New Drug Overview

Exxua (gepirone)

PDL Category: Antidepressants

Introduction

Disease Background:

- Major depressive disorder (MDD) is described as an unrelenting low mood, a deficiency of positive affect, and no interest in activities that generally are pleasurable (anhedonia) that varies from ones usual self and results in substantial suffering or impairment for ≥2 weeks (*Garakani et al 2026*).
  - Worldwide, it is estimated that the MDD annual prevalence is 4-6% in adults (*Garakani et al 2026*).
  - It has been estimated that about 21 million adults in the United States had a minimum of one major depressive episode in 2021. This is approximately 8.3% of adults in the United States (*NIH 2023*).
    - In this same year, MDD prevalence was higher for adult females than males (10.3% vs 6.2%) and was highest for those 18-25 years of age (18.6%) (*NIH 2023*).
- While a first episode can happen at any age, a noteworthy number of patients with MDD have their first episode of MDD before they turn 30 years of age (*Gaynes 2026*).
- A majority of patients with MDD experience the following symptoms: sad, irritable, or anxious mood; loss of pleasure in activities; impaired concentration and decision-making; worthlessness and inappropriate guilt; hopelessness; fatigue or loss of energy; or sleep disturbance (*Gaynes 2026*).
- Criteria for MDD diagnosis per Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) includes that at least 5 of the listed symptoms below have occurred during the same two-week span and characterize a change from prior functioning. In addition, at least one of the symptoms is depressed mood or loss of interest or pleasure, the symptoms result in substantial distress or impairment in social or other areas of functioning, and the episode is not due to another medical condition (*Gaynes 2026*).
  - Symptoms include:
    - Depressed mood a majority of the day, almost every day reported by the patient or observed by others.
    - Reduced interest or pleasure in all, or about all, activities most the day, practically every day.
    - Substantial weight loss with no dieting or weight gain, or a change in appetite almost every day.
    - Insomnia or hypersomnia almost every day.
    - Psychomotor agitation or delay almost every day.
    - Fatigue or loss of energy almost every day.
    - Feeling worthless or having inappropriate guilt almost every day.
    - Decreased ability to think or concentration, or being indecisive almost every day.
    - Persistent thoughts of death, suicidal ideation or suicide attempt, or a plan to commit suicide.
- Cognitive behavioral therapy (CBT) and various pharmacologic agents are available for MDD management (*Garakani et al 2026*).
- Exxua was FDA approved in 2023.

Pharmacology/Usage

- Exxua (gepirone) is an extended-release tablet for oral administration. White its exact mechanism of action is not fully understood, it is thought to be related to its modulation of serotonergic activity in the CNS through selective agonist activity at 5HT1A receptors.

Indications

Table 1. Food and Drug Administration Approved Indications

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Indication	Exxua (gepirone)
• For the treatment of major depressive disorder (MDD) in adults.	✔

(Prescribing information: Exxua 2025)

- Information on indications, mechanism of action, pharmacokinetics, dosing, safety, and clinical efficacy summary has been obtained from the prescribing information for the individual products, except where noted otherwise.

Dosing and administration

Table 2. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Exxua (gepirone)	Extended-Release (ER) tablets	Oral	Once daily, with food. Increase the dosage based on clinical response and tolerability.	• Correct electrolyte abnormalities prior to starting 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. • Perform an electrocardiogram prior to starting, during dosage titration, and periodically during treatment. • Do not start Exxua if QTc is >450msec at baseline. • Monitor ECGs more frequently in certain patient populations. • Screen patients for a personal or family history of bipolar disorder, mania, or hypomania prior to starting treatment.

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Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				• In geriatric patients, patients with moderate hepatic impairment, and patients with creatinine clearance <50ml/min, the maximum dosage is 36.3mg QD after day 7.

See the current prescribing information for full details.

Clinical Efficacy Summary

- The efficacy of Exxua was assessed in two eight-week randomized, double-blind, placebo-controlled, flexible-dose studies that included adults (age 18 to 69 years old) who met Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for MDD.
- *Study 1* included adult patients aged 18 to 69 years who met DSM-IV criteria for MDD, with a median age of 39 years. In addition, about 61% were female and 73% were Caucasian.
- *Study 2* included adult patients aged 18 to 64 years who met DSM-IV criteria for MDD, with a median age of 39 years. In addition, about 69% were female and 65% were Caucasian.
- In both studies, the primary efficacy measure was the change from baseline in the Hamilton Depression Rating Scale (HAMD-17) total score at week 8.
  - In both studies, results suggested that patients in the Exxua groups experienced statistically significantly greater improvement on the primary endpoint compared to patients in the placebo groups.
  - Results are presented in the table below, which was adapted from the prescribing information.

