

RESEARCH MONOGRAPH . COMPOUND PROFILE

Prilocaine

An amide local anesthetic with the lowest systemic toxicity in the class but the dose-dependent risk of methemoglobinemia from o-toluidine metabolite generation.

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COMPOUND CLASS	Amide local anesthetic (intermediate-acting, low-toxicity)

ABSTRACT

Prilocaine (N-(2-methylphenyl)-2-(propylamino)propanamide; CAS 721-50-6; molecular formula C₁₃H₂₀N₂O; molecular weight 220.31) is an amide local anesthetic developed at AB Astra in the late 1950s and introduced clinically in the 1960s (Citanest). The compound has the lowest systemic toxicity in the amide class (CNS and cardiac toxic doses higher than lidocaine, mepivacaine, or bupivacaine on a milligram-per-kilogram basis), reflecting rapid hepatic clearance and high tissue redistribution. Prilocaine is the principal component of the EMLA cream alongside lidocaine, where the eutectic mixture of the two oils provides effective topical anesthesia of intact skin for venipuncture and minor superficial procedures. The principal clinical limitation is dose-dependent methemoglobinemia: prilocaine is hydrolyzed in the liver to o-toluidine, which is hydroxylated to a methemoglobin-generating metabolite. Cumulative doses above approximately 600 mg in adults or 8 mg/kg in children produce clinically significant methemoglobinemia that may require methylene blue therapy. The risk is amplified in patients with G6PD deficiency, NADH-methemoglobin reductase deficiency, or concurrent administration of other oxidant drugs (dapson, sulfamethoxazole, benzocaine). Mechanism is the standard amide voltage-gated sodium channel block. Onset and duration are intermediate (similar to lidocaine and mepivacaine). Prilocaine is widely used in dental anesthesia in Europe and Asia and is the principal component of dental cartridges in several markets. Maximum recommended dose is 8 mg/kg without epinephrine.

1. Compound Identification

Prilocaine is described as amide local anesthetic (intermediate-acting, low-toxicity). An amide local anesthetic with the lowest systemic toxicity in the class but the dose-dependent risk of methemoglobinemia from o-toluidine metabolite generation.

1.1 Class summary

Amide local anesthetic (intermediate-acting, low-toxicity)

1.2 Subtitle

An amide local anesthetic with the lowest systemic toxicity in the class but the dose-dependent risk of methemoglobinemia from o-toluidine metabolite generation.

2. Abstract

Prilocaine (N-(2-methylphenyl)-2-(propylamino)propanamide; CAS 721-50-6; molecular formula $C_{13}H_{20}N_2O$; molecular weight 220.31) is an amide local anesthetic developed at AB Astra in the late 1950s and introduced clinically in the 1960s (Citanest). The compound has the lowest systemic toxicity in the amide class (CNS and cardiac toxic doses higher than lidocaine, mepivacaine, or bupivacaine on a milligram-per-kilogram basis), reflecting rapid hepatic clearance and high tissue redistribution. Prilocaine is the principal component of the EMLA cream alongside lidocaine, where the eutectic mixture of the two oils provides effective topical anesthesia of intact skin for venipuncture and minor superficial procedures. The principal clinical limitation is dose-dependent methemoglobinemia: prilocaine is hydrolyzed in the liver to o-toluidine, which is hydroxylated to a methemoglobin-generating metabolite. Cumulative doses above approximately 600 mg in adults or 8 mg/kg in children produce clinically significant methemoglobinemia that may require methylene blue therapy. The risk is amplified in patients with G6PD deficiency, NADH-methemoglobin reductase deficiency, or concurrent administration of other oxidant drugs (dapsone, sulfamethoxazole, benzocaine). Mechanism is the standard amide voltage-gated sodium channel block. Onset and duration are intermediate (similar to lidocaine and mepivacaine). Prilocaine is widely used in dental anesthesia in Europe and Asia and is the principal component of dental cartridges in several markets. Maximum recommended dose is 8 mg/kg without epinephrine.

3. Mechanism of Action

Voltage-gated sodium channel block. Hepatic hydrolysis to o-toluidine drives the methemoglobinemia risk.

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

8 mg/kg without epinephrine. EMLA cream 2.5 percent topical with lidocaine 2.5 percent.

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. Hjelm M, Holmdahl MH. Methaemoglobinaemia induced by prilocaine. Acta Anaesthesiol Scand 1965.
2. Vasters FG, et al. Risk factors for postoperative methaemoglobinaemia after regional anaesthesia. Acta Anaesthesiol Scand 2006.
3. Buckley MM, Benfield P. Eutectic lidocaine/prilocaine cream. Drugs 1993.

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.