median age of 39 years and were 69% female, 65% Caucasian, 23% Black, 1% Asian, and 11% Hispanic. After an initial dosage of 18.2 mg daily, the dosage was titrated to 36.3 mg daily on Days 4 to 7 of treatment. The dosage could then be increased to 54.5 mg daily after Day 7, and to 72.6 mg daily after an additional 7 days. In patients that received EXXUA, the final daily dose of EXXUA was 72.6 mg in 66% of patients, 54.5 mg in 22% of patients, 36.3 mg in 10% of patients, and 18.2 mg in 2% of patients.

In Study 1 and Study 2, the primary efficacy measure was the change from baseline in the Hamilton Depression Rating Scale (HAM-D-17) total score at Week 8. In both studies, patients in the EXXUA groups experienced statistically significantly greater improvement on the primary endpoint compared to patients in the placebo groups (see Table 4).

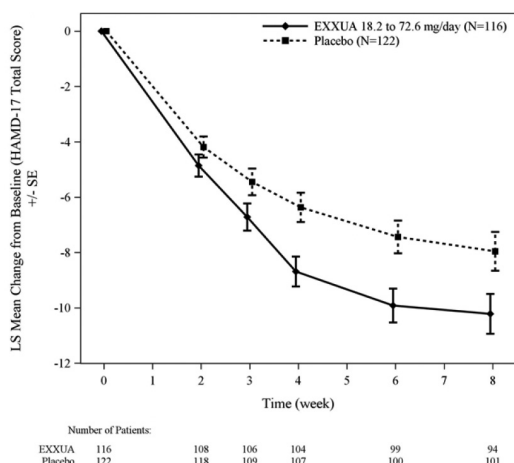
Table 2 Results for the Primary Endpoint: Change from Baseline in the HAM-D-17 Total Score at Week 8 in Adult Patients with MDD (Study 1 and Study 2)

Study Number	Treatment Group	N	Mean Baseline Score (SD)	LS Mean CFB (SE)	Placebo-subtracted Difference (95% CI)
1	EXXUA (18.2 to 72.6 mg/day)	101	22.7 (2.45)	-9.04 (0.78)	-2.47 (-4.41, -0.53)
	Placebo	103	22.8 (2.51)	-6.75 (0.77)	
2	EXXUA (18.2 to 72.6 mg/day)	116	23.9 (2.69)	-10.22 (0.75)	-2.45 (-4.47, -0.43)
	Placebo	122	24.2 (2.93)	-7.96 (0.73)	

N= number of patients in the primary efficacy analysis set; CFB=Change from baseline; LS=Least Squares; SD=Standard Deviation; SE=Standard Error
In Study 1, the final dose of EXXUA was 72.6, 54.5, and 36.3 mg/day in 64%, 20%, and 17% of patients, respectively.
In Study 2, the final dose of EXXUA was 72.6, 54.5, 36.3, and 18.2 mg/day in 66%, 22%, 10%, and 2% of patients, respectively.

The change from baseline in HAM-D-17 total score by week compared to placebo for Study 2 is shown in Figure 3.

Figure 3 Mean Change from Baseline in HAM-D-17 Total Score by Treatment Week (Study 2)



LS=Least squares; SE=Standard Error

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

EXXUA (gepirone) extended-release tablets are supplied in bottles of 30 with child-resistant caps and in four dosage strengths:

- **18.2-mg Tablets** – pink, modified rectangular, with “FK” debossed on one side and “1” on the other side.
Bottles of 30 NDC 23594-150-30
- **36.3-mg Tablets** – off-white, modified rectangular, with “FK” debossed on one side and “7” on the other side.
Bottles of 30 NDC 23594-151-30
- **54.5-mg Tablets** – yellow, modified rectangular, with “FK” debossed on one side and “11” on the other side.
Bottles of 30 NDC 23594-152-30
- **72.6-mg Tablets** – red-brown, modified rectangular, with “FK” debossed on one side and “17” on the other side.
Bottles of 30 NDC 23594-153-30

EXXUA (gepirone) extended-release tablets Titration Pack is supplied with child-resistant cap in the following configuration:

- **18.2-mg Tablets** – pink, modified rectangular, with “FK” debossed on one side and “1” on the other side.
Bottles of 32 NDC 23594-150-32

Storage

Store at 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from high humidity and moisture.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Suicidal Thoughts and Behaviors

Advise patients and caregivers to look for the emergence of suicidal ideation and behavior, especially during early treatment and when the dose is adjusted up or down and instruct them to report such symptoms to their healthcare provider [see Box Warning and Warnings and Precautions (5.1)].

QT Prolongation

Inform patients to consult their physician immediately if they feel faint, lose consciousness, or have heart palpitations [see Warnings and Precautions (5.2)]. Advise patients to inform their healthcare provider if they are taking, or plan to take, any prescription or over-the-counter medications because there is an increased risk for drug interactions with EXXUA [see Drug Interactions (7)].

Serotonin Syndrome

Caution patients about the risk of serotonin syndrome, particularly with the concomitant use of EXXUA with SSRIs or tricyclic antidepressants. Instruct patients to contact their health care provider or report to the emergency room if they experience signs or symptoms of serotonin syndrome [see Warnings and Precautions (5.3) and Drug Interactions (7)].

Activation of Mania or Hypomania

Advise patients to observe for signs of activation of mania or hypomania and instruct them to report such symptoms to their healthcare provider [see Warnings and Precautions (5.4)].

Administration Information

Advise patients to swallow EXXUA whole and not to split, chew, or crush the tablets. Advise patients to take EXXUA at approximately the same time every day with food [see Dosage and Administration (2.2)].

Pregnancy

Advise pregnant women to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with EXXUA.

Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in women exposed to EXXUA during pregnancy.

Advise patients that EXXUA use late in pregnancy may lead to an increased risk for neonatal complications requiring prolonged hospitalization, respiratory support, tube feeding, and/or persistent pulmonary hypertension of the newborn (PPHN) [see Use in Specific Populations (8.1)].

Lactation

Advise breastfeeding individuals using EXXUA to monitor infants for excess sedation, restlessness, agitation, poor feeding and poor weight gain and to see medical care if they notice these signs [see Use in Specific Populations (8.2)].

Product of Italy

Manufactured by:

Mission Pharmacal Company
San Antonio, TX USA 78230

Distributed by:

Aytu Therapeutics, LLC
Denver, CO USA 80237

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