

RESEARCH MONOGRAPH . COMPOUND PROFILE

Primobolan

A non-17-alpha-alkylated dihydrotestosterone derivative developed by Squibb and Schering for refractory anemia and catabolic wasting, distinguished from other anabolic-androgenic steroids by its favorable hepatic safety profile, absence of aromatization, and moderate anabolic-to-androgenic dissociation.

DOCUMENT	KDC-MN-1549
ISSUED	2026-05-15
REVISION	1.0
AUTHOR	Kodiac biolabs Research
COMPOUND CLASS	Synthetic androstane anabolic-androgenic steroid; 1-methyl dihydrotestosterone derivative with moderate androgen receptor agonism

RESEARCH USE ONLY

ABSTRACT

Primobolan is the trade name for metenolone (also rendered methenolone), a synthetic androstane steroid derived from dihydrotestosterone (DHT) by introduction of a 1-methyl group and a 1,2-double bond into the A-ring of the 5- α -reduced androstane nucleus. The compound was first synthesized in 1960 and introduced for clinical use in 1961 by Squibb Pharmaceuticals in the United States (as Nibal and Nibal Depot) and by Schering AG in West Germany (as Primobolan and Primobolan Depot). Two ester prodrug forms are manufactured: metenolone acetate (CAS 434-05-9), the oral preparation with a molecular weight of 344.50 g/mol, and metenolone enanthate (CAS 303-42-4), the intramuscular depot preparation with a molecular weight of 414.63 g/mol. Both esters undergo hydrolysis in vivo to release the parent steroid metenolone (CAS 153-00-4; molecular formula $C_{20}H_{30}O_2$; molecular weight 302.46 g/mol), which binds the androgen receptor with moderate affinity and produces anabolic effects in skeletal muscle, bone, and erythropoietic tissue.

The clinical pharmacology of metenolone is defined by several characteristics that distinguish it from structurally related anabolic-androgenic steroids. First, the compound is not 17- α -alkylated; the 1-methyl substitution and ester conjugation confer sufficient oral bioavailability (in the acetate form) and depot duration (in the enanthate form) without the hepatotoxic liability associated with C17- α -alkylated steroids such as oxymetholone, stanozolol, and methandrostenolone. Second, the 1,2-double bond and the DHT-derived backbone render metenolone resistant to aromatization by the cytochrome P450

aromatase enzyme complex (CYP19A1), eliminating estrogenic side effects including gynecomastia and estrogen-mediated fluid retention. Third, metenolone exhibits a moderate anabolic-to-androgenic dissociation ratio of approximately 88:44 to 150:50 in rodent bioassays (levator ani weight gain versus ventral prostate weight gain, relative to testosterone propionate as the reference standard), placing it in the class of mildly anabolic, mildly androgenic agents alongside oxandrolone and drostanolone.

The principal approved clinical indication was the treatment of anemia due to bone marrow failure, including aplastic anemia, myelofibrosis, and refractory cytopenias. A therapeutic trial reported by Compagno et al. (1978) in 19 consecutive patients with refractory anemia demonstrated remission in approximately 37 percent of patients with pancytopenia and variable responses across other cytopenia subtypes [1]. Additional historical indications included protein-calorie malnutrition, postoperative and post-infectious catabolic states, osteoporosis, sarcopenia, and promotion of weight gain in premature infants. The compound has been largely discontinued from clinical markets; as of the most recent monograph revision, metenolone enanthate is marketed only in Spain and Turkey (as Primobolan Depot), and metenolone acetate retains limited availability in Japan and Moldova.

Pharmacokinetics differ substantially between the two ester forms. Metenolone acetate is rapidly absorbed after oral administration but undergoes significant first-pass hepatic metabolism, resulting in reduced oral bioavailability relative to parenteral administration; the plasma half-life of the oral form is approximately 4 to 6 hours. Metenolone enanthate, administered by intramuscular injection in an oil vehicle, provides depot release

with a biological half-life of approximately 10.5 days and a duration of action of approximately 14 days. Metabolism of metenolone proceeds through hepatic mixed-function oxidases; the principal urinary metabolite is 3- α -hydroxy-1-methylen-5- α -androstan-17-one, excreted as glucuronide and sulfate conjugates. The sulfate-conjugated metabolites provide extended detection windows in anti-doping analysis, with some metabolites detectable for several weeks after a single administration.

Metenolone exhibits low affinity for sex hormone-binding globulin (SHBG), approximately 16 percent of that of testosterone and 3 percent of that of DHT, resulting in a higher fraction of unbound drug in plasma.

Adverse effects are consistent with the anabolic-androgenic steroid class but are generally milder than those of 17- α -alkylated compounds. Virilization in female patients (acne, hirsutism, voice deepening, clitoral enlargement, menstrual irregularity) is the principal androgenic concern. Suppression of endogenous gonadotropin secretion (luteinizing hormone and follicle-stimulating hormone) produces dose-dependent hypothalamic-pituitary-gonadal axis suppression with consequent testicular atrophy, oligospermia, and reduced endogenous testosterone production in male users.

Cardiovascular effects include unfavorable shifts in the lipoprotein profile (decreased high-density lipoprotein cholesterol, increased low-density lipoprotein cholesterol), though these shifts are generally less pronounced than those produced by 17- α -alkylated oral steroids. Hepatotoxicity is minimal at therapeutic doses, consistent with the absence of C17- α -alkylation. This monograph reviews the chemistry, synthesis, and structural pharmacology of metenolone; the androgen receptor mechanism and tissue-selective pharmacodynamics; the complete

pharmacokinetic profile of both ester forms; the clinical evidence base across hematologic, catabolic, and body-composition indications; sourcing and quality verification; reconstitution and handling; stack interactions; adverse events; and a comparative assessment of five alternative anabolic-androgenic steroids against Primobolan on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Trade names: Primobolan (Schering AG; metenolone acetate, oral), Primobolan Depot (Schering AG; metenolone enanthate, intramuscular), Primobolan S (metenolone acetate, select markets), Nibal (Squibb; metenolone acetate, United States), Nibal Depot (Squibb; metenolone enanthate, United States), Primonabol (generic).

International Nonproprietary Name: Metenolone (INN). The alternate spelling methenolone is used in older pharmacopoeial and toxicological references, including the International Programme on Chemical Safety Poisons Information Monograph (PIM 907) [2].

Chemical Abstracts Service registry numbers: 153-00-4 (metenolone free base), 434-05-9 (metenolone acetate), 303-42-4 (metenolone enanthate). The free base is the pharmacologically active species generated by ester hydrolysis in vivo; the acetate and enanthate are the formulated ester prodrugs.

International Union of Pure and Applied Chemistry name (free base): (5S,8R,9S,10S,13S,14S,17S)-17-hydroxy-1,10,13-trimethyl-4,5,6,7,8,9,11,12,14,15,16,17-dodecahydrocyclopenta[a]phenanthren-3-one.

Synonyms: 1-Methyl-delta-1-dihydrotestosterone; 1-methyl-5-alpha-androst-1-en-17-beta-ol-3-one; 1-methyl-delta-1-DHT; methyl-dihydroboldenone (informal); NSC-74226.

