

RESEARCH MONOGRAPH . COMPOUND PROFILE

Latrepirdine (Dimebon)

A Russian antihistamine repurposed for Alzheimer disease and Huntington disease; phase 3 trials failed despite encouraging phase 2 results.

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ABSTRACT

Latrepirdine (Dimebon, dimebolin; CAS 3613-73-8; molecular formula C₂₁H₂₅N₃; molecular weight 319.45) is a tetrahydro-gamma-carboline antihistamine developed in the USSR in the 1960s and approved in Russia for allergic conditions. The compound is a non-selective receptor blocker (H₁, alpha-1, alpha-2, 5-HT_{2A}, 5-HT_{5A}, 5-HT₆, D₁, D₂). The Alzheimer disease application emerged from drug repurposing screens in the 2000s; preclinical studies suggested mitochondrial protective effects independent of the receptor binding. Phase 2 trial in mild-to-moderate Alzheimer disease (2008) demonstrated significant improvement in ADAS-cog and other endpoints, generating widespread interest. Phase 3 trials (CONNECTION, CONCERT) in 2010-2012 failed to replicate the phase 2 effects, marking one of the highest-profile late-stage failures in CNS drug development. The compound is no longer in clinical development. Used as a research compound for multi-target receptor pharmacology.

1. Compound Identification

Latrepidine (Dimebon) is described as multi-target antihistamine / mitochondrial protectant. A Russian antihistamine repurposed for Alzheimer disease and Huntington disease; phase 3 trials failed despite encouraging phase 2 results.

1.1 Class summary

Multi-target antihistamine / mitochondrial protectant

1.2 Subtitle

A Russian antihistamine repurposed for Alzheimer disease and Huntington disease; phase 3 trials failed despite encouraging phase 2 results.

2. Abstract

Latrepirdine (Dimebon, dimebolin; CAS 3613-73-8; molecular formula C₂₁H₂₅N₃; molecular weight 319.45) is a tetrahydro-gamma-carboline antihistamine developed in the USSR in the 1960s and approved in Russia for allergic conditions. The compound is a non-selective receptor blocker (H₁, alpha-1, alpha-2, 5-HT_{2A}, 5-HT_{5A}, 5-HT₆, D₁, D₂). The Alzheimer disease application emerged from drug repurposing screens in the 2000s; preclinical studies suggested mitochondrial protective effects independent of the receptor binding. Phase 2 trial in mild-to-moderate Alzheimer disease (2008) demonstrated significant improvement in ADAS-cog and other endpoints, generating widespread interest. Phase 3 trials (CONNECTION, CONCERT) in 2010-2012 failed to replicate the phase 2 effects, marking one of the highest-profile late-stage failures in CNS drug development. The compound is no longer in clinical development. Used as a research compound for multi-target receptor pharmacology.

3. Mechanism of Action

Multi-target receptor antagonist (H1, α -1/2, 5-HT_{2A/5A/6}, D_{1/2}). Possible mitochondrial protective activity. Phase 3 efficacy not replicated.

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

Trial doses 5 to 20 mg per oral administration three times daily.

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. Doody RS, et al. Effect of dimebon on cognition, activities of daily living, behaviour, and global function in patients with mild-to-moderate Alzheimer's disease: a randomised, double-blind, placebo-controlled study. Lancet 2008.
2. Doody RS, et al. A phase 3 trial of latrepirdine in patients with mild to moderate Alzheimer's disease. Arch Neurol 2014.
3. Bachurin SO, et al. Antihistamine agent Dimebon as a novel neuroprotector and a cognition enhancer. Ann N Y Acad Sci 2001.

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