

RESEARCH MONOGRAPH . COMPOUND PROFILE

Alfaxalone

A 3-alpha-hydroxy-5-alpha-pregnane neurosteroid intravenous anesthetic in veterinary use (Alfaxan) and a research tool in mammalian general anesthetic mechanism studies.

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RESEARCH USE ONLY

ABSTRACT

Alfaxalone (3- α -hydroxy-5- α -pregnane-11,20-dione; CAS 23930-19-0; molecular formula C₂₁H₃₂O₃; molecular weight 332.48) is a neurosteroid intravenous anesthetic developed at Glaxo in the 1970s, originally formulated with alfadolone in the human anesthetic Althesin (withdrawn 1984 owing to anaphylactoid reactions traced to the Cremophor EL solubilizer rather than the steroid itself). The compound was reformulated with a 2-hydroxypropyl- β -cyclodextrin solubilizer as Alfaxan and approved for veterinary use in dogs, cats, and rabbits in the 2000s. Alfaxalone is the principal modern synthetic neurosteroid in clinical use; structurally it is a 3- α -hydroxy-5- α -pregnane that mirrors the endogenous neurosteroid allopregnanolone. Mechanism is positive allosteric modulation of GABA-A receptors at a steroid-binding site distinct from the benzodiazepine and barbiturate sites, with prolongation of chloride channel open time and direct channel opening at higher concentrations. The cardiovascular profile is favorable for an IV induction agent (less hypotension than propofol at induction doses), and the respiratory profile is similarly favorable (apnea threshold higher than propofol at typical induction doses); these characteristics drive widespread veterinary adoption for cardiac-compromised patients. Human clinical use was discontinued with Althesin and has not returned despite the favorable steroid pharmacology, owing principally to the veterinary market priority and absence of human clinical development. Alfaxalone serves as the canonical reference compound for synthetic neurosteroid GABA-A pharmacology and underpins the design of subsequent neurosteroid drugs including brexanolone, ganaxolone, and

zuranolone. Plasma half-life is short (less than 30 minutes); clearance is hepatic and rapid.

1. Compound Identification

Alfaxalone is described as neurosteroid intravenous anesthetic (veterinary). A 3-alpha-hydroxy-5-alpha-pregnane neurosteroid intravenous anesthetic in veterinary use (Alfaxan) and a research tool in mammalian general anesthetic mechanism studies.

1.1 Class summary

Neurosteroid intravenous anesthetic (veterinary)

1.2 Subtitle

A 3-alpha-hydroxy-5-alpha-pregnane neurosteroid intravenous anesthetic in veterinary use (Alfaxan) and a research tool in mammalian general anesthetic mechanism studies.

2. Abstract

Alfaxalone (3- α -hydroxy-5- α -pregnane-11,20-dione; CAS 23930-19-0; molecular formula C₂₁H₃₂O₃; molecular weight 332.48) is a neurosteroid intravenous anesthetic developed at Glaxo in the 1970s, originally formulated with alfadolone in the human anesthetic Althesin (withdrawn 1984 owing to anaphylactoid reactions traced to the Cremophor EL solubilizer rather than the steroid itself). The compound was reformulated with a 2-hydroxypropyl- β -cyclodextrin solubilizer as Alfaxan and approved for veterinary use in dogs, cats, and rabbits in the 2000s. Alfaxalone is the principal modern synthetic neurosteroid in clinical use; structurally it is a 3- α -hydroxy-5- α -pregnane that mirrors the endogenous neurosteroid allopregnanolone. Mechanism is positive allosteric modulation of GABA-A receptors at a steroid-binding site distinct from the benzodiazepine and barbiturate sites, with prolongation of chloride channel open time and direct channel opening at higher concentrations. The cardiovascular profile is favorable for an IV induction agent (less hypotension than propofol at induction doses), and the respiratory profile is similarly favorable (apnea threshold higher than propofol at typical induction doses); these characteristics drive widespread veterinary adoption for cardiac-compromised patients. Human clinical use was discontinued with Althesin and has not returned despite the favorable steroid pharmacology, owing principally to the veterinary market priority and absence of human clinical development. Alfaxalone serves as the canonical reference compound for synthetic neurosteroid GABA-A pharmacology and underpins the design of subsequent neurosteroid drugs including brexanolone, ganaxolone, and zuranolone. Plasma half-life is short (less than 30 minutes); clearance is hepatic and rapid.

3. Mechanism of Action

Neurosteroid GABA-A positive allosteric modulation at a steroid binding site. Prolongs chloride channel open time and opens channels directly at higher concentrations.

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

Veterinary IV induction 2 to 5 mg/kg in dogs and cats; CRI 6 to 12 mg/kg/h.

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. Child KJ, et al. The pharmacological properties of CT1341, a new steroid anaesthetic agent. Br J Anaesth 1971.
2. Belelli D, Lambert JJ. Neurosteroids: endogenous regulators of GABA-A. Nat Rev Neurosci 2005.
3. Warne LN, et al. Cardiopulmonary effects of alfaxalone in dogs. Vet Anaesth Analg 2014.

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