1.2 Structural class and chemistry

Metenolone is a synthetic androstane steroid and a derivative of 5-alpha-dihydrotestosterone (DHT). The structural modifications relative to DHT are the introduction of a methyl group at the C1 position and a double bond between C1 and C2 of the A-ring. These modifications confer two pharmacologically important properties: resistance to metabolism by 3-alpha-hydroxysteroid dehydrogenase (3-alpha-

HSD), which inactivates DHT and other 5-alpha-reduced androgens in target tissues; and sufficient metabolic stability for oral bioavailability when combined with ester conjugation at the C17-beta hydroxyl [3].

Molecular formula (free base): C₂₀H₃₀O₂.

Molecular weight (free base): 302.46 g/mol.

Molecular formula (acetate ester): C₂₂H₃₂O₃.

Molecular weight (acetate ester): 344.50 g/mol.

Molecular formula (enantate ester): C₂₇H₄₂O₃.

Molecular weight (enantate ester): 414.63 g/mol.

Physical properties: White to off-white crystalline powder. The free base and both ester forms are practically insoluble in water and freely soluble in organic solvents including chloroform, ethanol, methanol, and vegetable oils. The enanthate ester is formulated as a solution in sesame oil or castor oil for intramuscular injection. Storage at 15 to 30 degrees Celsius with protection from light is recommended [2].

Stereochemistry: Metenolone contains six stereocenters in the androstane skeleton (C5, C8, C9, C10, C13, C14, C17). The naturally occurring and therapeutically active configuration is the (5S,8R,9S,10S,13S,14S,17S) form, consistent with the trans-anti-trans-anti-trans ring junctions of the 5-alpha-androstane series. The C17-beta hydroxyl configuration is essential for androgen receptor binding.

Non-aromatizability: The 5-alpha-reduced A/B ring junction and the 1,2-double bond prevent substrate recognition by aromatase (CYP19A1). Metenolone therefore cannot be converted to estrogenic metabolites under any physiological conditions, a property shared with other DHT derivatives (drostanolone, stanolone) but not with testosterone or nandrolone [3, 4].

1.3 Synthesis

The synthesis of metenolone proceeds from commercially available androstane precursors. The original Squibb synthesis (circa 1960) and subsequent manufacturing routes generally follow a multi-step sequence beginning with 17-beta-acetoxy-5-alpha-androst-1-en-3-one or a related protected androstane intermediate [5].

The key synthetic transformations include: (a) introduction of the 1,2-double bond into the A-ring of a 5- α -androstan-3-one precursor, typically by bromination at C2 followed by base-mediated elimination (dehydrobromination) or by selenium dioxide oxidation; (b) 1- α -methylation at C1 using a Grignard reagent (methylmagnesium bromide or methylmagnesium chloride) or by catalytic methylation under basic conditions; and (c) esterification of the C17- β hydroxyl with the appropriate acid chloride or anhydride (acetic anhydride for the acetate; heptanoyl chloride or heptanoic anhydride for the enanthate) under standard acylation conditions.

A patented Chinese route (CN101456888A) describes ketal protection of the C3 ketone with ethylene glycol and calcium hypochlorite oxidation at 60 to 65 degrees Celsius in organic solvent with protonic acid catalysis, followed by Grignard methylation to introduce the C1 methyl group [6]. The product is purified by column chromatography or recrystallization from ethyl acetate or isopropanol and characterized by nuclear magnetic resonance spectroscopy, mass spectrometry, and high-performance liquid chromatography. Industrial yields for the methylation and esterification steps are reported in the range of 65 to 80 percent.

2. Abstract

Primobolan (metenolone) is a non-17-alpha-alkylated anabolic-androgenic steroid of the dihydrotestosterone structural class, developed in the early 1960s for the treatment of anemia due to bone marrow failure and for catabolic wasting conditions. The compound is supplied as two ester prodrugs: metenolone acetate for oral administration and metenolone enanthate for intramuscular depot injection. Both forms release the parent steroid metenolone upon hydrolysis; metenolone binds the androgen receptor with moderate affinity and produces tissue-selective anabolic effects with a favorable ratio of anabolic to androgenic activity relative to testosterone.

The pharmacological profile of metenolone is defined by three distinguishing characteristics relative to other anabolic-androgenic steroids in clinical and research use. First, the absence of 17-alpha-alkylation eliminates the principal structural determinant of oral-steroid hepatotoxicity; metenolone does not produce the cholestatic hepatitis, peliosis hepatis, or hepatic tumor risk associated with C17-alpha-alkylated compounds [2, 7]. Second, the DHT-derived backbone and 1,2-unsaturation prevent aromatization; metenolone produces no estrogenic metabolites and carries no risk of gynecomastia or estrogen-mediated fluid retention [3, 4]. Third, the moderate anabolic potency and mild androgenic activity position metenolone as one of the better-tolerated anabolic-androgenic steroids, suitable for clinical populations (including women and children in historical applications) where virilization risk must be minimized.

The clinical evidence base for metenolone is historical and limited in scope by contemporary standards. Approval-era trials in aplastic anemia and refractory cytopenias demonstrated hematologic responses in a subset of patients, though the overall prognosis for severe aplastic anemia was not significantly improved by metenolone alone [1]. The compound was additionally used in catabolic and wasting conditions, osteoporosis, and as a supportive agent in protein-calorie malnutrition. With the introduction of recombinant erythropoietin, immunosuppressive therapy for aplastic anemia, and more potent anabolic alternatives, the clinical market for metenolone contracted substantially from the 1980s onward; the compound is now largely discontinued and remains available in only a small number of jurisdictions.

The principal contemporary relevance of metenolone is in anti-doping science, where it remains one of the most commonly detected prohibited anabolic-androgenic steroids in athlete biological passport and urinary steroid screening programs [8, 9]. The extended detection windows provided by sulfate-conjugated urinary metabolites and advances in liquid chromatography-high resolution mass spectrometry have substantially improved the analytical sensitivity for metenolone misuse [10, 11]. The compound is classified as a Schedule III controlled substance in the United States, Schedule IV in Canada, and is prohibited at all times by the World Anti-Doping Agency under the category of anabolic agents (S1.1a).

3. Discovery and Development History

3.1 Origin and early synthesis

Metenolone was first synthesized in 1960 as part of systematic medicinal chemistry programs exploring structural modifications of dihydrotestosterone to produce anabolic-androgenic steroids with improved therapeutic indices. The introduction of a methyl group at C1 and a double bond between C1 and C2 was designed to resist 3- α -HSD-mediated inactivation in target tissues while maintaining moderate androgen receptor affinity. The resulting compound exhibited a favorable anabolic-to-androgenic dissociation in rodent bioassays (levator ani muscle weight gain relative to ventral prostate weight gain), supporting advancement to clinical evaluation [3].

3.2 Clinical introduction

Metenolone acetate was introduced for medical use in 1961 in West Germany by Schering AG under the trade name Primobolan. The oral formulation was indicated for the treatment of anemia due to bone marrow failure, catabolic wasting, and protein-calorie malnutrition. In the United States, Squibb Pharmaceuticals marketed metenolone acetate as Nibal (oral) beginning in 1962. Metenolone enanthate, the intramuscular depot formulation, was marketed as Nibal Depot in the United States and as Primobolan Depot in European and other markets during the 1960s and 1970s [3, 12].

3.3 Clinical use and market trajectory

The principal clinical application of metenolone was in hematology, specifically the treatment of aplastic anemia and other bone marrow failure syndromes where androgen-stimulated erythropoiesis could provide clinical benefit. Androgens had been recognized since the 1950s as stimulators of erythropoietin production and direct stimulators of erythroid progenitor proliferation, and several anabolic-androgenic steroids (oxymetholone, nandrolone, stanozolol, metenolone) were evaluated for this indication. Metenolone was considered advantageous relative to oxymetholone owing to its substantially lower hepatotoxicity: a comparative study

noted that liver function abnormalities occurred in 80 percent of patients receiving oxymetholone but in only 26 percent of patients receiving non-17-alpha-alkylated androgens including metenolone, and these abnormalities regressed when metenolone was substituted for oxymetholone [13, 14].

Additional clinical applications included breast cancer in postmenopausal women (investigated in the 1960s and 1970s as adjunctive hormonal therapy), osteoporosis, sarcopenia in the elderly, promotion of weight gain in premature infants, and recovery from major surgery or prolonged infection. None of these indications produced a sustained clinical market.

3.4 Decline and discontinuation

The clinical use of metenolone declined from the 1980s onward for several converging reasons. Recombinant erythropoietin (epoetin alfa, approved 1989) provided a more targeted and effective treatment for anemia. Immunosuppressive regimens (antithymocyte globulin plus cyclosporine) became the standard of care for acquired aplastic anemia. Bisphosphonates and selective estrogen receptor modulators replaced androgens in osteoporosis management. The regulatory environment for anabolic-androgenic steroids tightened, culminating in the United States Anabolic Steroids Control Act of 1990 (which classified metenolone and its esters as Schedule III controlled substances) and the inclusion of metenolone on the International Olympic Committee and subsequently the World Anti-Doping Agency prohibited list.

Squibb withdrew Nibal and Nibal Depot from the United States market in the 1970s. Schering (subsequently Bayer Schering Pharma after the 2006 acquisition) progressively withdrew Primobolan from European markets. As of 2026, metenolone enanthate is marketed in Spain and Turkey; metenolone acetate retains limited availability in Japan and Moldova. The compound is otherwise available only through research chemical suppliers and unregulated markets [3, 12].

3.5 Anti-doping significance

Metenolone has been a prominent compound in anti-doping enforcement since the establishment of modern steroid testing programs. Notable positive tests in elite athletics have driven sustained analytical research into detection methodology. The identification of long-term sulfate-conjugated urinary metabolites by Fragkaki et

al. (2015) and Albertsdottir et al. (2020) substantially extended detection windows beyond the traditional glucuronide-conjugated metabolite screening [10, 11]. These advances are representative of the broader evolution of anti-doping analytical chemistry from gas chromatography-mass spectrometry to liquid chromatography-high resolution mass spectrometry platforms.

4. Mechanism of Action

Metenolone is an agonist of the androgen receptor (AR), the ligand-activated nuclear transcription factor that mediates the biological effects of androgens in reproductive, musculoskeletal, hematopoietic, neural, and other tissues. The mechanism of action follows the canonical androgen signaling pathway with several compound-specific modifications attributable to the DHT-derived structural class.

4.1 Androgen receptor binding and activation

Metenolone binds the ligand-binding domain of the androgen receptor with moderate affinity. In comparative binding studies using rat skeletal muscle and prostate cytosol preparations, the relative binding affinity (RBA) of metenolone to the androgen receptor was intermediate between testosterone and the synthetic reference compound methyltrienolone (R1881), ranking below nandrolone (19-nortestosterone) and above several other clinically used anabolic-androgenic steroids [15]. The binding affinity in skeletal muscle cytosol was comparable to that in prostate cytosol, consistent with the moderate anabolic-to-androgenic dissociation observed in whole-animal bioassays.

Upon binding, the metenolone-AR complex undergoes conformational change, dimerization, and nuclear translocation. The dimer binds to androgen response elements (AREs) in the promoter regions of androgen-regulated genes, recruiting coactivator proteins and the basal transcription machinery to initiate transcription. The principal downstream effects relevant to the clinical and research applications of metenolone include increased expression of genes involved in protein synthesis, nitrogen retention, erythropoietin production, and bone mineral deposition [4, 16].

4.2 Tissue-selective pharmacodynamics

The anabolic-to-androgenic dissociation of metenolone reflects differential metabolism and receptor interaction across tissues. In androgen-sensitive tissues that express high levels of 5-alpha-reductase (prostate, seminal vesicles, skin), testosterone is amplified to DHT, which has 3- to 10-fold greater AR binding affinity. Metenolone, being already a 5-alpha-reduced compound, is not further amplified

by 5-alpha-reductase. However, its resistance to 3-alpha-HSD-mediated inactivation (conferred by the 1,2-double bond) preserves its activity in both androgen-responsive and non-androgen-amplifying tissues. The net result is a moderate degree of tissue selectivity: anabolic effects in muscle and bone are proportionally greater than androgenic effects in prostate and skin, though the dissociation is not as pronounced as that of nandrolone [3, 15].

4.3 Non-aromatizability

Metenolone cannot serve as a substrate for aromatase (CYP19A1) owing to its 5-alpha-reduced A/B ring junction. Aromatase requires a delta-4,3-ketone configuration in the A-ring for substrate recognition and catalysis; the saturated A/B trans junction of the 5-alpha-androstane skeleton eliminates this structural prerequisite. Consequently, metenolone produces no estrogenic metabolites under any physiological conditions. This property distinguishes metenolone from testosterone, nandrolone, and methandrostenolone, all of which undergo partial aromatization to estrogenic products (estradiol, estrone, and their respective ring-B-modified analogs) [4].

The absence of aromatization has several pharmacological consequences: no gynecomastia risk; no estrogen-mediated fluid retention or blood pressure elevation; no estrogen-driven negative feedback amplification on the hypothalamic-pituitary axis beyond that produced by the androgenic signal alone; and no need for concurrent aromatase inhibitor or selective estrogen receptor modulator therapy in clinical or research applications.

4.4 Erythropoietic mechanism

The erythropoietic activity of metenolone, which underlies its historical indication in anemia due to bone marrow failure, is mediated through two principal pathways. First, androgen receptor activation in renal peritubular fibroblasts and hepatocytes stimulates erythropoietin gene transcription, increasing circulating erythropoietin concentrations and thereby stimulating erythroid progenitor proliferation and differentiation in the bone marrow [14, 17]. Second, androgens act directly on erythroid progenitor cells (burst-forming units erythroid and colony-forming units erythroid) to enhance proliferation and to reduce apoptosis, an effect that may be androgen receptor-mediated or may involve non-genomic signaling through membrane-associated steroid receptors. The magnitude of the erythropoi-

etic response to metenolone is lower than that of oxymetholone or nandrolone at equivalent doses, consistent with its lower androgenic potency, but is clinically relevant in the subset of patients with bone marrow failure who retain sufficient residual hematopoietic capacity [1, 13].

4.5 Effects on nitrogen balance and protein metabolism

Metenolone, like other anabolic-androgenic steroids, reduces nitrogen excretion and promotes positive nitrogen balance in androgen-deficient and catabolic states [2]. The mechanism involves AR-mediated upregulation of protein synthesis in skeletal muscle, suppression of glucocorticoid-induced protein catabolism (through competition for glucocorticoid response elements and through direct anti-catabolic gene regulation), and enhancement of amino acid uptake and incorporation into myofibrillar protein. These effects are the pharmacological basis for the historical clinical applications in postoperative wasting, protein-calorie malnutrition, and age-related sarcopenia.

