

RESEARCH MONOGRAPH . COMPOUND PROFILE

Arimistane

A naturally occurring androstadienedione metabolite of 7-keto-DHEA that functions as an irreversible steroidal aromatase inactivator, distinguished from pharmaceutical aromatase inhibitors by its endogenous biosynthetic origin and concurrent reported activity on cortisol regulation through competitive inhibition of 11-beta-hydroxysteroid dehydrogenase type 1.

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ABSTRACT

Androsta-3,5-diene-7,17-dione, marketed and commonly known as Arimistane, is a steroidal mechanism-based irreversible inhibitor of aromatase (cytochrome P450 19A1, CYP19A1) that occupies a distinctive position in the landscape of estrogen-modulating compounds. Structurally, it is an androstadienedione bearing conjugated 3,5-diene unsaturation in the A/B ring system and a 7-oxo group on the B ring, with the characteristic 17-ketone of the androstane series. The compound is a downstream metabolite of 7-keto-dehydroepiandrosterone (7-keto-DHEA, 3-beta-hydroxyandrost-5-ene-7,17-dione), itself produced from dehydroepiandrosterone (DHEA) by hepatic cytochrome P450 7B1 (CYP7B1) or CYP3A-mediated 7-alpha-hydroxylation followed by 11-beta-hydroxysteroid dehydrogenase (11-beta-HSD) oxidation at the 7-position and subsequent dehydration. This endogenous biosynthetic origin distinguishes Arimistane from fully synthetic aromatase inhibitors such as exemestane, letrozole, and anastrozole.

The aromatase-inhibitory mechanism of Arimistane belongs to the type I (steroidal, mechanism-based) class characterized by Covey and colleagues in the early 1980s for the structurally related androst-5-ene-7,17-dione series [1, 2]. Mechanism-based inhibition proceeds through initial competitive binding of the steroidal inhibitor to the substrate-binding pocket of aromatase, followed by enzyme-catalyzed oxidative processing that generates a reactive intermediate capable of forming a covalent bond with amino acid residues at or near the active site. The covalent modification permanently inactivates the enzyme molecule;

restoration of aromatase activity requires de novo protein synthesis rather than simple inhibitor dissociation. This irreversible ("suicide") mechanism produces sustained estrogen suppression that persists beyond the plasma residence time of the parent compound, a pharmacodynamic feature shared with the clinically approved steroidal aromatase inactivator exemestane.

Beyond aromatase inhibition, Arimistane has been reported to modulate cortisol metabolism through competitive inhibition of 11-beta-hydroxysteroid dehydrogenase type 1 (11-beta-HSD1), the microsomal enzyme that catalyzes the reduction of cortisone to the biologically active glucocorticoid cortisol in liver, adipose tissue, and central nervous system. This activity, attributed to the 7-oxo-androstane structural motif shared with 7-keto-DHEA and its metabolites, is proposed to reduce local cortisol regeneration without affecting adrenal cortisol synthesis directly. The dual aromatase-inhibitory and cortisol-modulatory profile has driven interest in Arimistane within the bodybuilding and sports-performance supplement industry, where the compound has been marketed as a post-cycle therapy agent and estrogen-control supplement.

The regulatory status of Arimistane is restrictive. The United States Food and Drug Administration (FDA) has determined that androsta-3,5-diene-7,17-dione does not meet the statutory definition of a dietary ingredient under section 201(ff)(1) of the Federal Food, Drug, and Cosmetic Act, and has issued multiple warning letters to supplement manufacturers marketing products containing the compound [3]. The World Anti-Doping Agency (WADA) added Arimistane to the Prohibited List in 2017 under the category of hormone and metabolic modulators (class S4),

specifically as an aromatase inhibitor [4]. The compound is not approved as a pharmaceutical in any jurisdiction.

The clinical evidence base for Arimistane is sparse relative to pharmaceutical aromatase inhibitors. No registration-quality clinical trials have been conducted. Published human data are limited to manufacturer-sponsored tolerability assessments and analytical chemistry studies characterizing the compound as a urinary metabolite of 7-keto-DHEA in anti-doping contexts [5]. The pharmacological characterization rests principally on in vitro aromatase inhibition assays, structure-activity relationship inference from the broader androstene-7,17-dione series studied by Covey, Brodie, and colleagues in the 1980s and 1990s [1, 2, 6], and extrapolation from the more extensive clinical pharmacology of the structurally related steroidal aromatase inactivator exemestane. This monograph reviews the chemistry, biosynthetic origin, mechanism of aromatase inactivation, reported pharmacokinetics, preclinical and clinical evidence, sourcing and quality considerations, stack interactions, adverse-event signal, and a comparative assessment of Arimistane against five alternative aromatase-modulating compounds on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Common name: Arimistane.

Systematic chemical name (IUPAC): Androsta-3,5-diene-7,17-dione.

Alternative chemical names: Androst-3,5-dien-7,17-dione; 3,5-androstadiene-7,17-dione.

National Cancer Institute identifier: NSC 134910.

Chemical Abstracts Service registry number: 1420-49-1.

FDA Unique Ingredient Identifier (UNII): 77POLYX19T.

PubChem CID: 150910.

InChIKey: VHDOTNMSJDQVEE-ZENYQMPMSA-N.

MDL number: MFCD28368998.

The compound is referenced in the early aromatase-inhibitor literature under its systematic steroid name rather than under the trade name "Arimistane," which was introduced in the dietary supplement market in the 2010s. The NCI identifier NSC 134910 appears in the National Cancer Institute screening database and in Covey's early publications on steroid-based aromatase inhibition [1].

1.2 Structural class and chemistry

Arimistane is a C19 androstane steroid bearing two oxo (ketone) groups at positions 7 and 17 and a conjugated diene system spanning positions 3,4 and 5,6 of the A/B ring junction. It belongs to the 7-oxo-androstane structural subclass, a group of endogenous and semi-synthetic steroids that includes 7-keto-DHEA (3-beta-hydroxyandrost-5-ene-7,17-dione), 7-alpha-hydroxy-DHEA, and 7-beta-hydroxy-DHEA. The conjugated 3,5-diene system distinguishes Arimistane from the saturated or monoene members of this subclass and is the structural feature responsible for the

mechanism-based aromatase-inhibitory activity, as the conjugated diene provides the electronic framework for enzyme-catalyzed generation of a reactive electrophilic intermediate at the active site [1, 2].

Molecular formula: C₁₉H₂₄O₂.

Exact mass: 284.1776 g/mol (monoisotopic).

Molecular weight: 284.39 g/mol.

Physical properties: Off-white to pale beige crystalline solid. Melting point 167 to 168 degrees Celsius. Predicted boiling point approximately 449 degrees Celsius. Predicted density approximately 1.14 g/cm³. Sparingly soluble in chloroform; slightly soluble in methanol; poorly soluble in water. Storage at minus 20 degrees Celsius is recommended for the solid form [7].

Stereochemistry: The compound retains the natural (8S,9S,10R,13S,14S) stereochemistry of the androstane skeleton at the ring junction stereocenters. No additional stereocenters are introduced by the 3,5-diene or the 7-oxo functionalities.

1.3 Synthesis

Arimistane can be obtained by two principal routes. The first is chemical dehydration of 7-keto-DHEA (3- β -hydroxyandrost-5-ene-7,17-dione): elimination of the 3- β -hydroxyl group under acidic conditions (p-toluenesulfonic acid, sulfuric acid, or Lewis acid catalysis) with concomitant introduction of the 3,4-double bond and isomerization to the thermodynamically favored 3,5-diene system. This route is operationally simple and is the principal commercial manufacturing method for supplement-grade material [8]. The second route is total or partial synthesis from androstane precursors through selective introduction of the 7-oxo group (by chromium trioxide or pyridinium chlorochromate oxidation of a 7-hydroxy intermediate, or by Oppenauer oxidation) followed by generation of the 3,5-diene system by acid-catalyzed dehydration or by DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) oxidation [2]. Research-grade material is typically characterized by high-performance liquid chromatography (HPLC) purity greater than 97 percent, confirmed by mass spectrometry and nuclear magnetic resonance spectroscopy.

The compound is also generated artifactually from 7-keto-DHEA during sample preparation procedures in anti-doping analytical laboratories, a finding reported by Brooker et al. in the WADA-funded study on DHEA, 7-keto-DHEA, and Arimistane

metabolic relationships [5]. This artifactual formation complicates the interpretation of urinary steroid profiles in anti-doping testing and necessitates isotope ratio mass spectrometry (IRMS) to distinguish exogenous administration from endogenous biosynthesis or analytical artifact.

2. Abstract

Androsta-3,5-diene-7,17-dione (Arimistane) is a steroidal, mechanism-based, irreversible inhibitor of aromatase (CYP19A1) and a downstream metabolite of the endogenous neurosteroid precursor dehydroepiandrosterone (DHEA) via the 7-keto-DHEA intermediate. The compound inactivates aromatase through a suicide-substrate mechanism: it binds competitively to the substrate pocket of the enzyme, undergoes oxidative processing by the catalytic heme-iron center, and generates a reactive electrophilic species that forms a covalent bond with the enzyme protein, permanently destroying catalytic activity [1, 2]. This mechanism is shared with the pharmaceutical aromatase inactivator exemestane (Aromasin) and with the earlier clinical candidate formestane (4-hydroxyandrost-4-ene-3,17-dione), though Arimistane differs from both in ring-system substitution pattern and in its 7-oxo rather than 4-ene-3-oxo pharmacophore.

The principal pharmacological consequence of aromatase inactivation is suppression of estrogen biosynthesis. Aromatase catalyzes the final and rate-limiting step in the conversion of C19 androgens (androstenedione and testosterone) to C18 estrogens (estrone and estradiol). Irreversible inhibition reduces circulating and local tissue estrogen concentrations in a manner that persists until new aromatase protein is synthesized, a process requiring approximately 24 to 48 hours for restoration of baseline enzyme levels in human tissues [9]. The resulting hormonal shift toward relative androgen excess and estrogen deficiency is the basis of the compound's use in post-cycle therapy contexts in the bodybuilding community, where estrogen rebound following cessation of exogenous androgen administration is a recognized concern.

A secondary reported activity is modulation of cortisol metabolism through competitive inhibition of 11-beta-hydroxysteroid dehydrogenase type 1, the enzyme that converts inactive cortisone to active cortisol in peripheral tissues [10, 11]. This activity, attributed to the 7-oxo-androstane structural motif, has been characterized primarily for 7-keto-DHEA and is inferred for Arimistane on the basis of shared structural features. The cortisol-modulatory activity has not been independently confirmed in human clinical studies specifically for Arimistane.

The compound has no approved pharmaceutical indication in any jurisdiction. The FDA has classified it as a non-dietary ingredient that cannot be legally marketed in dietary supplements [3]. WADA lists it as a prohibited substance under the hormone and metabolic modulators category [4]. The clinical evidence base is limited to tolerability assessments at oral doses up to 200 mg per day for periods of up to four weeks, without controlled efficacy endpoints. Investigators considering the compound for research applications should weigh the limited clinical validation against the well-characterized mechanism of aromatase inhibition and the extensive preclinical literature on the 7-oxo-androstane steroid class.

3. Discovery and Development History

3.1 Origins in aromatase inhibitor research

The scientific foundation for Arimistane traces to the pioneering work on steroidal aromatase inhibitors conducted during the late 1970s and early 1980s. Covey and colleagues at Washington University reported in 1981 that androst-5-ene-7,17-dione, the 5-ene congener of Arimistane, functioned as a novel class of suicide substrate of human placental aromatase [1]. This discovery was part of a broader program to identify mechanism-based aromatase inactivators that could serve as pharmacological tools and potential therapeutic agents for estrogen-dependent breast cancer. The Covey group subsequently extended the characterization to derivatives including the 19-nor and 5-beta,6-beta-epoxy analogs, establishing structure-activity relationships for the 7-oxo-androstene series and confirming time-dependent, NADPH-dependent inactivation consistent with mechanism-based inhibition [2].

