

RESEARCH MONOGRAPH . COMPOUND PROFILE

Exemestane

A steroidal mechanism-based aromatase inhibitor; irreversibly inactivates aromatase by covalent suicide adduction.

DOCUMENT	KDC-MN-278
ISSUED	2026-05-09
REVISION	1.0
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COMPOUND CLASS	Steroidal (suicide) aromatase inhibitor

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ABSTRACT

Exemestane (6-methylenandrosta-1,4-diene-3,17-dione; CAS 107868-30-4; molecular formula C₂₀H₂₄O₂; molecular weight 296.40) is a steroidal third-generation aromatase inhibitor developed at Pharmacia (now Pfizer) and approved by the FDA in 1999 under the trade name Aromasin. Distinct from anastrozole and letrozole by mechanism: exemestane is a substrate analog of androstenedione that aromatase begins to process but cannot release, producing irreversible covalent inactivation of the enzyme. Recovery of aromatase activity requires de novo enzyme synthesis. Plasma estradiol suppression is comparable to anastrozole (approximately 85 to 95 percent at 25 mg daily). The steroidal scaffold confers weak intrinsic androgenic activity and unique side effect profile (less estrogen-deprivation symptoms in some patients). Plasma half-life is approximately 24 hours; metabolism is hepatic via CYP3A4. Approved for adjuvant and metastatic ER-positive postmenopausal breast cancer. Used as the canonical steroidal suicide aromatase inhibitor in mechanism studies.

1. Compound Identification

Exemestane is described as steroidal (suicide) aromatase inhibitor. A steroidal mechanism-based aromatase inhibitor; irreversibly inactivates aromatase by covalent suicide adduction.

1.1 Class summary

Steroidal (suicide) aromatase inhibitor

1.2 Subtitle

A steroidal mechanism-based aromatase inhibitor; irreversibly inactivates aromatase by covalent suicide adduction.

2. Abstract

Exemestane (6-methylenandrosta-1,4-diene-3,17-dione; CAS 107868-30-4; molecular formula $C_{20}H_{24}O_2$; molecular weight 296.40) is a steroidal third-generation aromatase inhibitor developed at Pharmacia (now Pfizer) and approved by the FDA in 1999 under the trade name Aromasin. Distinct from anastrozole and letrozole by mechanism: exemestane is a substrate analog of androstenedione that aromatase begins to process but cannot release, producing irreversible covalent inactivation of the enzyme. Recovery of aromatase activity requires de novo enzyme synthesis. Plasma estradiol suppression is comparable to anastrozole (approximately 85 to 95 percent at 25 mg daily). The steroidal scaffold confers weak intrinsic androgenic activity and unique side effect profile (less estrogen-deprivation symptoms in some patients). Plasma half-life is approximately 24 hours; metabolism is hepatic via CYP3A4. Approved for adjuvant and metastatic ER-positive postmenopausal breast cancer. Used as the canonical steroidal suicide aromatase inhibitor in mechanism studies.

3. Mechanism of Action

Irreversible suicide inactivation of aromatase via substrate-analog covalent adduction. Steroidal scaffold confers weak androgenic activity.

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

Clinical 25 mg per oral administration daily. Off-label use 12.5 to 25 mg daily. Rodent studies 1 to 10 mg/kg/day.

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. Lonning PE. Pharmacology of new aromatase inhibitors. Breast 1996.
2. Coombes RC, et al. Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study). Lancet 2007.
3. Buzdar AU, et al. An overview of the use of non-steroidal aromatase inhibitors in the treatment of breast cancer. Cancer 2002.

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