5. Pharmacokinetics and Routes of Administration

5.1 Metenolone acetate (oral)

Absorption: Metenolone acetate is rapidly absorbed from the gastrointestinal tract after oral administration. The acetate ester and the 1-methyl modification confer sufficient resistance to first-pass hepatic metabolism to achieve systemic bioavailability, though oral bioavailability is substantially lower than that of 17- α -alkylated oral steroids. The acetate ester is hydrolyzed by esterases in the gastrointestinal mucosa, plasma, and liver to release the parent steroid metenolone [2, 3].

Distribution: Metenolone is distributed widely to tissues including skeletal muscle, bone marrow, liver, kidney, and reproductive organs. Plasma protein binding is moderate; notably, metenolone has very low affinity for sex hormone-binding globulin (SHBG), approximately 16 percent of that of testosterone and 3 percent of that of DHT [3]. This low SHBG affinity results in a higher free fraction of metenolone in plasma relative to testosterone at equivalent total concentrations. Binding to albumin accounts for the majority of plasma protein binding.

Metabolism: Metenolone undergoes hepatic metabolism by mixed-function oxidases. The principal metabolic pathways are reduction of the 3-keto group, hydroxylation at various positions on the androstane skeleton, and oxidation of the 17- β -hydroxyl to the 17-ketone. The major urinary metabolite is 3- α -hydroxy-1-methylen-5- α -androstan-17-one. Other identified metabolites include metenolone itself, 17-epimenolone, and various hydroxylated and reduced derivatives [8, 9]. Metabolites are excreted in urine predominantly as glucuronide and sulfate conjugates. Approximately 90 percent of administered radioactivity is recovered in urine and approximately 6 percent in feces [2].

Elimination: The plasma elimination half-life of oral metenolone acetate is approximately 4 to 6 hours, reflecting rapid hepatic clearance. The short half-life necessitates multiple daily administrations (typically two to three times daily) to maintain therapeutic plasma concentrations in clinical use.

5.2 Metenolone enanthate (intramuscular)

Absorption: Metenolone enanthate is administered by deep intramuscular injection, typically in the gluteal or deltoid muscle, formulated as a solution in sesame oil or castor oil. Absorption from the injection site is slow and sustained, governed by the hydrolysis rate of the enanthate (heptanoate) ester and by diffusion from the oil depot. The biological half-life of metenolone enanthate by intramuscular injection is approximately 10.5 days, with a duration of action of approximately 14 days [3, 12].

Distribution: Following ester hydrolysis and release of metenolone from the depot, distribution is similar to that described for the oral form. The prolonged absorption phase results in lower peak plasma concentrations but more sustained plasma levels compared to oral administration.

Metabolism and elimination: Identical to the oral form once the parent metenolone is released. The extended absorption phase from the intramuscular depot governs the overall pharmacokinetic profile; elimination of metenolone from plasma follows the same hepatic metabolic pathways.

5.3 Anti-doping pharmacokinetics

The urinary detection of metenolone and its metabolites is of substantial importance in anti-doping analysis. Traditional screening relies on the glucuronide-conjugated metabolite 3-alpha-hydroxy-1-methylen-5-alpha-androstan-17-one, detectable by gas chromatography-mass spectrometry for approximately 4 to 6 weeks after a single intramuscular dose of metenolone enanthate. The identification of sulfate-conjugated metabolites by Fragkaki et al. (2015) extended the analytical detection window; sulfate conjugates bind plasma proteins with higher affinity than glucuronide conjugates, increasing residence time in the body [10]. Albertsdottir et al. (2020) identified eight sulfate metabolites of metenolone, of which four were considered analytically important for long-term detection: sulfate conjugates of metenolone itself, 3-alpha-hydroxy-1-methylen-5-alpha-androstan-17-one, 3-zeta-hydroxy-1-beta-methyl-5-alpha-androstan-17-one, and 16-beta-hydroxy-1-methyl-5-alpha-androst-1-ene-3,17-dione [11]. These sulfate metabolites provided the longest detection windows.

Advances in Girard's Reagent T derivatization have enabled simultaneous detection of free, intact glucuronide, and intact sulfate metabolites by liquid chromatography-tandem mass spectrometry, further enhancing detection sensitivity and extending identification time windows [18].

5.4 Special populations

Pediatric pharmacokinetics of metenolone have not been formally characterized in contemporary studies; historical clinical use in premature infants and children employed empirical weight-based dosing. Hepatic impairment is expected to prolong metenolone clearance. Renal impairment has minimal effect on elimination, as excretion is predominantly metabolic rather than renal. Metenolone is contraindicated in pregnancy owing to the risk of fetal virilization; it is classified as FDA pregnancy category X [2].

6. Clinical Evidence Base

6.1 Anemia due to bone marrow failure

The principal clinical indication for metenolone was the treatment of anemia in bone marrow failure syndromes. Compagno et al. (1978) reported a therapeutic trial of metenolone in 19 consecutive patients with refractory anemia of various types: pancytopenia (6 patients), bicytopenia (4 patients), refractory anemia with hyperplastic marrow (5 patients), and myelofibrosis (4 patients). Remission was observed in 3 of 6 patients with pancytopenia, 2 of 4 with bicytopenia, 1 of 5 with hyperplastic marrow anemia, and 1 of 4 with myelofibrosis. The overall remission rate was approximately 37 percent. The authors noted that the prognosis for pancytopenia remained very serious and was not significantly altered by metenolone treatment [1].

The comparative position of metenolone relative to oxymetholone in aplastic anemia was favorable on safety grounds but less favorable on efficacy. Oxymetholone, as a 17-alpha-alkylated compound, produced higher response rates in aplastic anemia but at the cost of substantially greater hepatotoxicity (liver function abnormalities in 80 percent of patients versus 26 percent with non-alkylated androgens). When liver function deterioration necessitated discontinuation of oxymetholone, substitution with metenolone was employed to maintain androgen therapy with a more favorable hepatic safety profile [13, 14].

The introduction of recombinant erythropoietin and immunosuppressive therapy (antithymocyte globulin plus cyclosporine) for acquired aplastic anemia in the late 1980s and 1990s progressively displaced anabolic-androgenic steroids from frontline hematologic use. Androgens, including metenolone, remain in some treatment algorithms for refractory cases and for patients in resource-limited settings where recombinant erythropoietin and immunosuppressive agents are unavailable [17].

6.2 Catabolic and wasting conditions

Metenolone was used historically in the management of catabolic states following major surgery, prolonged infection, and chronic corticosteroid therapy. The rationale was the promotion of positive nitrogen balance and lean body mass preservation through anabolic-androgenic steroid-mediated enhancement of protein synthesis and suppression of glucocorticoid-driven catabolism. Published evidence in these indications is limited to small case series and uncontrolled observational reports from the 1960s and 1970s; no randomized controlled trial of metenolone in catabolic wasting has been published [2].

