

RESEARCH MONOGRAPH . COMPOUND PROFILE

Gepirone

*An azapirone 5-HT_{1A} partial agonist
developed for major depressive disorder;
FDA-approved in 2023 after a 30-year
development cycle.*

DOCUMENT	KDC-MN-250
ISSUED	2026-05-09
REVISION	1.0
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COMPOUND CLASS	5-HT _{1A} partial agonist

ABSTRACT

Gepirone (4,4-dimethyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-2,6-piperidinedione; CAS 83928-76-1; molecular formula C₁₉H₂₉N₅O₂; molecular weight 359.47) is an azapirone 5-HT_{1A} partial agonist developed by Bristol-Myers Squibb and Fabre-Kramer over a 30-plus-year development cycle, ultimately approved by the FDA in 2023 under the trade name Exxua for major depressive disorder. The compound is structurally and mechanistically similar to buspirone: 5-HT_{1A} affinity approximately 19 nM with intrinsic activity approximately 60 percent; minimal D₂ affinity; active metabolite 1-PP. Distinct from buspirone in development trajectory (positioned for depression rather than anxiety) and in being formulated as extended-release for once-daily dosing. The approved indication is MDD; the principal selling point versus SSRIs is absence of sexual dysfunction (a major SSRI tolerability complaint). Plasma half-life is 18 hours (ER formulation); metabolism is via CYP3A4. Used as a reference 5-HT_{1A} partial agonist with depression-focused clinical development.

1. Compound Identification

Gepirone is described as 5-HT_{1A} partial agonist. An azapirone 5-HT_{1A} partial agonist developed for major depressive disorder; FDA-approved in 2023 after a 30-year development cycle.

1.1 Class summary

5-HT_{1A} partial agonist

1.2 Subtitle

An azapirone 5-HT_{1A} partial agonist developed for major depressive disorder; FDA-approved in 2023 after a 30-year development cycle.

2. Abstract

Gepirone (4,4-dimethyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-2,6-piperidine-dione; CAS 83928-76-1; molecular formula C₁₉H₂₉N₅O₂; molecular weight 359.47) is an azapirone 5-HT_{1A} partial agonist developed by Bristol-Myers Squibb and Fabre-Kramer over a 30-plus-year development cycle, ultimately approved by the FDA in 2023 under the trade name Exxua for major depressive disorder. The compound is structurally and mechanistically similar to buspirone: 5-HT_{1A} affinity approximately 19 nM with intrinsic activity approximately 60 percent; minimal D₂ affinity; active metabolite 1-PP. Distinct from buspirone in development trajectory (positioned for depression rather than anxiety) and in being formulated as extended-release for once-daily dosing. The approved indication is MDD; the principal selling point versus SSRIs is absence of sexual dysfunction (a major SSRI tolerability complaint). Plasma half-life is 18 hours (ER formulation); metabolism is via CYP3A4. Used as a reference 5-HT_{1A} partial agonist with depression-focused clinical development.

3. Mechanism of Action

5-HT_{1A} partial agonist (intrinsic activity ~60 percent). Same azapirone class as buspirone. Approved for MDD; absent sexual dysfunction.

The mechanistic profile described above represents the consensus position from peer-reviewed literature where available; for compounds with sparse formal characterization, this section reflects vendor-grade reports and structurally-related class pharmacology and should be interpreted with appropriate caution.

4. Pharmacokinetics and Routes of Administration

Pharmacokinetic data are summarized within the abstract for compounds with formal Phase 1 records. Compounds without published human pharmacokinetic studies are noted as such; investigators should treat the absence of data as a research limitation.

5. Reported Research Dose Ranges

Clinical 18.2 to 72.6 mg per oral administration daily (ER). Rodent studies 1 to 30 mg/kg/day.

Doses are scaled from clinical use where the compound is approved as a medicine, from Phase 2/3 trials where development advanced, or from rodent dose-response data scaled by allometric assumptions where the compound has no human clinical record. Investigators should treat dose ranges from research-chemical-grade vendors as starting points for their own pharmacokinetic and tolerability characterization rather than validated dosing recommendations.

6. Sourcing and Quality Verification

Investigators should obtain analytical confirmation of identity (mass spectrometry; for peptides, additionally amino acid analysis or N-terminal sequencing) and purity (HPLC area-percent, ideally greater than 95 percent) on every lot. Vendor certificates of analysis vary in quality; third-party analytical confirmation through independent laboratories (e.g., Janoshik Analytical, Anabolic Lab) is the gold standard for research-grade peptides and small molecules.

For compounds with established pharmaceutical-grade marketing in any jurisdiction, sourcing from the marketed product (where legal and accessible) provides the highest quality assurance.

7. Reconstitution and Handling

Peptides should be reconstituted in bacteriostatic water or sterile water for injection in the volume appropriate to the desired concentration; lyophilized peptides should be allowed to come to room temperature before reconstitution to minimize precipitation. Reconstituted peptides should be stored refrigerated and used within the timeframe specified by the manufacturer (typically 14 to 30 days for bacteriostatic water reconstitutions, shorter for sterile water).

Small molecules: storage conditions vary by compound; consult the certificate of analysis for the specific product. Most are stable at room temperature in dry, dark conditions; oxidation-sensitive compounds (e.g., catecholamine precursors) require cool storage and protection from light.

8. Stack Interaction Considerations

Investigators combining this compound with other research substances should consider receptor-level interactions (additive effects at shared targets), enzyme-level interactions (CYP-mediated drug-drug interactions where applicable), and pharmacodynamic interactions (additive sedation, additive serotonergic activity, additive hemodynamic effects).

The stack interaction section in published monographs of well-characterized compounds is necessarily incomplete for any specific combination; investigators should treat novel combinations with elevated caution and titrate gradually.

9. References

1. Cooper TB, et al. Gepirone: pharmacology and clinical development. Neuropsychopharmacology 1992.
2. Feiger AD, et al. Gepirone extended-release in the treatment of major depressive disorder. J Clin Psychopharmacol 2003.
3. FDA Approval Package for Exxua (gepirone) extended-release tablets. 2023.

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly.