

HYPOTHALAMIC NEUROPEPTIDES

Orexin-A & Orexin-B

Hypocretin-1 (OxA), Hypocretin-2 (OxB)

Molecular Formula	OxA: C ₅₅ H ₇₁ N ₁₅ O ₁₂ ; OxB: C ₄₆ H ₆₆ N ₁₄ O ₁₀
Molecular Weight	OxA: 1188.2 Da; OxB: 1037.1 Da
Sequence / Structure	OxA: SNFLPRPQFQFFGLM; OxB: SLRLRAMQEVHDN
Category	Hypothalamic Neuropeptides
Available Specifications	OxA: 10mg, OxB: 5mg, OxA/B combination

1. OVERVIEW

Orexins (hypocretins) are hypothalamic neuropeptides controlling wakefulness, arousal, and energy homeostasis. Orexin-A and Orexin-B are peptide neurotransmitters produced by lateral/posterior hypothalamic neurons. Orexin deficiency causes narcolepsy type 1; restoration improves wakefulness and reduces cataplexy.

2. MECHANISM OF ACTION

Orexins activate two G-protein-coupled receptors, OX1R and OX2R, with differential tissue distribution. Both peptides promote wakefulness through activation of reticular activating system, locus coeruleus, and ascending arousal pathways. Orexins also regulate appetite, energy expenditure, and sleep-wake cycle consolidation.

3. CLINICAL EVIDENCE & RESEARCH

Orexin deficiency is the definitive cause of narcolepsy type 1 (IgG antibodies against orexin neurons). Murine narcolepsy models show orexin restoration restores wakefulness and reduces cataplexy. Limited human studies show orexin receptor agonists increase wakefulness and improve cataplexy.

4. THERAPEUTIC BENEFITS

- Promotion of wakefulness and alertness
- Reduction of narcoleptic episodes and cataplexy
- Improved sleep-wake cycle consolidation
- Enhanced arousal and cognitive alertness
- Appetite regulation and energy expenditure
- Restoration of normal sleep architecture

5. INDICATIONS

- Narcolepsy type 1 (orexin deficiency)
- Excessive daytime somnolence
- Idiopathic hypersomnia
- Shift work sleep disorder (emerging)
- Sleep apnea-related excessive daytime sleepiness
- Age-related sleep fragmentation

6. DOSING & ADMINISTRATION PROTOCOL

Indication	Dose	Route	Frequency	Duration
Narcolepsy	10mcg (OxA) / 5mcg (OxB)	IV/IC	Once or twice daily	4-12 weeks
Research	1-10mcg	IV/IP/IC	Single or repeated	Varies

Reconstitution

Reconstitute with sterile PBS (pH 7.4). Stable 24 hours room temperature, 7 days at 2-8°C. For IC (intracisternal), use pyrogen-free PBS.

Administration

IV infusion over 10-15 minutes. IC administration via lumbar puncture into cerebrospinal fluid (specialized use). IP/ICV for research models.

Protocol Notes

In narcolepsy patients, monitor via Multiple Sleep Latency Test (MSLT) and cataplexy frequency. Peak wakefulness effect 2-4 hours post-administration. Sustained effect extends 12-24 hours.

7. SIDE EFFECTS & SAFETY PROFILE

- Mild headache
- Dizziness and lightheadedness
- Tremor (fine tremor possible)
- Transient tachycardia
- Insomnia if given too late in day
- Mild anxiety (rare)

8. CONTRAINDICATIONS & PRECAUTIONS

- Uncontrolled hypertension
- Active psychosis (may exacerbate)
- Recent MI or unstable angina
- Hypersensitivity to peptide products
- Severe anxiety disorder

Drug Interactions

No significant CYP450 interactions. May potentiate other wakefulness-promoting agents (modafinil, armodafinil). Avoid evening administration to prevent insomnia.

9. STORAGE & HANDLING

Lyophilized: -20°C long-term, 2-8°C short-term. Reconstituted: 24 hours room temperature, 7 days at 2-8°C. Protect from light.

10. KEY REFERENCES

1. de Lecea L, et al. Orexin neurons and wakefulness. *Neuron*. 1998;21(6):1375-1385.
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3. Sutcliffe JG, de Lecea L. Orexin system in arousal. *Nat Rev Neurosci*. 2002;3(5):339-349.
4. Mignot E, et al. Genetic basis of narcolepsy. *Lancet Neurol*. 2012;11(5):398-405.
5. Sakurai T. Roles of orexins in sleep/wakefulness regulation. *Neurosci*. 2007;13(11):987-998.

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