6.3 Osteoporosis

Metenolone was evaluated for osteoporosis on the basis of androgenic stimulation of osteoblast activity and bone mineral deposition. Clinical use in postmenopausal osteoporosis was limited by virilization risk in female patients and by the availability of more targeted agents (bisphosphonates, calcitonin, estrogen replacement). No contemporary clinical data support the use of metenolone in osteoporosis management.

6.4 Breast cancer

Metenolone enanthate was investigated in the 1960s and 1970s as adjunctive hormonal therapy for advanced breast cancer in postmenopausal women, on the rationale that androgenic agents could suppress estrogen-dependent tumor growth. This application has been entirely superseded by aromatase inhibitors, selective estrogen receptor modulators, and targeted therapies.

6.5 Pediatric applications

Historical use of metenolone in premature infants for promotion of weight gain and in children with growth failure was reported in the 1960s literature. Contemporary pediatric use is not supported, and the compound carries the risk of premature epiphyseal closure in growing children.

7. Reported Research Dose Ranges

7.1 Historical therapeutic doses

Metenolone acetate (oral): 10 to 50 mg per day in divided doses (two to three administrations daily). Doses at the lower end of this range (10 to 25 mg/day) were used in women, children, and elderly patients; doses of 25 to 50 mg/day were used in adult men with aplastic anemia or catabolic wasting. Treatment durations ranged from 4 weeks to several months depending on clinical response [2, 3].

Metenolone enanthate (intramuscular): 100 to 200 mg every one to two weeks by deep intramuscular injection. In aplastic anemia, treatment durations of 3 to 6 months were common, with hematologic response assessed at 8- to 12-week intervals [1, 12].

7.2 Anti-doping research doses

Anti-doping excretion studies have typically administered single doses of metenolone enanthate (50 to 200 mg intramuscular) or metenolone acetate (25 to 75 mg oral) to healthy volunteers for metabolite identification and detection window characterization [8, 9, 10, 11].

7.3 Dose considerations for research applications

Investigators acquiring metenolone for in vitro or in vivo research should consider the moderate androgen receptor binding affinity of the compound when selecting concentrations for cell-based assays (typically 1 to 100 nanomolar for AR transactivation assays) and doses for animal models (typically 1 to 10 mg/kg in rodents for anabolic endpoint studies). The absence of aromatization simplifies experimental design by eliminating the estrogenic confound present with testosterone and nandrolone.

8. Sourcing and Quality Verification

Pharmaceutical-grade metenolone is available in a limited number of jurisdictions. Primobolan Depot (metenolone enanthate 100 mg/mL in oil, 1 mL ampoules) is marketed in Spain and Turkey by Bayer. Metenolone acetate tablets (various strengths) retain limited availability in Japan and Moldova. Pharmaceutical sourcing outside these markets requires importation under research exemptions or controlled substance licenses.

Research-grade metenolone (free base and both ester forms) is supplied by multiple chemical and pharmaceutical research suppliers (Sigma-Aldrich, Cayman Chemical, Cerilliant, LGC Standards, Toronto Research Chemicals, BenchChem, and others) at greater than 98 percent purity by HPLC. Supply is in milligram to gram quantities. Certified reference standards for anti-doping and forensic applications are available from the World Anti-Doping Agency accredited reference material suppliers and from commercial reference standard providers [19].

Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity (target: greater than 98 percent)
- Mass spectrometry confirmation of molecular weight (expected $[M+H]^+$ values: 303.23 for free base, 345.24 for acetate, 415.32 for enanthate)
- Gas chromatography-mass spectrometry for metabolite profiling and purity assessment
- Nuclear magnetic resonance spectroscopy (1H -NMR and ^{13}C -NMR) for structural confirmation
- Karl Fischer or loss-on-drying analysis for residual moisture content
- Residual solvent analysis by gas chromatography

Third-party analytical verification is advisable for any lot intended for quantitative pharmacological research, given the prevalence of counterfeit and underdosed metenolone preparations in unregulated markets [19].

9. Reconstitution and Handling

9.1 Metenolone acetate (solid)

Metenolone acetate is supplied as a white to off-white crystalline powder. For in vitro research, stock solutions are prepared in dimethyl sulfoxide (DMSO) at concentrations of 10 to 100 millimolar, or in ethanol at 10 to 50 millimolar. Aqueous solubility is negligible; the compound requires organic co-solvents or cyclodextrin complexation for aqueous-based experimental systems. Stock solutions in DMSO are stable at minus 20 degrees Celsius for at least 12 months; aliquoting for single-use is recommended to avoid freeze-thaw degradation.

For in vivo rodent studies, metenolone acetate may be administered by oral gavage in a vehicle of sesame oil or corn oil, or dissolved in a propylene glycol/ethanol/saline vehicle. Subcutaneous implantation of slow-release pellets has been used in some chronic-dosing protocols.

9.2 Metenolone enanthate (oil solution)

Pharmaceutical-grade metenolone enanthate is supplied as a sterile solution in sesame oil at 100 mg/mL in glass ampoules. Research-grade bulk material is supplied as an oily liquid or semi-solid and is dissolved in sesame oil, castor oil, or grape seed oil at concentrations of 100 to 200 mg/mL for intramuscular or subcutaneous injection in animal models. The oil vehicle should be sterilized by filtration through a 0.22-micrometer polyethersulfone or polyvinylidene fluoride membrane filter prior to use. Storage at room temperature (15 to 30 degrees Celsius) with protection from light is adequate; refrigeration is not required and may increase viscosity of the oil vehicle.

9.3 Handling precautions

Metenolone and its esters are controlled substances in most jurisdictions. Investigators must hold appropriate controlled substance research licenses. Handling should follow standard laboratory safety practices for steroid hormones,

including use of nitrile gloves, avoidance of dermal exposure (metenolone is absorbed through intact skin), and appropriate waste disposal in compliance with institutional and regulatory guidelines.

10. Stack Interactions and Combinations

Metenolone interacts with other pharmacological agents through its androgen receptor agonism, its effects on hepatic metabolism, and its modulation of the hypothalamic-pituitary-gonadal axis. Investigators should consider the following interactions in research protocols and in the interpretation of polypharmacy scenarios.

Other anabolic-androgenic steroids: Concurrent use with other AR agonists (testosterone, nandrolone, oxandrolone, stanozolol, trenbolone) produces additive or synergistic effects on androgen-responsive endpoints (muscle protein synthesis, erythropoiesis, hypothalamic-pituitary suppression). The absence of aromatization makes metenolone a complementary agent to aromatizable steroids in protocols where estrogenic modulation is undesirable.

Aromatase inhibitors: Concurrent aromatase inhibitors (anastrozole, letrozole, exemestane) are pharmacologically redundant with metenolone, as metenolone does not produce estrogenic metabolites. The combination is encountered in polypharmacy contexts where metenolone is co-administered with aromatizable compounds.

Selective estrogen receptor modulators: Concurrent tamoxifen or clomiphene does not interact directly with metenolone pharmacology but may be used in post-cycle recovery protocols to restore hypothalamic-pituitary-gonadal axis function after androgen-induced suppression.

Hepatotoxic agents: Although metenolone itself has low hepatotoxicity, concurrent administration with hepatotoxic compounds (17-alpha-alkylated steroids, certain anti-tuberculosis agents, acetaminophen at supratherapeutic doses) should be approached with monitoring of hepatic function.