Table 3. Efficacy results

Study	Treatment	N	Mean Baseline Score	Least Squares Mean Change from baseline	Placebo-subtracted difference
1	Exxua (18..2 to 72.6mg/day)	101	22.7	-9.04	-2.47
	Placebo	103	22.8	-6.75	
2	Exxua (18..2 to 72.6mg/day)	116	23.9	-10.22	-2.45
	Placebo	122	24.2	-7.96	

Clinical guidelines

- Note that the guidelines have not been updated to include Exxua as they were published prior to Exxua being FDA approved.
- **Nonpharmacologic and Pharmacologic Treatments of Adults in the acute phase of Major Depressive Disorder: A Living Clinical Guideline from the American College of Physicians (ACP; Version 1, Update Alert 3): 2025** (*Qaseem et al 2025*)
  - ACP Recommendations include the following:
    - Monotherapy with cognitive behavioral therapy or a second-generation antidepressant is recommended as initial treatment for the acute phase of moderate to severe MDD.

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- Combination therapy with cognitive behavioral therapy and a second-generation antidepressant is suggested as initial treatment for the acute phase of moderate to severe MDD.
- Cognitive behavioral therapy is suggested as initial treatment for the acute phase of mild MDD.
- For acute phase of moderate to severe MDD, one of the options listed below is suggested if patients had an inadequate response to initial treatment with an adequate dose of a second-generation antidepressant:
  - Switching to or augmenting with cognitive behavioral therapy
  - Switching to a different second-generation antidepressant or augmenting with a second pharmacologic agent.

- **Veterans Affair (VA)/Department of Defense (DoD) Clinical Practice Guideline for the management of Major Depressive Disorder: 2022** (*VA/DoD Clinical Practice Guideline 2022*).
  - Recommendations for treatment of uncomplicated MDD include:
    - Per patient preference, it is recommended to treat MDD with psychotherapy or pharmacotherapy as monotherapy.
    - It is suggested to offer one of the following interventions if it is decided to use psychotherapy for MDD treatment (not ranked in order):
      - Acceptance and commitment therapy.
      - Behavioral therapy/behavioral activation.
      - Cognitive behavioral therapy.
      - Interpersonal therapy.
      - Mindfulness-based cognitive therapy.
      - Problem-solving therapy.
      - Short-term psychodynamic psychotherapy.
    - With mild to moderate MDD, it is suggested to offer cognitive behavioral therapy as adjunct to pharmacotherapy or as a first-line treatment, per patient preference.
    - It is suggested to offer one of the following when deciding on an initial pharmacotherapy, or for those with previous response to pharmacotherapy (not ranked in order):
      - Bupropion.
      - Mirtazapine.
      - A selective-norepinephrine reuptake inhibitor (SNRI).
      - Trazodone, vilazodone, or vortioxetine.
      - A selective serotonin reuptake inhibitor (SSRI).
    - It is suggested to not use as initial pharmacotherapy:
      - Esketamine.
      - Ketamine.
      - Monoamine oxidase inhibitors.
      - Nefazodone.
      - Tricyclic antidepressants

Safety summary

- **Contraindications:**
  - In patients:
    - With known hypersensitivity to gepirone or any component of the product.
    - With prolonged QTc interval >450msec at baseline.
    - With congenital long QT syndrome.
    - Receiving concomitant strong CYP3A4 inhibitors.
    - With severe hepatic impairment.

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- Taking, or within 14 days of stopping, MAO inhibitors due to the risk of serious and possibly fatal drug interactions, including hypertensive crisis and serotonin syndrome. Starting Exxua in a patient treated with reversible MAO inhibitors such as linezolid or IV methylene blue is also contraindicated.

- **Box Warning:**
  - Exxua has a box warning regarding 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. Exxua is not approved for use in pediatric patients.

- **Warnings and precautions:**
  - Exxua prolongs the QTc interval. Do not start Exxua if QTc is >450msec at baseline. Refer to the dosing and administration, as well as the contraindications section for additional information. Monitor patients with ECGs more frequently:
    - If Exxua is used concomitantly with drugs known to prolong the QT interval.
    - In patients who develop QTc ≥450msec during Exxua treatment. Do not escalate the Exxua dosage if QTcF is >450msec.
    - 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, bradyarrhythmia, uncontrolled hypertension, high degree atrioventricular block, severe aortic stenosis, or uncontrolled hypothyroidism.
  - Concomitant use of Exxua with SSRIs or TCAs may cause serotonin syndrome. The concomitant use of Exxua with MAOIs is contraindicated. 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 symptoms occur and start supportive symptomatic treatment.
  - 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 starting Exxua, screen patients for a history of bipolar disorder and the presence of risk factors for bipolar disorder.

- **Common adverse drug reactions:** Listed % incidence for adverse drug reactions= reported % incidence for drug (Exxua) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.
  - The most frequently reported adverse events included dizziness (39%), nausea (22%), headache (11%), feeling sleepy or tired (1%), insomnia (9%), diarrhea (1%), upper respiratory tract infection (1%), dry mouth (3%), vomiting (3%), abdominal pain (4%), dyspepsia (4%), increased appetite (2%), constipation (1%), nasopharyngitis (1%), nasal congestion (2%), paresthesia (3%), hyperhidrosis (4%), palpitations (4%), weight increased (2%), agitation (3%), feeling jittery (3%), heart rate increased (2%), and lethargy (2%).

- **Drug interactions:**
  - Exxua is contraindicated in patients taking strong CYP3A4 inhibitors.
  - If Exxua is used with a moderate CYP3A4 inhibitor, reduce the dosage of Exxua. Refer to the prescribing information for additional information.
  - Exxua is contraindicated in patients taking MAO inhibitors, including MAO inhibitors such as linezolid or IV methylene blue, or in patients who have taken MAO inhibitors within the preceding 14 days.

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- 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. Monitor patients with ECGs more frequently if Exxua is administered with other drugs known to prolong the QT interval.
- Avoid concomitant use of Exxua in patients taking strong CYP3A4 inducers.
- Concomitant use of Exxua and serotonergic drugs increases the risk of serotonin syndrome. 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.

- **Special populations:**
  - There is no pregnancy category for this medication; however, the risk summary indicates that based on animal reproduction studies, Exxua has been shown to have adverse effects on embryo/fetal and postnatal development. There are not sufficient clinical data on use during pregnancy to assess 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. There are risks associated with untreated depression during pregnancy. Consider if the risks outweigh the benefits of treatment with Exxua during pregnancy.
    - 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.
  - The safety and efficacy of use in the pediatric population have not been established.

Conclusion

- Major depressive disorder (MDD) is described as an unrelenting low mood, a deficiency of positive affect, and no interest in activities that generally are pleasurable (anhedonia) that varies from ones usual self and results in substantial suffering or impairment for ≥2 weeks (*Garakani et al 2026*).
- Exxua extended-release tablets are indicated for the treatment of MDD in adults.
  - It has a box warning regarding suicidal thoughts and behaviors.
  - It prolongs the QTc interval, and is contraindicated in patients with prolonged QTc interval >450msec at baseline and with congenital long QT syndrome, as well as in patients with severe hepatic impairment, in patients receiving concomitant strong CYP3A4 inhibitors, and in patients taking (or within 14 days of stopping) MAOIs.
- The efficacy of Exxua was assessed in two eight-week randomized, double-blind, placebo-controlled, flexible-dose studies in adults that met DSM-IV criteria for MDD.
  - The primary efficacy measure for both studies was the change from baseline in the HAMD-17 total score at week 8.
  - Results of both studies suggested that patients in the Exxua groups experienced statistically significantly greater improvement on the primary endpoint as compared to patients in the placebo groups.
- Guidelines for MDD do not currently include Exxua as they were published prior to Exxua being FDA approved, but they do discuss use of second-generation antidepressants as a first-line treatment option in those deciding to use pharmacotherapy.
  - Exxua provides patients with a new treatment option.

- There is no evidence to suggest that Exxua is safer or more effective than other currently preferred, more cost-effective medications. It is therefore recommended that Exxua remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

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- **PDL Placement:**
  - ☐ Preferred
  - ☒ Non-Preferred with Conditions

References

- Exxua Package insert. Aytu Therapeutics, LLC; July 2025.
- Garakani A, Zaderenko S, Rae-Grant A, et al. Major Depressive Disorder. Dynamed Web site. Updated January 21, 2026. Accessed February 5, 2026. www.dynamed.com.
- Gaynes BN. Depression in adults: Clinical features and diagnosis. UpToDate Web site. Updated January 30, 2026. Accessed February 5, 2026. www.uptodate.com
- National Institute of Health (NIH). National Institute of Mental Health. Major Depression. Updated July 2023. Accessed February 5, 2026. Major Depression - National Institute of Mental Health (NIMH).
- Qaseem A, Owens DK, Etxeandia-Ikobaltzeta I, et al. Nonpharmacologic and pharmacologic treatments of adults in the acute phase of major depressive disorder: A living clinical guideline from the American College of Physicians (Version 1, Update Alert 3). Ann Intern Med. 2025; 178(9): 1-3.
- VA/DoD Clinical Practice Guideline. (2022). The management of Major Depressive Disorder. Washington, DC: U.S. Government Printing Office. Accessed February 5, 2026. Website:
- https://www.healthquality.va.gov/guidelines/MH/mdd/VADODMDDCPGFinal508.pdf.

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