Contemporaneously, Brodie and colleagues at the University of Maryland developed 4-hydroxyandrost-4-ene-3,17-dione (formestane), the first selective steroidal aromatase inhibitor to enter clinical use for breast cancer, and characterized the mechanism-based inactivation of aromatase by androsta-1,4-diene-3,17-dione and androsta-4-ene-3,6,17-trione [6, 12]. The collective body of work from Covey, Brodie, and others established the mechanistic principles governing steroidal aromatase suicide inhibition: the requirement for enzyme-catalyzed activation, the formation of reactive intermediates, and the covalent modification of the enzyme active site.

3.2 Relationship to 7-keto-DHEA

The biosynthetic relationship between Arimistane and 7-keto-DHEA was clarified through steroid metabolism studies conducted in the 1990s and 2000s. DHEA, the most abundant circulating steroid in humans and a precursor to both androgens and estrogens, is metabolized in the liver by CYP7B1 and CYP3A4 to 7-alpha-hydroxy-DHEA, which is subsequently oxidized by 11-beta-hydroxysteroid dehydrogenase to 7-keto-DHEA (3-beta-hydroxyandrost-5-ene-7,17-dione) [10, 13]. Under conditions of acid-catalyzed dehydration (which can occur during metabolic processing or during analytical sample preparation), 7-keto-DHEA loses the 3-beta-hy-

droxyl group to yield androsta-3,5-diene-7,17-dione (Arimistane). The extent to which this dehydration occurs endogenously versus artifactually remains a subject of investigation in anti-doping science [5].

7-keto-DHEA was itself the subject of commercial development as a dietary supplement beginning in the late 1990s, marketed primarily for weight management and metabolic enhancement on the basis of animal thermogenesis studies and limited human clinical data [14]. The 7-oxo-androstane structural motif was characterized as a competitive inhibitor of 11-beta-HSD1, providing a mechanistic rationale for cortisol-modulatory claims [10, 11].

3.3 Emergence as a supplement ingredient

Arimistane entered the bodybuilding and sports-performance supplement market in the early 2010s, marketed as a natural aromatase inhibitor for estrogen control during and after anabolic steroid cycles. The marketing positioned the compound as a legal, over-the-counter alternative to prescription aromatase inhibitors such as anastrozole (Arimidex) and exemestane (Aromasin). Product labels typically claimed aromatase inhibition, testosterone elevation, cortisol reduction, and estrogen suppression at oral doses of 25 to 75 mg per day.

3.4 Regulatory actions

The FDA began issuing warning letters to manufacturers of Arimistane-containing supplements in 2017 and 2018, determining that androsta-3,5-diene-7,17-dione does not qualify as a dietary ingredient under federal law and that products containing it are adulterated [3]. The FDA's Scientific Memorandum on Arimistane (2021) reviewed the pharmacological evidence and concluded that the compound's aromatase-inhibiting activity raised safety concerns analogous to those associated with pharmaceutical aromatase inhibitors, including potential adverse effects on bone mineral density, lipid metabolism, and reproductive function [15].

WADA added Arimistane to the Prohibited List effective January 2017 under class S4 (hormone and metabolic modulators), subclass 4.1 (aromatase inhibitors) [4]. The United States Anti-Doping Agency (USADA) and other national anti-doping organizations have subsequently tested for and reported adverse analytical findings involving Arimistane in athlete biological samples.

4. Mechanism of Action

4.1 Aromatase (CYP19A1) inactivation

Aromatase (CYP19A1) is a cytochrome P450 enzyme complex comprising the CYP19A1 heme protein and its ubiquitous electron-transfer partner NADPH-cytochrome P450 reductase. It catalyzes the three-step oxidative conversion of C19 androgens (androstenedione and testosterone) to C18 estrogens (estrone and estradiol), with each step consuming one molecule of NADPH and one molecule of molecular oxygen. The reaction sequence involves sequential hydroxylation at C-19, oxidation to the 19-aldehyde, and oxidative removal of the C-19 angular methyl group with concomitant aromatization of the A ring. Aromatase is expressed in the gonads, placenta, brain, adipose tissue, bone, breast, liver, and other tissues, and is the sole enzyme responsible for estrogen biosynthesis in humans [9, 16].

Arimistane inhibits aromatase through a mechanism-based (suicide) inactivation pathway. The compound binds to the substrate pocket of aromatase in competition with the natural substrates androstenedione and testosterone. The initial binding is reversible and competitive, with the steroidal skeleton of Arimistane recognized by the same hydrophobic contacts and hydrogen-bonding interactions that accommodate the natural androstenedione substrates. Following binding, the catalytic heme-iron center of aromatase initiates oxidative processing of the Arimistane molecule, analogous to the initial hydroxylation steps of the normal catalytic cycle. However, the conjugated 3,5-diene system and the 7-oxo group of Arimistane direct the oxidative processing toward generation of a chemically reactive electrophilic intermediate (proposed to include an epoxide or a Michael acceptor species at the conjugated diene) that reacts covalently with nucleophilic amino acid residues (cysteine, histidine, or lysine) at or near the active site [1, 2, 6].

The covalent modification permanently inactivates the individual enzyme molecule. Unlike competitive or reversible inhibitors (which dissociate and permit enzyme reactivation as inhibitor concentration falls), the suicide mechanism produces irreversible loss of catalytic activity that can only be restored by de novo synthesis of new aromatase protein. The half-life of aromatase protein turnover in hu-

man tissues is estimated at approximately 24 to 48 hours, meaning that a single saturating exposure to a suicide inhibitor produces estrogen suppression lasting one to two days per inactivated enzyme molecule [9].

The key experimental criteria for mechanism-based inactivation, as established by Covey et al. for the androst-5-ene-7,17-dione series, are: (a) time-dependent loss of enzyme activity that follows pseudo-first-order kinetics; (b) dependence on NADPH (the electron donor required for aromatase catalytic turnover); (c) protection by the natural substrate androstenedione (consistent with competitive binding at the active site); and (d) irreversibility upon dialysis or gel filtration to remove unbound inhibitor [1, 2]. These criteria were satisfied for androst-5-ene-7,17-dione and its derivatives in human placental microsomal aromatase assays.

4.2 Relationship to the steroidal aromatase inhibitor pharmacophore

The mechanism-based aromatase inactivation by Arimistane shares fundamental features with the clinically approved steroidal aromatase inactivator exemestane (6-methylenandrosta-1,4-diene-3,17-dione) and with the earlier clinical candidate formestane (4-hydroxyandrost-4-ene-3,17-dione). All three compounds are androstenedione derivatives that exploit the substrate-recognition machinery of aromatase for initial binding, followed by enzyme-catalyzed generation of a covalently reactive species. The structural differences determine the specific reactive intermediate generated and the specific active-site residue modified: exemestane generates a reactive methylene intermediate at C-6 that alkylates Asp309 in the substrate channel [17]; formestane generates a reactive species at C-4 or C-6; and Arimistane generates a reactive species at the 3,5-diene or 7-oxo positions [1, 2].

Structure-activity studies on the broader androstene-7,17-dione series revealed that the 5-ene-7-one motif is the minimal pharmacophore for mechanism-based aromatase inactivation in this structural class, and that additional unsaturation (the 3,4-double bond yielding the 3,5-diene of Arimistane) modulates potency and kinetic parameters [2]. The 19-nor derivative of androst-5-ene-7,17-dione and the 5-beta,6-beta-epoxide were also characterized as time-dependent inactivators, consistent with the mechanistic requirement for enzyme-catalyzed processing rather than simple chemical reactivity [2].

4.3 11-beta-hydroxysteroid dehydrogenase type 1 inhibition

A secondary pharmacological activity attributed to Arimistane is competitive inhibition of 11-beta-hydroxysteroid dehydrogenase type 1 (11-beta-HSD1). This enzyme catalyzes the NADPH-dependent reduction of cortisone (the inactive 11-oxo glucocorticoid) to cortisol (the active 11-beta-hydroxy glucocorticoid) in the endoplasmic reticulum of hepatocytes, adipocytes, and neurons [10, 18]. 11-beta-HSD1 amplifies local glucocorticoid action in these tissues independently of adrenal cortisol secretion and has been implicated as a therapeutic target in metabolic syndrome, visceral obesity, type 2 diabetes, and cognitive decline associated with glucocorticoid excess.

The 7-oxo-androstane structural motif is a recognized competitive substrate and inhibitor of 11-beta-HSD1. 7-keto-DHEA and its metabolites (including 7-alpha-hydroxy-DHEA and 7-beta-hydroxy-DHEA) compete with cortisone for binding to 11-beta-HSD1, thereby reducing local cortisol regeneration [10, 11]. The activity has been demonstrated in vitro in human hepatic microsomal preparations and in vivo in animal models of glucocorticoid excess. Arimistane, as a 7-oxo-androstane bearing the same C-7 carbonyl that is the pharmacophoric element for 11-beta-HSD1 interaction, is inferred to share this activity, although direct in vitro or in vivo confirmation specific to Arimistane (as opposed to 7-keto-DHEA) has not been published in the peer-reviewed literature.

4.4 Composite pharmacology

The composite pharmacological profile of Arimistane at reported supplement doses (25 to 75 mg orally) is expected to produce: (a) irreversible inactivation of a fraction of tissue aromatase, resulting in reduced conversion of androstenedione and testosterone to estrone and estradiol; (b) a consequent relative increase in circulating androgen concentrations (both through reduced aromatization and through feedback-mediated increases in luteinizing hormone secretion from reduced estrogen negative feedback at the hypothalamus and pituitary); and (c) competitive inhibition of 11-beta-HSD1, reducing local cortisol regeneration in liver and adipose tissue. The magnitude and clinical significance of each of these effects at the doses used in supplement contexts have not been rigorously characterized in controlled human studies.

5. Pharmacokinetics

5.1 Absorption

Formal pharmacokinetic studies of Arimistane in humans have not been published in the peer-reviewed literature. The compound is a lipophilic steroid (molecular weight 284.39, low aqueous solubility) that is expected to be absorbed from the gastrointestinal tract by passive diffusion through the intestinal epithelium, consistent with the absorption characteristics of other orally administered steroidal compounds of similar molecular weight and lipophilicity (exemestane, DHEA, androstenedione). Oral bioavailability has not been formally determined but is expected to be subject to first-pass hepatic metabolism, as is characteristic of C19 steroids administered orally.

Supplement manufacturers have reported oral doses of 25 to 75 mg per day, with some products claiming enhanced absorption through cyclodextrin complexation or liposomal delivery systems. The bioavailability enhancement claims have not been validated by independent pharmacokinetic studies.

5.2 Distribution

Volume of distribution, plasma protein binding, and tissue distribution have not been characterized for Arimistane. By analogy with structurally related C19 steroids (androstenedione, DHEA, 7-keto-DHEA), moderate to high plasma protein binding (predominantly to albumin and sex hormone-binding globulin) and substantial tissue distribution (including adipose tissue partitioning for lipophilic steroids) are anticipated.

5.3 Metabolism

The metabolic fate of Arimistane has not been formally characterized in human metabolic studies. By structural analogy and by inference from the metabolism of related 7-oxo-androstanes, the compound is expected to undergo: (a) hepatic reduction of the 7-oxo group to 7- α -hydroxy and 7- β -hydroxy metabolites (by 11- β -HSD and related short-chain dehydrogenase/reductase enzymes); (b) reduc-

tion of the 17-oxo group to 17-beta-hydroxy metabolites (by 17-beta-hydroxysteroid dehydrogenases); (c) reduction of the conjugated 3,5-diene; and (d) phase II conjugation (glucuronidation and sulfation) of hydroxylated metabolites for renal excretion [5, 13].

The WADA-funded study by Brooker and colleagues on the metabolic relationship between DHEA, 7-keto-DHEA, and Arimistane established that Arimistane appears in urine following oral administration of 7-keto-DHEA, confirming the metabolic connection and raising the possibility that urinary detection of Arimistane may reflect either direct administration or metabolism of 7-keto-DHEA [5]. Isotope ratio mass spectrometry (IRMS) is required to distinguish exogenous from endogenous origin in anti-doping testing.

5.4 Elimination

Elimination is expected to proceed predominantly through hepatic metabolism followed by renal excretion of conjugated metabolites, consistent with the elimination pathway of other C19 steroids. The terminal elimination half-life of Arimistane has not been determined in human pharmacokinetic studies. However, the irreversible nature of the aromatase-inhibitory mechanism means that the pharmacodynamic duration of estrogen suppression extends substantially beyond the plasma elimination half-life of the parent compound, as new aromatase protein must be synthesized to restore catalytic activity.

5.5 Routes of administration

The compound has been administered exclusively by the oral route in supplement contexts. Oral dosage forms include capsules and tablets at 25, 50, and 75 mg strengths. Parenteral administration has not been reported in the published literature for Arimistane specifically, though related steroidal compounds (formestane) have been administered by intramuscular injection in clinical settings.

6. Preclinical Pharmacology

6.1 In vitro aromatase inhibition

The foundational in vitro characterization of the 7-oxo-androstene series as aromatase inhibitors was conducted by Covey et al. using human placental microsomal aromatase preparations with tritiated androstenedione as substrate [1, 2]. Androst-5-ene-7,17-dione (the 5-ene congener of Arimistane) produced time-dependent, NADPH-dependent, substrate-protectable inactivation of aromatase consistent with mechanism-based inhibition. The apparent K_i for competitive binding was in the low micromolar range, and the k_{inact} (rate constant for inactivation) was consistent with efficient enzyme-catalyzed conversion to the reactive intermediate.

Subsequent studies by Numazawa and colleagues extended the structure-activity characterization to additional 7-oxo-androstane derivatives and confirmed the requirement for the 5-ene or 3,5-diene unsaturation for mechanism-based (as opposed to simple competitive) inhibition [2, 19]. The 3,5-diene system of Arimistane provides additional conjugation that may modulate the partition ratio (the ratio of productive catalytic turnovers to inactivation events) relative to the 5-ene parent compound, though direct comparative kinetic data for Arimistane versus androst-5-ene-7,17-dione have not been published.

6.2 11-beta-HSD1 inhibition in vitro

The inhibition of 11-beta-HSD1 by 7-oxo-androstane steroids has been demonstrated in human hepatic microsomal preparations and in recombinant enzyme assays [10, 11]. 7-keto-DHEA inhibits cortisone-to-cortisol conversion with IC_{50} values in the low micromolar range. The inhibition is competitive with respect to cortisone, consistent with binding at the substrate-recognition site of 11-beta-HSD1. Arimistane retains the 7-oxo group but lacks the 3-beta-hydroxyl of 7-keto-DHEA; the effect of this structural modification on 11-beta-HSD1 inhibitory potency has not been characterized directly.

6.3 Animal pharmacology

Formal animal pharmacology studies specifically for Arimistane have not been published in the peer-reviewed literature. The preclinical pharmacology of the 7-oxo-androstane class is derived primarily from studies of 7-keto-DHEA, which has been evaluated in rodent models of obesity, thermogenesis, and immune function [14, 20]. In these models, 7-keto-DHEA at oral doses of 50 to 200 mg/kg produced reductions in body weight, increases in thermogenic enzyme activity (mitochondrial sn-glycerol-3-phosphate dehydrogenase, cytosolic malic enzyme, fatty acid acyl-CoA oxidase), and modulation of immune parameters [20]. The contribution of aromatase inhibition versus 11-beta-HSD1 inhibition versus other mechanisms to these in vivo effects has not been dissected for 7-keto-DHEA or for Arimistane.

7. Clinical Evidence Base

7.1 Human tolerability data

Published human clinical data specifically for Arimistane are extremely limited. Manufacturer-sponsored assessments have reported tolerability at oral doses of up to 200 mg per day for four weeks, with blood chemistry markers (hepatic transaminases, renal function, lipid panel, complete blood count) remaining within normal reference ranges [21]. These assessments were not controlled, were not powered for efficacy endpoints, and were conducted in small cohorts of healthy adult males. They do not constitute clinical trials in the regulatory sense and do not provide evidence of efficacy for any claimed endpoint.

7.2 Hormonal effects in humans

Anecdotal and observational reports from the bodybuilding community describe reductions in estradiol concentrations, increases in total and free testosterone, increases in luteinizing hormone, and reductions in cortisol following oral Arimistane supplementation at 25 to 75 mg per day for two to six weeks. These reports are not controlled, are confounded by concurrent use of other supplements and by post-cycle recovery dynamics, and do not meet the evidentiary standard for characterization of pharmacodynamic effects.

7.3 Anti-doping analytical chemistry

The most rigorous published human data on Arimistane concern its detection and metabolism in the anti-doping context. The WADA-funded study on DHEA, 7-keto-DHEA, and Arimistane metabolic relationships established the urinary excretion profile of Arimistane and its metabolites following oral administration and demonstrated the requirement for IRMS to distinguish exogenous from endogenous origin [5]. These studies provide confirmation that the compound is absorbed and systemically available after oral administration but do not characterize dose-response, pharmacodynamic magnitude, or clinical efficacy.

7.4 Extrapolation from related compounds

In the absence of direct clinical evidence for Arimistane, pharmacological inferences are drawn from: (a) the clinical pharmacology of exemestane, a structurally related steroidal aromatase inactivator with extensive Phase 3 clinical data in breast cancer and documented effects on estrogen suppression (greater than 97 percent at 25 mg/day), bone mineral density, lipid metabolism, and endocrine function [17, 22]; (b) the clinical pharmacology of 7-keto-DHEA, which has been evaluated in small clinical studies for weight management and immune modulation [14]; and (c) the clinical pharmacology of DHEA, the upstream precursor, which has been evaluated in multiple clinical contexts including adrenal insufficiency, aging, and immune function. The validity of these extrapolations is limited by differences in potency, selectivity, pharmacokinetics, and the specific structural features that determine the partition between aromatase inactivation, 11-beta-HSD1 inhibition, and other activities.

8. Sourcing and Quality Verification

Research-grade androsta-3,5-diene-7,17-dione is available from multiple chemical suppliers including Cayman Chemical (catalog number 23086), Sigma-Aldrich, BenchChem, GlpBio, MedChemExpress, EvitaChem, and SmoleCule, at purities of 97 percent or greater by HPLC [7, 23]. Supply is in milligram to gram quantities as the free steroid (no salt form is required, as the compound lacks ionizable groups at physiological pH). Pricing is moderate, in the range of \$30 to \$150 per 100 milligrams of research-grade material.

Supplement-grade Arimistane is marketed by multiple companies (Hi-Tech Pharmaceuticals, Innovative Research Technology, and others) at doses of 25 to 75 mg per capsule. However, the FDA has determined that these products are adulterated under federal law, and their continued availability is subject to ongoing enforcement action [3]. Investigators requiring the compound for research should obtain analytical-grade material from established chemical suppliers rather than from supplement sources.

Quality verification on every research lot should include:

- High-performance liquid chromatography area-percent purity (target greater than 97 percent)
- Mass spectrometry confirmation of molecular ion at m/z 285.18 $[M+H]^+$ or 284.18 $[M]^+$ by electron ionization
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) confirming the 3,5-diene system and the 7-oxo and 17-oxo groups
- Melting point determination (expected 167 to 168 degrees Celsius)
- Thin-layer chromatography or HPLC comparison to an authenticated reference standard

Third-party analytical verification is appropriate for studies where accurate dose-response characterization is required, particularly given the history of variable quality in the supplement market.

9. Reconstitution and Handling

Arimistane is supplied as a crystalline solid that is sparingly soluble in chloroform and slightly soluble in methanol. For in vitro research applications, stock solutions are typically prepared in dimethyl sulfoxide (DMSO) at concentrations of 10 to 100 mM, or in ethanol at lower concentrations (1 to 10 mM). Aqueous solubility is poor; for cell-based assays, the final DMSO concentration in the assay medium should be maintained below 0.1 percent (v/v) to avoid solvent cytotoxicity, and the effective working concentration range is limited by solubility to approximately 10 to 50 micromolar in aqueous media with DMSO vehicle.

Storage of the solid should be at minus 20 degrees Celsius in a desiccated container protected from light and moisture. Under these conditions, the compound is stable for at least 24 months as assessed by HPLC purity retention. Stock solutions in DMSO are stable at minus 20 degrees Celsius for at least 6 months; repeated freeze-thaw cycles should be minimized by preparing single-use aliquots.

For animal pharmacology studies requiring oral or parenteral administration, the compound can be formulated in corn oil, sesame oil, or propylene glycol/ethanol vehicles at concentrations up to approximately 10 mg/mL. Cyclodextrin complexation (hydroxypropyl-beta-cyclodextrin) has been used commercially to enhance aqueous solubility for oral formulations.

10. Stack Interactions and Combinations

Investigators conducting research with Arimistane, particularly in contexts involving concurrent administration of other hormonal or metabolic agents, should consider the following interaction categories.

Exogenous androgens and anabolic steroids: Arimistane is most frequently used in combination with or following cessation of exogenous androgen administration (testosterone, nandrolone, oxandrolone, and others). The aromatase-inhibitory mechanism reduces conversion of administered androgens to estrogens, which is the primary rationale for co-administration during anabolic steroid cycles. Following cessation of exogenous androgens ("post-cycle therapy"), Arimistane is used to accelerate recovery of endogenous testosterone production by reducing estrogen-mediated negative feedback at the hypothalamic-pituitary-gonadal axis.

Selective estrogen receptor modulators (SERMs): Concurrent use with tamoxifen, clomiphene, or raloxifene produces complementary estrogen-axis modulation: aromatase inhibition reduces estrogen synthesis, while SERMs block estrogen receptor activation by remaining estrogen. This combination is common in post-cycle therapy protocols in the bodybuilding community. Pharmacokinetic interactions are not characterized for Arimistane specifically; however, tamoxifen is a CYP2D6 substrate and potential competitive interactions at the CYP level should be considered.

Other aromatase inhibitors: Concurrent use with pharmaceutical aromatase inhibitors (anastrozole, letrozole, exemestane) is pharmacologically redundant for the aromatase-inhibitory effect and may produce excessive estrogen suppression with attendant risks to bone mineral density, lipid metabolism, and sexual function. The combination is not recommended.

11-beta-HSD1 substrates and inhibitors: Concurrent use with other 7-oxo-androstane steroids (7-keto-DHEA) or with pharmaceutical 11-beta-HSD1 inhibitors (in clinical development for metabolic syndrome) may produce additive cortisol-modulatory effects. The clinical significance of such interactions has not been characterized.

CYP450 substrates and inhibitors: The metabolic pathways of Arimistane have not been formally characterized; by analogy with other C19 steroids, hepatic CYP3A4 involvement is likely. Strong CYP3A4 inhibitors (ketoconazole, itraconazole, ritonavir, clarithromycin) may increase Arimistane exposure, while strong CYP3A4 inducers (rifampin, carbamazepine, phenytoin) may reduce it.

Bone-active agents: Because aromatase inhibition reduces estrogen, which is essential for bone mineral homeostasis in both sexes, concurrent use of Arimistane with other agents that reduce bone density (glucocorticoids, proton pump inhibitors at chronic high doses, loop diuretics) may increase the risk of bone mineral density loss. Conversely, co-administration with calcium, vitamin D, or bisphosphonates may partially mitigate this risk.

11. Adverse Events and Safety Signal

11.1 Anticipated class-effect adverse events

The adverse-event profile of Arimistane is inferred primarily from the class effects of aromatase inhibitors, as compound-specific clinical safety data are limited. The principal anticipated adverse events associated with aromatase inhibition in males include:

- Joint pain and stiffness (arthralgia): the most frequently reported adverse event with pharmaceutical aromatase inhibitors in clinical use, attributed to estrogen depletion in articular cartilage and synovial tissue. Incidence with third-generation aromatase inhibitors in breast cancer patients is approximately 20 to 35 percent [22].
- Bone mineral density reduction: estrogen is essential for maintenance of bone mass in both sexes. Prolonged aromatase inhibition increases bone resorption and reduces bone mineral density, increasing fracture risk. This effect is dose-dependent and duration-dependent [22].
- Lipid profile alterations: estrogen exerts favorable effects on lipid metabolism (increasing HDL cholesterol, reducing LDL cholesterol). Aromatase inhibition may reverse these effects, producing unfavorable lipid shifts [22].
- Sexual dysfunction: reduced estrogen can contribute to decreased libido, erectile dysfunction, and reduced spermatogenesis in males.
- Mood alterations: estrogen modulates serotonergic and dopaminergic neurotransmission; estrogen depletion may produce mood disturbance, irritability, or depressive symptoms.
- Hot flashes and vasomotor symptoms: common with pharmaceutical aromatase inhibitors.

11.2 Reported adverse events specific to Arimistane

Adverse events specifically attributed to Arimistane in the published literature and in supplement community reports include headache, fatigue, joint stiffness, dry skin, and mood changes at typical supplement doses of 25 to 75 mg per day [15]. The FDA Scientific Memorandum on Arimistane noted safety concerns related to the

possibility of adverse effects analogous to those documented for pharmaceutical aromatase inhibitors, including effects on reproductive function, bone health, and cardiovascular risk markers [15].

11.3 Hepatotoxicity and nephrotoxicity

The potential for hepatic and renal toxicity has been raised in general safety assessments but has not been demonstrated in the limited available human data at supplement doses for short durations (up to four weeks). The manufacturer-sponsored tolerability assessments reported hepatic transaminases and renal function markers within normal ranges [21]. However, these assessments were short-term, small-cohort, and uncontrolled. Long-term safety data are absent.

11.4 Reproductive health concerns

The FDA has specifically noted that aromatase inhibition by Arimistane may disrupt endocrine signaling with adverse consequences for male and female reproductive health [3, 15]. In males, excessive estrogen suppression can impair spermatogenesis (estrogen is required for normal Sertoli cell function and sperm maturation) and reduce bone density. In females of reproductive age, aromatase inhibition suppresses ovarian estrogen synthesis and can disrupt menstrual cycling, ovulation, and fertility. The compound should be considered contraindicated in pregnant women on the basis of the known teratogenic potential of aromatase inhibitors.

11.5 Drug interactions of safety concern

Concurrent use of Arimistane with other agents that suppress estrogen (pharmaceutical aromatase inhibitors, GnRH agonists, SERMs at high doses) may produce additive or synergistic estrogen depletion with increased risk of the class-effect adverse events described above.

12. Comparative Assessment

This section presents a structured comparative assessment of five alternative aromatase-modulating compounds against Arimistane, evaluated on five competency standards: novelty, effect size (magnitude of aromatase inhibition and clinical endpoints), promising potential (current regulatory and development status), side-effect profile, and overall validation. The five comparators were selected to span the mechanistic and clinical landscape of aromatase inhibition: two pharmaceutical steroidal inhibitors (exemestane, formestane), two pharmaceutical non-steroidal inhibitors (letrozole, anastrozole), and one closely related supplement-market compound (1,4,6-androstatriene-3,17-dione, ATD).

12.1 Exemestane (Aromasin)

Mechanism: Steroidal mechanism-based (suicide) aromatase inactivator. Irreversible, covalent modification of aromatase active site via enzyme-catalyzed processing of the 6-methylene group. Third-generation steroidal aromatase inhibitor [17, 22].

Novelty: Moderate. The mechanism is well established within the steroidal AI class. Exemestane is the only orally bioavailable third-generation steroidal AI in clinical use.

Effect size: At 25 mg/day oral, exemestane produces greater than 97 percent suppression of whole-body aromatase activity and greater than 95 percent reduction in plasma estradiol in postmenopausal women. Clinical efficacy in breast cancer (adjuvant and advanced settings) is well documented in multiple Phase 3 trials [22].

Promising potential: High. Exemestane is an established pharmaceutical with regulatory approval in multiple jurisdictions for hormone-receptor-positive breast cancer. Generic exemestane is widely available.

Side-effect profile: Well characterized. Principal adverse events include arthralgia (approximately 25 percent), hot flashes, fatigue, headache, bone mineral density reduction, and modest adverse lipid shifts. The androgenic metabolite 17-hydroexemestane provides partial mitigation of bone and lipid effects relative to non-steroidal AIs [22].

Overall validation: Very high. Extensive Phase 3 clinical data, regulatory approval, decades of clinical experience.

Comparison to Arimistane: Exemestane shares the irreversible (suicide) mechanism but is substantially more potent, more thoroughly characterized, and clinically validated. Arimistane lacks the clinical evidence base, the regulatory approval, and the pharmacokinetic characterization of exemestane. The 6-methylene pharmacophore of exemestane is mechanistically distinct from the 7-oxo/3,5-diene pharmacophore of Arimistane, though both exploit enzyme-catalyzed activation. Exemestane is the appropriate clinical reference for the steroidal suicide AI mechanism.

12.2 Formestane (4-hydroxyandrost-4-ene-3,17-dione; Lentaron)

Mechanism: Steroidal mechanism-based aromatase inactivator. Second-generation. Administered by intramuscular injection (poor oral bioavailability) [6, 12].

Novelty: Low. Historically significant as the first selective steroidal AI but superseded by exemestane.

Effect size: Moderate. At 250 mg intramuscular every two weeks, formestane produces approximately 60 to 85 percent suppression of aromatase activity, less than third-generation agents [12].

Promising potential: Low. The compound has been largely withdrawn from clinical use and superseded by exemestane and third-generation non-steroidal AIs.

Side-effect profile: Injection-site reactions (local inflammation, pain) were the principal tolerability limitation. Systemic adverse events were similar to other AIs.

Overall validation: Moderate historically. The compound demonstrated proof of concept for steroidal aromatase inhibition in breast cancer and contributed foundational mechanistic knowledge.

Comparison to Arimistane: Formestane is the closest clinical precedent for a 7-oxo-bearing steroidal AI, though its pharmacophore (4-hydroxy-4-ene-3-oxo) differs from Arimistane's (3,5-diene-7-oxo). Both require enzyme-catalyzed activation for irreversible inactivation. Formestane's clinical validation, while more limited than exemestane's, far exceeds that of Arimistane.

12.3 Letrozole (Femara)

Mechanism: Non-steroidal (triazole) competitive reversible aromatase inhibitor. Third-generation. Binds to the heme-iron center of aromatase via the triazole nitrogen, producing potent and highly selective reversible inhibition [24, 25].

Novelty: Moderate. The triazole AI mechanism is well established.

Effect size: At 2.5 mg/day oral, letrozole produces greater than 99 percent suppression of aromatase activity and the most complete estrogen suppression among the third-generation AIs. Considered the most potent aromatase inhibitor in clinical use [24, 25].

Promising potential: Very high. First-line adjuvant and advanced breast cancer therapy. Regulatory approval worldwide.

Side-effect profile: Well characterized. Arthralgia, hot flashes, fatigue, bone mineral density reduction (more pronounced than exemestane due to absence of androgenic metabolites), and adverse lipid shifts.

Overall validation: Very high. Extensive Phase 3 clinical data.

Comparison to Arimistane: Letrozole represents the opposite end of the AI mechanistic spectrum: non-steroidal, reversible, triazole-based, and the most potent clinical AI. Arimistane is steroidal, irreversible, and of unknown potency in human aromatase suppression. The comparison illustrates the vast gap between Arimistane's uncertain clinical pharmacology and the precision of third-generation pharmaceutical AIs.

12.4 Anastrozole (Arimidex)

Mechanism: Non-steroidal (triazole) competitive reversible aromatase inhibitor. Third-generation. Mechanistically similar to letrozole [24].

Novelty: Moderate. Established mechanism.

Effect size: At 1 mg/day oral, anastrozole produces approximately 96 to 97 percent suppression of aromatase activity. Slightly less potent than letrozole in comparative studies [24, 25].

Promising potential: Very high. Regulatory approval worldwide for breast cancer. Also used off-label in male hypogonadism to raise testosterone-to-estradiol ratio.

Side-effect profile: Similar to letrozole. Arthralgia, musculoskeletal pain, hot flashes, bone mineral density reduction.

Overall validation: Very high. Multiple Phase 3 trials, extensive postmarketing experience.

Comparison to Arimistane: Anastrozole is the compound most frequently cited as a comparison by Arimistane supplement marketers (the trade name "Arimistane" appears designed to evoke "Arimidex"). However, the compounds are fundamentally different in mechanism (reversible competitive vs. irreversible suicide), structure (triazole vs. steroidal), and evidence base. Anastrozole has extensive clinical validation; Arimistane has essentially none.

12.5 1,4,6-Androstatriene-3,17-dione (ATD)

Mechanism: Steroidal competitive aromatase inhibitor. ATD binds to the aromatase active site but has been characterized as a competitive (reversible) rather than mechanism-based (irreversible) inhibitor in most assay systems, though some reports suggest partial irreversibility [26, 27].

Novelty: Low. The compound has been known since the 1960s as an aromatase inhibitor.

Effect size: Moderate in vitro aromatase inhibition. Human pharmacodynamic data are limited.

Promising potential: Low. ATD has been banned by WADA and removed from the dietary supplement market in multiple jurisdictions (included in the Anabolic Steroid Control Act amendment in some jurisdictions). Not in pharmaceutical development.

Side-effect profile: ATD has been reported to have partial androgenic and estrogenic metabolites (it can be converted to active androgens and estrogens in vivo), complicating its safety profile relative to the simpler pharmacology of Arimistane.

Overall validation: Low. No clinical trials. Primarily a research tool and historical supplement ingredient.

Comparison to Arimistane: ATD is the compound most directly comparable to Arimistane in the supplement market. Both are steroidal aromatase inhibitors sold in dietary supplement contexts, both have been subject to regulatory action, and both lack clinical validation. Arimistane has the theoretical advantage of irreversible (suicide) inhibition versus the reversible inhibition of ATD, and Arimistane lacks the androgenic/estrogenic metabolic complications of ATD. Arimistane therefore represents an incremental improvement within the supplement-grade steroidal AI class, though neither compound approaches the clinical validation of pharmaceutical AIs.

12.6 Comparator summary

The five comparators occupy distinct positions in the aromatase-inhibitor landscape. **Exemestane** is the most directly mechanistically comparable pharmaceutical (irreversible, steroidal), with extensive clinical validation and regulatory approval. **Formestane** is the historical clinical precedent for steroidal suicide AIs, now largely superseded. **Letrozole** is the most potent aromatase inhibitor in clinical use, representing the non-steroidal reversible mechanism class. **Anastrozole** is a well-validated non-steroidal AI with extensive clinical data. **ATD** is the closest supplement-market comparator, sharing the regulatory profile and evidence limitations of Arimistane while differing in mechanism (reversible vs. irreversible) and metabolic complications.

Arimistane occupies the lowest tier of clinical validation among these comparators. It is the only compound in the panel without clinical trial data supporting efficacy for any therapeutic endpoint. Its theoretical advantages (irreversible mechanism, endogenous metabolic origin, reported cortisol modulation) are not supported by controlled human evidence. The compound's scientific interest resides principally in its mechanism-based aromatase inactivation, its metabolic relationship to the endogenous DHEA/7-keto-DHEA pathway, and its potential as a research tool for studying the 7-oxo-androstane structural class. Investigators should consider the pharmaceutical aromatase inhibitors (exemestane, letrozole, anastrozole) as the validated clinical reference points and should treat Arimistane as a research-grade compound with unvalidated clinical pharmacology.

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