Anticoagulants: Anabolic-androgenic steroids potentiate the effects of coumarin anticoagulants (warfarin). Concurrent use requires increased monitoring of the international normalized ratio and potential dose reduction of the anticoagulant [2].

Insulin and oral hypoglycemic agents: Anabolic-androgenic steroids may enhance insulin sensitivity and reduce blood glucose; concurrent use with insulin or sulfonylureas may require dose adjustment to avoid hypoglycemia [2].

Corticosteroids: Concurrent corticosteroid therapy may produce additive fluid retention (sodium and water), though this effect is minimal with metenolone owing to its non-aromatizable and weakly mineralocorticoid profile. The combination has been used clinically in aplastic anemia protocols where immunosuppression and androgen-stimulated erythropoiesis are both desired [14].

Gonadotropin-releasing hormone analogs: In research contexts, concurrent GnRH agonists or antagonists produce complete gonadotropin suppression; the combination has been used in male contraception research and in prostate cancer research where controlled androgen milieu is required.

11. Adverse Events and Safety

11.1 Androgenic adverse events

The principal androgenic adverse events of metenolone are virilization symptoms in female users: acne, increased facial and body hair growth, male-pattern scalp hair loss, voice deepening (often irreversible), clitoral enlargement, and menstrual irregularity [2, 3]. In male users, androgenic adverse events include acne, acceleration of male-pattern baldness in genetically predisposed individuals, and prostatic stimulation (though the latter is less pronounced than with testosterone owing to the absence of 5-alpha-reductase amplification in prostate tissue).

11.2 Hypothalamic-pituitary-gonadal axis suppression

Metenolone, like all exogenous anabolic-androgenic steroids, suppresses endogenous gonadotropin secretion through negative feedback at the hypothalamus and anterior pituitary. In male users, this produces dose-dependent reductions in luteinizing hormone, follicle-stimulating hormone, and endogenous testosterone production, with consequent testicular atrophy, oligospermia or azospermia, and reversible infertility. Recovery of the hypothalamic-pituitary-gonadal axis after cessation of metenolone depends on dose, duration, and individual factors; recovery may require weeks to months [4, 16].

11.3 Cardiovascular and metabolic adverse events

Metenolone produces unfavorable shifts in the serum lipoprotein profile, decreasing high-density lipoprotein (HDL) cholesterol and increasing low-density lipoprotein (LDL) cholesterol. As a non-aromatizable, non-17-alpha-alkylated steroid, the magnitude of HDL suppression is generally intermediate: greater than that produced by physiological testosterone replacement (which aromatizes to estradiol and thereby partially preserves HDL through estrogenic hepatic effects) but substantially less than that produced by 17-alpha-alkylated oral steroids such as stanozolol (which suppress HDL by 33 to 71 percent) [20, 21]. The cardiovascular risk associated with chronic metenolone use is proportional to the magnitude and duration of lipoprotein perturbation.

Left ventricular hypertrophy, elevated blood pressure, and premature coronary artery disease have been reported in chronic users of anabolic-androgenic steroids as a class; specific data for metenolone are limited but the risk is considered to be present [2, 22].

11.4 Hepatic safety

Metenolone has a favorable hepatic safety profile relative to 17-alpha-alkylated oral steroids. Significant elevations in alanine aminotransferase and aspartate aminotransferase are uncommon at therapeutic doses. Cholestatic hepatitis, peliosis hepatis, and hepatic tumors (hepatocellular adenoma, hepatocellular carcinoma), which are well-documented complications of 17-alpha-alkylated steroids, have not been reported with metenolone at therapeutic doses [2, 7]. Rare cases of mild jaundice have been reported with prolonged or high-dose administration.

11.5 Psychiatric adverse events

Anabolic-androgenic steroids as a class are associated with psychiatric adverse events including irritability, aggression, mania, psychosis, hallucinations, and delusions during use, and depression, anxiety, and fatigue during withdrawal. These effects are dose-dependent and are generally considered less pronounced with milder anabolic agents such as metenolone than with more potent androgens, though individual susceptibility varies widely [2].

11.6 Other adverse events

Sodium and water retention (mild with metenolone owing to non-aromatizability), hypercalcemia (rare), insulin resistance, and premature epiphyseal closure in children and adolescents are additional class-related adverse events. Metenolone is contraindicated in patients with prostate cancer, breast cancer in males, pregnancy, and known hypersensitivity [2].

12. Comparative Assessment

This section presents a structured comparative assessment of five alternative anabolic-androgenic steroids against Primobolan (metenolone), evaluated on five competency standards: novelty of mechanism or structural advantage, effect size in the principal clinical or research indication, promising potential (current clinical trajectory and availability), side-effect profile, and overall validation. The five comparators were selected to represent the principal structural and pharmacological classes of anabolic-androgenic steroids with clinical or research applications overlapping those of metenolone.

12.1 Oxandrolone (Anavar)

Structural class: 17-alpha-alkylated dihydrotestosterone derivative; 2-oxa modification of the A-ring.

Mechanism: Androgen receptor agonist with high anabolic-to-androgenic dissociation ratio (approximately 322:24 in rodent bioassays). The 2-oxa modification reduces androgenic potency while preserving anabolic activity. The 17-alpha-methyl group confers oral bioavailability and resistance to first-pass hepatic metabolism [23].

Novelty: Moderate. The 2-oxa A-ring modification is a structurally distinctive approach to anabolic-androgenic dissociation, different from the 1-methyl/1,2-unsaturation strategy of metenolone.

Effect size: Oxandrolone has produced statistically significant improvements in lean body mass, body weight, and muscle strength in randomized controlled trials in burn patients, HIV-associated wasting, Turner syndrome, and involuntary weight loss. Effect sizes in burn recovery trials (Demling and DeSanti, 2003; Wolf et al., 2006) are substantial, with improvements in lean mass of 3 to 5 kg over 12-week treatment periods [23].

Promising potential: High. Oxandrolone is the most widely prescribed anabolic-androgenic steroid in current clinical practice, approved by the FDA for weight gain after weight loss due to surgery, chronic infections, trauma, and idiopathic

causes, and for offsetting protein catabolism associated with prolonged corticosteroid administration.

Side-effect profile: The 17-alpha-alkylation produces hepatotoxicity risk (elevated transaminases, rare cholestatic hepatitis) that metenolone does not carry. Oxandrolone produces substantial HDL suppression (up to 50 percent reduction) and LDL elevation (approximately 30 percent increase), more pronounced than metenolone. Virilization risk in females is lower than with most anabolic-androgenic steroids but present [23].

Overall validation: High. Extensive randomized controlled trial data in multiple clinical populations, current FDA approval, wide clinical availability.

Comparison to Primobolan: Oxandrolone has a stronger evidence base, current regulatory approval, and superior anabolic-to-androgenic dissociation. Metenolone has a more favorable hepatic safety profile (no 17-alpha-alkylation), milder lipoprotein perturbation, and availability as a long-acting injectable depot form (enanthate). For research applications requiring an anabolic-androgenic steroid without hepatotoxic liability or estrogenic confound, metenolone may be preferred; for clinical applications requiring established efficacy data, oxandrolone is the stronger candidate.

12.2 Nandrolone Decanoate (Deca-Durabolin)

Structural class: 19-nortestosterone derivative; C17-beta decanoate ester for intramuscular depot injection.

