

RESEARCH MONOGRAPH . COMPOUND PROFILE

Agomelatine

A Servier-developed antidepressant approved in Europe combining MT1/MT2 melatonin receptor agonism with 5-HT2C antagonism, characterized by hepatotoxicity monitoring requirement.

DOCUMENT	KDC-MN-072
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COMPOUND CLASS	Melatonin receptor agonist + 5-HT2C antagonist

ABSTRACT

Agomelatine (Valdoxan, Thymanax; S-20098; CAS 138112-76-2; molecular formula $C_{15}H_{17}NO_2$; molecular weight 243.30) is a structural analog of melatonin developed by Servier and approved by the EMA in 2009 for major depressive disorder. The compound combines MT1 and MT2 melatonin receptor agonism (similar potency to endogenous melatonin) with 5-HT_{2C} receptor antagonism. The melatonin agonism provides a circadian-resynchronizing effect that may underlie sleep architecture improvements; the 5-HT_{2C} antagonism increases dopamine and norepinephrine release in frontal cortex, providing the antidepressant component of activity. The compound does not increase serotonin transmission and does not produce the typical SSRI/SNRI adverse event profile. Pharmacokinetics: plasma half-life 1 to 2 hours; high oral bioavailability with substantial first-pass metabolism via CYP1A2. Approved doses are 25 to 50 mg once daily at bedtime. Hepatotoxicity is the principal safety concern; baseline and periodic ALT monitoring is required.

1. Compound Identification

Agomelatine is described as melatonin receptor agonist + 5-HT_{2C} antagonist. A Servier-developed antidepressant approved in Europe combining MT₁/MT₂ melatonin receptor agonism with 5-HT_{2C} antagonism, characterized by hepatotoxicity monitoring requirement.

1.1 Class summary

Melatonin receptor agonist + 5-HT_{2C} antagonist

1.2 Subtitle

A Servier-developed antidepressant approved in Europe combining MT₁/MT₂ melatonin receptor agonism with 5-HT_{2C} antagonism, characterized by hepatotoxicity monitoring requirement.

2. Abstract

Agomelatine (Valdoxan, Thymanax; S-20098; CAS 138112-76-2; molecular formula $C_{15}H_{17}NO_2$; molecular weight 243.30) is a structural analog of melatonin developed by Servier and approved by the EMA in 2009 for major depressive disorder. The compound combines MT1 and MT2 melatonin receptor agonism (similar potency to endogenous melatonin) with 5-HT_{2C} receptor antagonism. The melatonin agonism provides a circadian-resynchronizing effect that may underlie sleep architecture improvements; the 5-HT_{2C} antagonism increases dopamine and norepinephrine release in frontal cortex, providing the antidepressant component of activity. The compound does not increase serotonin transmission and does not produce the typical SSRI/SNRI adverse event profile. Pharmacokinetics: plasma half-life 1 to 2 hours; high oral bioavailability with substantial first-pass metabolism via CYP1A2. Approved doses are 25 to 50 mg once daily at bedtime. Hepatotoxicity is the principal safety concern; baseline and periodic ALT monitoring is required.

3. Mechanism of Action

MT1/MT2 melatonin receptor agonist + 5-HT2C antagonist. Circadian resynchronization plus DA/NE elevation in PFC.

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

25 to 50 mg once daily at bedtime.

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. Kennedy SH, Rizvi SJ. Agomelatine in the treatment of major depressive disorder: potential for clinical effectiveness. CNS Drugs 2010.

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