Mechanism: Androgen receptor agonist with high binding affinity (RBA greater than that of testosterone and metenolone). Undergoes 5-alpha-reduction to 5-alpha-dihydronandrolone, which has lower AR binding affinity than the parent compound, producing favorable anabolic-to-androgenic dissociation (myotrophic-to-androgenic ratio approximately 11:1). Aromatizable to estradiol-like metabolites at a rate approximately 20 percent that of testosterone [15, 24].

Novelty: Low. The 19-nortestosterone class is well established; nandrolone is the prototypical compound.

Effect size: Nandrolone has demonstrated significant improvements in lean body mass, hemoglobin, and bone mineral density in clinical trials in HIV-associated wasting, chronic kidney disease-associated anemia, and osteoporosis. Effect sizes

on lean mass are generally 2 to 4 kg over 12 to 24 weeks at 100 to 200 mg weekly [24].

Promising potential: Moderate. Nandrolone decanoate is approved in multiple jurisdictions for anemia of chronic renal failure and for select catabolic conditions. Active research continues in telomeropathies and age-related sarcopenia.

Side-effect profile: Nandrolone produces less HDL suppression than 17-alpha-alkylated oral steroids and less virilization than testosterone at equivalent anabolic doses. Partial aromatization produces mild estrogenic effects (fluid retention, possible gynecomastia at high doses). Progestogenic activity at the progesterone receptor may contribute to reproductive adverse effects. Hepatotoxicity is minimal (non-17-alpha-alkylated) [24].

Overall validation: High. Extensive clinical data spanning decades, current regulatory approval in multiple jurisdictions.

Comparison to Primobolan: Nandrolone has higher androgen receptor binding affinity, a larger clinical evidence base, greater anabolic potency, and current regulatory approval. Metenolone has the advantage of complete non-aromatizability (nandrolone aromatizes partially), the absence of progestogenic activity, and the availability of an oral form. For applications where estrogenic and progestogenic confounds must be eliminated, metenolone is preferred; for applications requiring maximum anabolic effect size, nandrolone is the stronger compound.

12.3 Stanozolol (Winstrol)

Structural class: 17-alpha-alkylated dihydrotestosterone derivative with a pyrazole ring fused to the A-ring.

Mechanism: Androgen receptor agonist with substantial anabolic-to-androgenic dissociation. The pyrazole fusion modifies AR binding geometry and tissue selectivity. Stanozolol also has documented effects on fibrinolysis (enhancement of tissue plasminogen activator activity and reduction of plasminogen activator inhibitor-1) that are independent of AR agonism [25].

Novelty: Moderate. The pyrazole-fused steroid nucleus and the fibrinolytic mechanism are structurally and pharmacologically distinctive.

Effect size: Stanozolol has demonstrated efficacy in hereditary angioedema (prophylaxis of attacks), aplastic anemia, and osteoporosis in clinical trials. Effect sizes in hereditary angioedema are large, with substantial reduction in attack frequency at 2 to 6 mg daily [25].

Promising potential: Moderate. Stanozolol retains FDA approval for hereditary angioedema. Clinical use in other indications has largely been supplanted.

Side-effect profile: The 17-alpha-alkylation produces significant hepatotoxicity risk (cholestatic hepatitis, peliosis hepatis). Stanozolol produces the most severe HDL suppression of the commonly used anabolic-androgenic steroids (HDL reduction of 33 to 71 percent; LDL increase of 29 percent) [20, 21]. These lipoprotein perturbations represent a substantially greater cardiovascular risk than metenolone produces.

Overall validation: Moderate. FDA-approved for hereditary angioedema; substantial clinical use history but significant safety concerns limit current application.

Comparison to Primobolan: Stanozolol has a current FDA-approved indication and documented fibrinolytic properties not shared by metenolone. Metenolone has a dramatically superior hepatic and cardiovascular safety profile owing to the absence of 17-alpha-alkylation. For research requiring an anabolic agent with minimal hepatic and lipoprotein perturbation, metenolone is strongly preferred.

12.4 Testosterone Enanthate

Structural class: Natural androgen; C17-beta enanthate ester for intramuscular depot injection.

Mechanism: The endogenous androgen and the reference compound for all anabolic-androgenic steroid pharmacology. Binds the androgen receptor with moderate affinity; undergoes 5-alpha-reduction to DHT in androgen-responsive tissues (amplifying androgenic effects) and aromatization to estradiol in adipose, hepatic, and neural tissue (producing estrogenic effects). The enanthate ester provides depot pharmacokinetics with a half-life of approximately 4.5 days [4, 16].

Novelty: None as a therapeutic agent (endogenous hormone). The reference standard for all comparative assessments.

Effect size: Testosterone replacement therapy produces large effect sizes on all androgen-dependent endpoints in hypogonadal men (muscle mass, bone density, erythropoiesis, libido, mood). At supraphysiological doses, testosterone increases lean mass and strength in a dose-dependent manner [16].

Promising potential: High. Testosterone is the foundational androgen replacement therapy and is approved in all major jurisdictions for male hypogonadism.

Side-effect profile: Aromatization to estradiol produces dose-dependent estrogenic effects (gynecomastia, fluid retention). 5-alpha-reduction amplifies androgenic effects in prostate and skin. Polycythemia is a dose-limiting adverse effect. Lipoprotein perturbation is milder than with oral 17-alpha-alkylated steroids but present [4, 16, 20].

Overall validation: Very high. The most extensively studied anabolic-androgenic steroid with comprehensive randomized controlled trial data.

Comparison to Primobolan: Testosterone is the physiological reference with a vastly larger evidence base and broader regulatory approval. Metenolone offers specific advantages for research applications requiring non-aromatizable, non-5-alpha-reducible androgen receptor agonism: the absence of estrogenic confound, the absence of DHT-amplified androgenic effects, and the availability of an oral non-hepatotoxic form. These properties make metenolone a useful research tool for dissecting AR-mediated effects from estrogen-mediated and DHT-mediated effects in experimental models.

12.5 Drostanolone Propionate (Masteron)

Structural class: 2-alpha-methyl dihydrotestosterone derivative; C17-beta propionate ester for intramuscular injection.

Mechanism: Androgen receptor agonist; non-aromatizable (DHT derivative). The 2-alpha-methyl modification confers resistance to 3-alpha-HSD metabolism, similar in principle to the 1-methyl modification of metenolone. Moderate anabolic-to-androgenic dissociation [4].

Novelty: Low. Structurally and pharmacologically the closest comparator to metenolone within this panel.

Effect size: Drostanolone was historically used in the treatment of advanced breast cancer in postmenopausal women. Clinical evidence in this indication is limited to historical trials from the 1970s and 1980s. No contemporary randomized controlled trial data exist for any indication.

Promising potential: Low. Drostanolone has been discontinued from pharmaceutical markets in most jurisdictions. It persists as a research compound and in unregulated markets.

Side-effect profile: Similar to metenolone: no hepatotoxicity (non-17-alpha-alkylated), no estrogenic effects (non-aromatizable), moderate virilization risk, moderate lipoprotein perturbation. Available only as an injectable (no oral form) [4].

Overall validation: Low. Limited clinical evidence; discontinued from most pharmaceutical markets.

Comparison to Primobolan: Drostanolone and metenolone are the most pharmacologically similar compounds in this comparator panel, sharing non-aromatizability, non-17-alpha-alkylation, DHT derivation, and moderate anabolic-to-androgenic dissociation. Metenolone has the advantage of availability as both oral and injectable forms, a marginally larger clinical evidence base, and continued pharmaceutical availability in select markets. Drostanolone has no clear pharmacological advantage over metenolone and is less well characterized.

12.6 Comparator summary

The five comparator compounds occupy distinct positions in the anabolic-androgenic steroid pharmacology space. **Oxandrolone** is the most clinically validated with current FDA approval and extensive randomized trial data, but carries hepatotoxic liability from 17-alpha-alkylation. **Nandrolone decanoate** has the highest androgen receptor binding affinity and the most favorable anabolic-to-androgenic dissociation among the injectables, but aromatizes partially and has progestogenic activity. **Stanozolol** has a unique fibrinolytic mechanism and an FDA-approved indication for hereditary angioedema, but produces the most severe hepatic and lipoprotein adverse effects. **Testosterone enanthate** is the physiological reference with the largest evidence base, but its aromatization and 5-alpha-reduction create pharmacological complexity absent from metenolone. **Drostanolone** is the closest structural analog to metenolone but has less clinical evidence and more restricted availability.

Primobolan occupies a distinctive position in this landscape as the only compound that combines all of the following properties: non-17-alpha-alkylation (favorable hepatic safety), complete non-aromatizability (no estrogenic confound), availability as both oral and injectable formulations, moderate anabolic-to-androgenic dissociation, and continued pharmaceutical availability in select markets. Its principal limitation is the small and historically dated clinical evidence base relative to oxandrolone, nandrolone, and testosterone. For research applications requiring a "clean" androgen receptor agonist without estrogenic, progestogenic, or hepatotoxic confounds, metenolone is among the most suitable compounds available. For clinical applications requiring regulatory approval and robust efficacy data, oxandrolone and nandrolone are the stronger candidates.

13. References

1. Compagno L, Luisi G, Caramella T. Treatment of refractory anemias with methenolone. *Haematologica*. 1978;63(6):489-496.
2. International Programme on Chemical Safety. Poisons Information Monograph 907: Methenolone. IPCS INTOX Databank. World Health Organization.
3. Llewellyn W. Anabolics. 11th ed. Molecular Nutrition; 2017. Metenolone acetate and metenolone enanthate compound profiles.
4. Kicman AT. Pharmacology of anabolic steroids. *Br J Pharmacol*. 2008;154(3):502-521.
5. Camerino B, Patelli B, Vercellone A. Synthesis of 1-methyl-5-alpha-androst-1-en-17-beta-ol-3-one (methenolone) and related steroids. *Gazz Chim Ital*. 1960;90:594-604.
6. Chen X. Method for preparing methenolone. Chinese Patent CN101456888A. 2009.
7. Kochakian CD, Murlin JR. The effect of male hormones on the protein and energy metabolism of castrate dogs. *J Nutr*. 1935;10:437-459; and subsequent reviews of anabolic steroid hepatotoxicity in the context of 17-alpha-alkylation versus non-alkylated compounds.
8. Schanzer W, Donike M. Metabolism of anabolic steroids in man: synthesis and use of reference substances for identification of anabolic steroid metabolites. *Anal Chim Acta*. 1993;275(1-2):23-48.
9. Masse R, Bi HG, Ayotte C, Dugal R. Identification of new urinary metabolites of methenolone acetate (Primobolan) in human by gas chromatography/mass spectrometry. *Biomed Environ Mass Spectrom*. 1990;19(3):161-174.
10. Fragkaki AG, Angelis YS, Kiouisi P, Georgakopoulos CG, Lyras E. Comparison of sulfo-conjugated and gluco-conjugated urinary metabolites for detection of methenolone misuse in doping control by LC-HRMS, GC-MS and GC-HRMS. *J Steroid Biochem Mol Biol*. 2015;153:69-78.

11. Albertsdottir AD, Holtze S, Gorelov V, Guddat S, Thomas A, Schanzer W, Thevis M. Searching for new long-term urinary metabolites of metenolone and drostanolone using gas chromatography-mass spectrometry with a focus on non-hydrolysed sulfates. *Drug Test Anal.* 2020;12(8):1128-1141.
12. Metenolone enanthate. In: Sweetman SC, ed. *Martindale: The Complete Drug Reference*. 36th ed. Pharmaceutical Press; 2009.
13. Sanchez-Medal L, Gomez-Leal A, Duarte L, Guadalupe-Rico M. Anabolic androgenic steroids in the treatment of acquired aplastic anemia. *Blood.* 1969;34(3):283-300.
14. Camitta BM, Thomas ED, Nathan DG, et al. A prospective study of androgens and bone marrow transplantation for treatment of severe aplastic anemia. *Blood.* 1979;53(3):504-514.
15. Saartok T, Dahlberg E, Gustafsson JA. Relative binding affinity of anabolic-androgenic steroids: comparison of the binding to the androgen receptors in skeletal muscle and in prostate, as well as to sex hormone-binding globulin. *Endocrinology.* 1984;114(6):2100-2106.
16. Bhasin S, Storer TW, Berman N, et al. The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. *N Engl J Med.* 1996;335(1):1-7.
17. Townsley DM, Dumitriu B, Liu D, et al. Danazol treatment for telomere diseases. *N Engl J Med.* 2016;374(20):1922-1931; and general reviews of androgen therapy in bone marrow failure.
18. Athanasiadou I, Angelis YS, Georgakopoulos CG. LC-MS/(MS) confirmatory doping control analysis of intact phase II metabolites of methenolone and mesoterolone after Girard's Reagent T derivatization. *Drug Test Anal.* 2023;15(5):504-515.
19. World Anti-Doping Agency. Technical Document TD2021MRPL: Minimum Required Performance Levels for Detection and Identification of Non-Threshold Substances. WADA; 2021.
20. Thompson PD, Cullinane EM, Sady SP, et al. Contrasting effects of testosterone and stanozolol on serum lipoprotein levels. *JAMA.* 1989;261(8):1165-1168.
21. Hartgens F, Kuipers H. Effects of androgenic-anabolic steroids in athletes. *Sports Med.* 2004;34(8):513-554.

22. Baggish AL, Weiner RB, Kanayama G, et al. Cardiovascular toxicity of illicit anabolic-androgenic steroid use. *Circulation*. 2017;135(21):1991-2002.
 23. Orr R, Fiatarone Singh M. The anabolic androgenic steroid oxandrolone in the treatment of wasting and catabolic disorders: review of efficacy and safety. *Drugs*. 2004;64(7):725-750.
 24. Pan MM, Kovac JR. Beyond testosterone cypionate: evidence behind the use of nandrolone in male health and wellness. *Transl Androl Urol*. 2016;5(2):213-219.
 25. Bork K, Bygum A, Hardt J. Benefits and risks of danazol in hereditary angioedema: a long-term survey of 118 patients. *Ann Allergy Asthma Immunol*. 2008;100(2):153-161; and pharmacology of stanozolol in hereditary angioedema.
-

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Metenolone and its esters are classified as controlled substances in most jurisdictions and are prohibited by the World Anti-Doping Agency. Investigators must hold appropriate controlled substance research licenses and should consult their local regulatory authority before any research application. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly.