

RESEARCH MONOGRAPH . COMPOUND PROFILE

Superdrol

A potent orally active 2-alpha,17-alpha-dimethylated dihydrotestosterone derivative with a high anabolic-to-androgenic dissociation ratio, originally synthesized by Syntex in 1956, never marketed pharmaceutically, and classified as a Schedule III controlled substance following its illicit distribution as an over-the-counter designer steroid supplement beginning in 2005.

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ABSTRACT

Superdrol (methasterone; 2- α ,17- α -dimethyl-5- α -androstan-17- β -ol-3-one) is a synthetic, orally active anabolic-androgenic steroid (AAS) of the 5- α -dihydrotestosterone (DHT) structural class. The compound was first synthesized by researchers at Syntex Corporation in 1956 and characterized in a 1959 publication as a potent orally active anabolic agent exhibiting only weak androgenic activity. Despite this favorable preclinical dissociation profile, methasterone was never advanced to clinical development or marketed as a prescription pharmaceutical. The compound resurfaced in 2005 when it was introduced to the United States consumer market under the trade name Superdrol, sold as an over-the-counter dietary supplement and marketed deceptively as a prohormone to circumvent the Anabolic Steroid Control Act of 1990. In preclinical rat bioassays using methyltestosterone as the reference standard, methasterone demonstrated approximately 400 percent anabolic potency and 20 percent androgenic potency, yielding a Q-ratio (anabolic-to-androgenic dissociation index) of 20, among the highest reported for any oral AAS. The compound's oral bioavailability (approximately 50 percent) is conferred by the 17- α -methyl group, which protects the steroid nucleus from hepatic first-pass metabolism but simultaneously renders the compound hepatotoxic through a mechanism common to all C17- α -alkylated androgens. Methasterone is non-aromatizable owing to its 5- α -reduced A-ring saturation, and therefore does not produce estrogenic effects such as gynecomastia or water retention. Hepatotoxicity is the principal and most serious adverse effect: a distinctive pattern of bland cholestatic liver injury,

characterized by severe hyperbilirubinemia with only modest aminotransferase elevation, has been documented in multiple case series and case reports. A comprehensive literature review of 52 reported cases identified a median presentation bilirubin of 314 micromol/L, peak bilirubin of 705 micromol/L occurring approximately 28 days after cessation, and resolution over a median of 90 days with supportive care alone; no deaths or liver transplantations were reported in the published literature. Acute kidney injury occurred in 43 percent of cases, with peak creatinine correlating with peak bilirubin. The World Anti-Doping Agency placed methasterone on its prohibited list in 2006. The United States Drug Enforcement Administration classified methasterone as a Schedule III controlled substance in January 2012 under the Controlled Substances Act, and the Designer Anabolic Steroid Control Act of 2014 further expanded regulatory authority over designer steroids of this class. Methasterone has no approved medical indication in any jurisdiction. This monograph documents the complete chemistry, synthesis, pharmacology, pharmacokinetics, hepatotoxicity profile, clinical case evidence, sourcing considerations, handling, combination interactions, adverse event signal, and a comparative assessment against five alternative oral anabolic-androgenic steroids (oxandrolone, oxymetholone, stanozolol, methyltestosterone, and epistane) on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Common name: Superdrol.

International Nonproprietary Name equivalent: Methasterone (no INN has been formally assigned, as the compound was never developed as a pharmaceutical; methasterone is the conventional pharmacological name used in the regulatory and scientific literature).

Other names: Methyldrostanolone, 2-alpha,17-alpha-dimethyl-DHT, methyl-drostanolone, 17-alpha-methyl-drostanolone.

Trade and supplement names: Superdrol (Anabolic Resources, the original 2005 supplement product), M-Drol (Competitive Edge Labs), Methadrol (various manufacturers). Multiple additional trade names have been used in the grey-market supplement industry; none represent registered pharmaceutical products [1, 2].

Chemical Abstracts Service registry number: 3381-88-2.

International Union of Pure and Applied Chemistry name: (2S,5S,8R,9S,10S,13S,14S,17S)-17-hydroxy-2,10,13,17-tetramethyl-1,2,3,4,5,6,7,8,9,11,12,14,15,16-tetradecahydrocyclopenta[a]phenanthren-3-one. The more commonly cited systematic name is 2-alpha,17-alpha-dimethyl-5-alpha-androstan-17-beta-ol-3-one.

Development codes: None. The compound was never assigned a pharmaceutical development code, as Syntex did not advance it beyond initial characterization.

1.2 Structural class and chemistry

Methasterone is a synthetic androstane steroid of the 5-alpha-dihydrotestosterone (DHT) structural class. It is formally the 2-alpha,17-alpha-dimethyl derivative of DHT, bearing two structural modifications relative to the endogenous androgen: an alpha-oriented methyl group at carbon 2 (C2) and an alpha-oriented methyl group at carbon 17 (C17). The C17-alpha-methyl group confers oral bioavailability by impeding hepatic first-pass oxidative metabolism at the 17-beta-hydroxyl position; the

C2-alpha-methyl group substantially increases anabolic potency while reducing androgenic activity, producing the high anabolic-to-androgenic dissociation ratio that characterizes the compound [1, 3].

Molecular formula: C₂₁H₃₄O₂.

Molecular weight: 318.49 g/mol (monoisotopic exact mass: 318.2559 g/mol).

Physical properties: White to off-white crystalline powder. Soluble in ethanol, methanol, and dimethyl sulfoxide; sparingly soluble in water. Melting point is approximately 192 to 196 degrees Celsius.

Stereochemistry: The compound contains seven stereocenters within the steroid nucleus. The configuration at C2 (alpha-methyl), C5 (alpha-hydrogen, conferring the 5-alpha-reduced, planar A/B ring junction), and C17 (alpha-methyl, beta-hydroxyl) are the pharmacologically critical elements. The 5-alpha reduction eliminates the delta-4,5 double bond present in testosterone and renders the A-ring fully saturated, preventing aromatization to estrogenic metabolites by the cytochrome P450 aromatase (CYP19A1) enzyme complex [1].

Relationship to drostanolone: Methasterone is the 17-alpha-methylated derivative of drostanolone (2-alpha-methyl-5-alpha-androstan-17-beta-ol-3-one), an injectable AAS marketed as Masteron (drostanolone propionate) for breast cancer therapy in some jurisdictions. The addition of the C17-alpha-methyl group to drostanolone confers oral bioavailability and substantially alters the hepatotoxicity profile [4, 5].

1.3 Synthesis

The synthesis of methasterone was first described in a 1956 Syntex Corporation research program and detailed in a 1959 journal publication [3]. The compound is accessible through several synthetic routes, all proceeding from commercially available steroid intermediates.

The classical approach proceeds from 5-alpha-androstan-3-one-17-beta-ol (dihydrotestosterone) or from the commercially available 2-alpha-methyldihydrotestosterone (drostanolone). In the drostanolone-based route, the 17-alpha-methylation is accomplished by treatment with methyl lithium or methylmagnesium bromide

(Grignard reagent) at the C17 ketone, followed by selective reduction or protection-deprotection sequences to install the 17-beta-hydroxyl configuration. The C3-ketone is retained in the final product.

In the de novo route from DHT, the C2-alpha-methylation is introduced by enolization of the A-ring ketone (formation of the 2,3-enol or enolate) followed by alkylation with methyl iodide under controlled conditions favoring alpha-face approach, typically using a sterically directing base such as lithium diisopropylamide (LDA). The C17-alpha-methylation proceeds as above. Yields for the overall sequence are in the range of 40 to 60 percent over multiple steps, with purity achieved by recrystallization from ethanol or ethyl acetate and confirmed by nuclear magnetic resonance spectroscopy, high-performance liquid chromatography, and mass spectrometry.

Industrial and grey-market synthesis of methasterone for the supplement market has been conducted principally in China; analytical quality of this material is variable and has been the subject of regulatory enforcement actions [2, 6].

2. Abstract

Methasterone (2- α ,17- α -dimethyl-5- α -androstan-17- β -ol-3-one; CAS 3381-88-2), known commercially as Superdrol, is a synthetic, orally active anabolic-androgenic steroid of the 5- α -dihydrotestosterone structural class. First synthesized by Syntex Corporation in 1956 and characterized in a 1959 publication as exhibiting high anabolic potency with weak androgenic activity, the compound was never developed pharmaceutically [3]. It entered the consumer market in 2005 when Anabolic Resources marketed it as an over-the-counter dietary supplement under the name Superdrol, exploiting a regulatory gap in the Anabolic Steroid Control Act of 1990 that had not specifically scheduled this compound [1, 2].

In castrated rat bioassays using methyltestosterone as the reference standard, methasterone demonstrated approximately 400 percent anabolic activity (measured by levator ani muscle weight) and approximately 20 percent androgenic activity (measured by ventral prostate and seminal vesicle weight), yielding a Q-ratio of 20 [3, 7]. This dissociation ratio is among the highest reported for any oral AAS and reflects the structural contribution of the C2- α -methyl group to receptor binding selectivity in anabolic target tissues versus androgenic target tissues.

The compound exerts its principal pharmacological effects through high-affinity binding to the androgen receptor (AR) in skeletal muscle and bone. Being 5- α -reduced and non-aromatizable, methasterone does not undergo conversion to estrogens or to 5- α -reduced intermediates and produces its effects exclusively through direct AR activation. The absence of estrogenic activity eliminates the risk of gynecomastia and estrogen-mediated water retention, producing the characteristic "dry" appearance associated with DHT-derived anabolic agents [1, 8].

Oral bioavailability is approximately 50 percent, conferred by the C17- α -methyl group that protects the 17- β -hydroxyl from oxidative first-pass metabolism. The plasma elimination half-life is 8 to 12 hours. Metabolism proceeds principally through hepatic hydroxylation at C2, C6, C12, and C16 positions, with glucuronidation as the major phase II conjugation pathway and sulfation as a minor pathway. Fifteen urinary metabolites have been identified, with the glucuronide conjugate G2 (18-nor-17- β -hydroxymethyl conjugate) serving as the most persistent biomarker, detectable up to 10 days post-administration [9].

The dominant clinical toxicity is hepatic. The C17-alpha-alkylation that confers oral bioavailability simultaneously renders the compound hepatotoxic through disruption of bile salt transport, producing a distinctive pattern of bland cholestatic liver injury characterized by severe hyperbilirubinemia (median peak bilirubin 705 micromol/L in published case series) with only modest aminotransferase elevation [10, 11, 12]. A comprehensive literature review of 52 published cases established the following clinical profile: median age 29 years; presentation at a median of 56 days from initiation of use; jaundice and pruritus as the most common presenting symptoms; cholestatic or mixed injury pattern in 81 percent of cases; acute kidney injury in 43 percent; resolution over approximately 90 days with supportive care; and no deaths or liver transplantations [12]. The severity of the cholestatic injury distinguishes methasterone from many other oral AAS and has generated the most substantial body of case literature of any designer steroid.

Methasterone was placed on the World Anti-Doping Agency prohibited list in 2006. The FDA issued warning letters regarding Superdrol-containing products in 2006. The DEA classified methasterone as a Schedule III controlled substance effective January 4, 2012 [7]. The Designer Anabolic Steroid Control Act of 2014 further expanded the regulatory framework for designer steroids [2]. Methasterone has no approved medical indication in any jurisdiction and is classified as a controlled substance in the United States, the United Kingdom, and multiple other jurisdictions.

3. Discovery and Development History

3.1 Origin at Syntex Corporation

Methasterone was first synthesized at Syntex Corporation in 1956 as part of a systematic structure-activity exploration of methylated androstane steroids, conducted in parallel with Syntex's broader steroid chemistry program that also produced norethindrone (the first oral contraceptive progestin), oxandrolone, and other clinically significant steroids. The synthesis was first reported in connection with research conducted to identify compounds with anti-tumor properties and favorable anabolic-to-androgenic dissociation [3].

A 1959 journal publication described the synthesis and biological characterization of methasterone, reporting it as "a potent orally active anabolic agent exhibiting only weak androgenic activity" based on standard rat bioassays of the era [3]. Despite this favorable profile, Syntex did not advance methasterone to clinical development. The historical reasons are not documented in the public literature but plausibly reflect the company's concurrent advancement of other androstane derivatives (notably oxandrolone, which offered a more favorable therapeutic index and was successfully registered) and the limited commercial incentive for additional oral AAS development in the 1960s regulatory environment.

3.2 Dormancy period (1959 to 2005)

For approximately 46 years following its initial characterization, methasterone remained an obscure entry in the steroid chemistry literature. The compound does not appear in published clinical trial registries, pharmaceutical patent applications beyond the original Syntex disclosure, or clinical pharmacology studies during this period. It was known principally to specialists in steroid structure-activity relationships through reference works such as the Vida compilation of androgen bioassay data [13].

3.3 Introduction as a designer steroid supplement (2005)

In 2005, Anabolic Resources introduced methasterone to the United States consumer market as an over-the-counter dietary supplement under the trade name Superdrol. The product was marketed as a "prohormone" or "pro-anabolic" agent, a categorization that was pharmacologically inaccurate (methasterone is a fully active AAS, not a precursor requiring metabolic conversion) but that served to position the product outside the regulatory scope of the Anabolic Steroid Control Act of 1990 and its 2004 amendment, which had not specifically listed methasterone among the scheduled substances [1, 2].

The regulatory strategy exploited the structure of the Controlled Substances Act, which at that time required specific compound-by-compound scheduling rather than broad structural class scheduling for anabolic steroids. Because methasterone had never been marketed pharmaceutically and was not listed in any pharmacopoeia, it fell outside the enumerated schedule despite being pharmacologically indistinguishable from other Schedule III anabolic steroids.

Superdrol rapidly gained popularity in the bodybuilding and strength-sport communities, driven by its potent anabolic effects, absence of estrogenic side effects, and the perception of legality. Multiple competing products containing methasterone were subsequently marketed under various trade names (M-Drol, Methadrol, and others) [2].

3.4 Regulatory response and scheduling

In late 2005, the presence of methasterone and several other designer steroids in the supplement market was brought to broad public attention through investigative journalism, including a Washington Post article that identified the compounds as undisclosed anabolic steroids being sold as dietary supplements [2].

In 2006, the United States Food and Drug Administration issued warning letters to manufacturers of Superdrol-containing products, stating that the products contained an unapproved new drug (methasterone) and were adulterated and misbranded under the Federal Food, Drug, and Cosmetic Act [2, 14].

The World Anti-Doping Agency added methasterone to its prohibited list in 2006, and subsequently updated the prohibition in 2009 under the broader category of exogenous anabolic agents [15].

On November 23, 2011, the DEA published a final rule in the Federal Register classifying methasterone (along with prostanazol) as Schedule III anabolic steroids under the Controlled Substances Act, effective January 4, 2012. The DEA determination was based on the following findings: (a) methasterone is chemically related to testosterone; (b) methasterone is pharmacologically related to testosterone based on published bioassay data demonstrating anabolic and androgenic activity; (c) methasterone is not an estrogen, progestogen, corticosteroid, or dehydroepiandrosterone; and (d) methasterone is not already controlled under the CSA [7].

The Designer Anabolic Steroid Control Act of 2014 (Public Law 113-260, signed December 18, 2014) further expanded the regulatory framework by adding methasterone and 24 other designer steroids to Schedule III by name and by granting the DEA broader authority to identify and schedule new designer anabolic steroids through structural similarity criteria rather than compound-by-compound rule-making [16].

3.5 Current status

Methasterone has no approved medical indication in any jurisdiction. It is classified as a Schedule III controlled substance in the United States. It is a controlled or prohibited substance under equivalent legislation in the United Kingdom, Canada, Australia, and most European Union member states. Illicit manufacture and distribution continue, primarily through underground laboratory production and online grey-market sales. The compound remains on the WADA prohibited list and is subject to anti-doping testing in competitive sport [15].

4. Mechanism of Action

4.1 Androgen receptor binding and transcriptional activation

Methasterone is a direct agonist of the androgen receptor (AR), a nuclear hormone receptor of the steroid receptor superfamily. The AR is expressed in virtually all human tissues but is present at highest functional density in skeletal muscle, bone, prostate, seminal vesicles, skin, liver, and the central nervous system. Upon ligand binding, the AR undergoes a conformational change, dissociates from heat-shock protein chaperones, dimerizes, translocates to the nucleus, and binds to androgen response elements (AREs) in the promoter regions of target genes, activating transcription of anabolic gene programs [8, 17].

In skeletal muscle, AR activation by methasterone stimulates transcription of genes encoding myosin heavy chain isoforms, insulin-like growth factor 1 (IGF-1), and components of the mTOR-dependent protein synthesis pathway, while simultaneously repressing catabolic pathways including the ubiquitin-proteasome system and myostatin signaling. The net effect is increased muscle protein synthesis, nitrogen retention, and lean body mass accretion [8].

The high anabolic-to-androgenic dissociation ratio of methasterone (Q-ratio of 20 in rat bioassays) reflects tissue-selective differences in AR-mediated transcription. This selectivity is attributable to several factors: differential co-regulator recruitment in muscle versus prostatic tissue; the absence of 5-alpha-reductase amplification (methasterone is already 5-alpha-reduced and therefore is not further potentiated in tissues such as prostate and skin that express high levels of 5-alpha-reductase); and the structural influence of the C2-alpha-methyl group on the conformation of the ligand-receptor complex, which may favor co-activator interactions in muscle over those in androgenic target tissues [1, 3, 17].

4.2 Non-aromatizability and estrogenic pathway

Methasterone cannot serve as a substrate for the cytochrome P450 aromatase (CYP19A1) enzyme, which converts delta-4,5 androgens to estrogens. The 5-alpha-reduction of the A-ring eliminates the delta-4,5 double bond that is the prerequisite

structural feature for aromatase activity. As a result, methasterone does not produce estrogenic metabolites, and its administration does not elevate circulating estradiol or estrone levels. This non-aromatizability eliminates the risk of gynecomastia, estrogen-mediated water retention, and estrogen-dependent fat deposition that are associated with aromatizable AAS such as testosterone and methandrostenolone [1, 8].

4.3 Hypothalamic-pituitary-gonadal axis suppression

Like all exogenous androgens, methasterone suppresses the hypothalamic-pituitary-gonadal (HPG) axis through negative feedback on gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus and on luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion from the anterior pituitary. Suppression of LH reduces endogenous testicular testosterone production; suppression of FSH impairs spermatogenesis. The duration and completeness of HPG axis suppression depend on the dose, duration of methasterone administration, and individual variability. Recovery of the HPG axis following cessation of short-duration methasterone use (4 to 6 weeks) is expected within 4 to 12 weeks in most individuals, though protracted hypogonadism has been reported following prolonged high-dose AAS use [8, 18].

4.4 Hepatotoxicity mechanism

The C17-alpha-alkylation that confers oral bioavailability simultaneously renders methasterone hepatotoxic through disruption of hepatocanicular bile transport. The established mechanism involves inhibition or downregulation of the bile salt export pump (BSEP; ABCB11) and multidrug resistance-associated protein 2 (MRP2; ABCC2), the primary canicular transporters responsible for bile salt and bilirubin conjugate secretion into the biliary canaliculus. Impairment of these transporters produces intrahepatic cholestasis: bile salts and conjugated bilirubin accumulate within hepatocytes and canaliculi, producing the characteristic "bland cholestasis" pattern observed on histopathology, with marked canicular and intrahepatocyte bilirubin pigment deposition and only mild inflammatory infiltrate [10, 11, 12, 19].

Individual susceptibility to methasterone-induced cholestasis may be modulated by genetic polymorphisms in bile salt transporter genes (ABCB11, ABCC2, ABCB4) and by concurrent exposure to other hepatotoxic substances. The severity of

cholestatic injury observed with methasterone appears to exceed that reported for several other C17-alpha-alkylated AAS at comparable doses, though controlled comparative data are not available [12, 19].

5. Pharmacokinetics

5.1 Absorption

Methasterone is absorbed from the gastrointestinal tract after oral administration. Oral bioavailability is approximately 50 percent, reflecting the protective effect of the C17-alpha-methyl group against hepatic first-pass metabolism at the 17-beta-hydroxyl position. The C17-alpha-methyl group sterically hinders oxidative metabolism by hepatic cytochrome P450 enzymes, allowing a substantial fraction of the administered dose to reach the systemic circulation in active form [1, 20].

Time to peak plasma concentration has not been precisely characterized in published human pharmacokinetic studies (owing to the compound's non-pharmaceutical status), but is estimated at 1 to 2 hours based on analogy with structurally related C17-alpha-alkylated AAS and on indirect evidence from the time course of reported effects.

5.2 Distribution

Volume of distribution has not been characterized in formal human pharmacokinetic studies. By analogy with structurally related DHT derivatives, methasterone is expected to exhibit moderate to high tissue distribution, with partitioning into skeletal muscle, liver, adipose tissue, and skin. Plasma protein binding is expected to be moderate, principally to albumin and sex hormone-binding globulin (SHBG), though methasterone (like other DHT derivatives) may have lower SHBG affinity than testosterone itself.

The compound is expected to cross the blood-brain barrier based on its lipophilicity and the known central nervous system effects of DHT-derived androgens (mood alteration, aggression, libido modulation).

5.3 Metabolism

Methasterone is metabolized principally in the liver. The metabolic profile has been characterized through in vitro studies using cryopreserved human hepatocytes and through in vivo urinary metabolite identification in human excretion

studies conducted for anti-doping purposes [4, 9].

Phase I metabolism proceeds principally through hydroxylation at positions C2, C6, C12, C16, and C20 of the steroid nucleus, catalyzed by hepatic cytochrome P450 enzymes. Reduction at the C3 ketone also occurs. Fifteen urinary metabolites have been identified, comprising seven glucuronide conjugates, six free (unconjugated) metabolites, and two sulfate conjugates [9].

Phase II metabolism is dominated by glucuronidation, which represents the major conjugation and elimination pathway. Sulfation is a minor metabolic pathway. Three metabolites (designated G4, G5, and M5 in the Zhang et al. 2016 study) were reported in human urine for the first time in 2016 [9].

The glucuronide conjugate G2 (18-nor-17-beta-hydroxymethyl glucuronide) is the most persistent urinary biomarker, detectable up to 10 days post-administration, substantially longer than the parent compound detection window of approximately 3 days. This metabolite has been proposed as the optimal biomarker for anti-doping detection of methasterone misuse [9].

Schänzer et al. (2006) and Gauthier et al. (2009) independently characterized methasterone metabolites produced by cryopreserved human hepatocytes, identifying hydroxylated and reduced metabolites consistent with the *in vivo* urinary profile [4, 21].

5.4 Elimination

The plasma elimination half-life of methasterone is 8 to 12 hours, supporting twice-daily dosing in the usage patterns reported in the bodybuilding literature [1, 20]. Elimination is predominantly renal, through urinary excretion of glucuronide-conjugated metabolites. A minor fraction undergoes biliary excretion. The parent compound is detectable in urine for approximately 3 days post-administration; the G2 glucuronide metabolite extends the detection window to approximately 10 days [9].

5.5 Routes of administration

Methasterone has been used exclusively by the oral route. No injectable, transdermal, or parenteral formulations have been developed or reported. The compound has been supplied in capsule form (typically 5 to 20 mg per capsule) in the supple-

ment and grey-market context. Sublingual administration has been reported anecdotally but has not been characterized pharmacokinetically [1, 20].

6. Preclinical Pharmacology

6.1 Anabolic and androgenic bioassays

The foundational preclinical data for methasterone derive from the Hershberger bioassay in castrated male rats, the standard preclinical assay for anabolic-androgenic dissociation at the time of the compound's initial characterization. In this assay, the anabolic endpoint is levator ani muscle weight and the androgenic endpoints are ventral prostate weight and seminal vesicle weight, each expressed relative to a reference compound (methyltestosterone) [3, 7, 13].

Methasterone demonstrated approximately 400 percent anabolic activity and approximately 20 percent androgenic activity relative to methyltestosterone, yielding a Q-ratio (anabolic-to-androgenic dissociation index) of 20. For comparison, testosterone propionate has a Q-ratio of approximately 1, oxandrolone approximately 10, stanozolol approximately 6, and nandrolone decanoate approximately 12. The Q-ratio of 20 places methasterone among the most anabolically dissociated oral AAS characterized in the classical bioassay literature [3, 7, 13].

It should be noted that rat Hershberger bioassay Q-ratios are directional indicators of tissue selectivity but do not translate quantitatively to the human anabolic-to-androgenic experience. Species differences in AR co-regulator expression, 5-alpha-reductase distribution, and steroid metabolism limit the predictive precision of rat bioassay data for human dose-response. The very high Q-ratio of methasterone is, however, consistent with the reported human experience of potent muscle-building effects with relatively low virilization at typical usage doses [8].

6.2 Anti-tumor activity

The original Syntex research program that produced methasterone was conducted in part to identify compounds with anti-tumor properties. The 1956 to 1959 characterization included screening for anti-tumor activity in standard rodent tumor models of the era. Published data on this activity are limited; the compound was not advanced in the anti-tumor context, and the subsequent history has been dominated by its anabolic profile rather than any oncology application [3].

6.3 Hepatotoxicity in preclinical models

Formal preclinical hepatotoxicity studies of methasterone have not been published in the peer-reviewed literature. The hepatotoxicity of C17- α -alkylated AAS as a class is well established from decades of clinical experience with methyltestosterone, oxymetholone, stanozolol, and methandrostenolone, and the mechanism (bile salt transporter inhibition producing bland cholestasis) is conserved across the class. The apparently increased severity of cholestatic injury with methasterone relative to some other C17- α -alkylated AAS may reflect dose, duration of exposure, or compound-specific potency at the bile salt transporter level, but controlled preclinical comparisons are not available [19].

7. Clinical Evidence Base

7.1 Absence of registration trials

Methasterone has never been the subject of formal clinical trials for any therapeutic indication. No Phase 1, Phase 2, or Phase 3 clinical trial data exist. The compound has no approved medical indication in any jurisdiction. The clinical evidence base therefore consists entirely of case reports and case series documenting adverse effects (principally hepatotoxicity) in individuals who self-administered the compound, plus the limited pharmacokinetic and metabolic characterization conducted for anti-doping purposes [9, 10, 11, 12].

7.2 Hepatotoxicity case literature

The hepatotoxicity of methasterone is documented in a substantial and consistent case literature spanning 2006 to the present. The principal publications are summarized below.

Jasiurkowski et al. (2006): First published case report. A case of cholestatic jaundice and IgA nephropathy attributed to Superdrol use, published in the American Journal of Gastroenterology. The patient was a young male who developed jaundice following use of an over-the-counter supplement marketed as having no hormonal activity. The case was notable for the concurrent development of IgA nephropathy, a renal complication not previously reported in association with AAS use [14].

Shah et al. (2008): Case series of five patients. Published in Clinical Gastroenterology and Hepatology. Five previously healthy male patients who used methasterone developed jaundice approximately 2 weeks after discontinuation. Bilirubin levels peaked within 2 to 3 weeks of presentation (one patient reached a peak total bilirubin of 41.8 mg/dL with direct bilirubin of 28.2 mg/dL). Liver biopsies demonstrated cholestasis with minimal inflammation. All five cases resolved within approximately 12 weeks of presentation with supportive care and no residual hepatic dysfunction [10].

Nasr and Ahmad (2009): Case report of severe cholestasis and renal failure in a patient who used Superdrol. Published in the Journal of Clinical Gastroenterology. The case documented concurrent hepatic and renal injury with eventual full recovery [22].

Abeles et al. (2020): Comprehensive review and two new cases. Published in BMJ Open Gastroenterology. The authors presented two detailed cases and conducted a systematic review of 50 additional cases from the published literature. Case 1: 30-year-old male; 6 weeks of methyltestosterone use; peak bilirubin 633 micromol/L; liver biopsy showing fibrous expansion of portal tracts with marked canalicular cholestasis and mild inflammation; prednisolone-responsive improvement; normalization over 2 months. Case 2: 36-year-old male; 2 months of methyltestosterone use; peak bilirubin 768 micromol/L; liver biopsy showing mild focal lymphocytic infiltration with marked cholestasis; prednisolone-responsive improvement; normalization over 2.5 months [12].

Aggregate literature review findings (Abeles et al. 2020, 52 cases): Median age 29 years (IQR 25 to 41). All male. Methyltestosterone was the most common causative agent, used alone or in combination. Median time to presentation: 56 days (IQR 42 to 72) from initiation. Most common presenting symptoms: jaundice and pruritus with constitutional symptoms. Biochemical profile at presentation: median bilirubin 314 micromol/L (IQR 174 to 590), median ALT 125 IU/L (IQR 85 to 233), median ALP 190 IU/L (IQR 123 to 287). Peak bilirubin: 705 micromol/L (IQR 549 to 872), occurring approximately 28 days after cessation of use. Liver injury pattern: cholestatic or mixed in 81 percent, hepatocellular in 19 percent. Liver biopsy histology: predominantly marked canalicular and intrahepatocyte cholestasis with mild or moderate inflammation. Acute kidney injury: 43 percent of patients, with peak creatinine 225 micromol/L (IQR 174 to 406); peak bilirubin greater than 440 micromol/L predicted development of AKI. RUCAM causality scores: probable in 38 percent, possible in 60 percent, unlikely in 2 percent. Treatment: variable (supportive care, ursodeoxycholic acid, corticosteroids, antihistamines for pruritus). Resolution: median 90 days (IQR 75 to 120) from peak bilirubin. Outcomes: no deaths, no liver transplantations. Fifty percent of cases met Hy's law criteria (elevated bilirubin with hepatocellular injury markers), but the excellent prognosis distinguished methasterone cholestasis from the Hy's law paradigm for idiosyncratic drug-induced liver injury [12].

7.3 Renal injury

Acute kidney injury has been documented as a concurrent adverse effect in methasterone hepatotoxicity cases. The Abeles et al. (2020) literature review identified AKI in 43 percent of the 52 reviewed cases, with a statistically significant correlation between peak bilirubin and peak creatinine. The mechanism is presumed to be bile salt nephrotoxicity (bile cast nephropathy) secondary to the extreme hyperbilirubinemia, a recognized complication of severe cholestatic liver disease from any cause. IgA nephropathy was reported in one case (Jasiurkowski et al. 2006) and may represent an independent immune-mediated renal injury [12, 14].

7.4 Usage patterns in the non-medical literature

In the bodybuilding and performance-enhancement literature (online forums, grey-market product guides, coaching protocols), methasterone has been used at oral doses of 10 to 40 mg daily for cycle durations of 3 to 6 weeks. The most commonly reported dosing protocol is 10 to 20 mg daily for 4 weeks, often in combination with injectable testosterone as a "kickstart" compound at the beginning of a longer AAS cycle. Higher doses (30 to 40 mg daily) and longer durations (6 or more weeks) are associated with substantially increased hepatotoxicity risk [1, 20].

8. Sourcing and Quality Verification

Methasterone is classified as a Schedule III controlled substance in the United States and is a controlled or prohibited substance in most jurisdictions. It has no approved medical indication and is not manufactured by any licensed pharmaceutical company.

Research-grade methasterone is supplied by chemical research suppliers (Sigma-Aldrich, Cayman Chemical, Cerilliant, Toronto Research Chemicals, LGC Standards) as a certified reference standard for anti-doping and forensic analytical applications. Purity is typically greater than 98 percent by HPLC. Supply is in milligram quantities (1 to 100 mg) as the free steroid; the compound is not supplied as a salt. Pricing for certified reference standard material is moderate to high (approximately \$100 to \$500 per 10 mg at the time of monograph preparation), reflecting the controlled-substance regulatory overhead [6, 23].

Grey-market and underground laboratory sources supply methasterone in capsule form (typically 5 to 20 mg per capsule) for non-medical use. Quality control from these sources is unreliable. Published analytical testing of grey-market AAS products has demonstrated frequent discrepancies between label claims and actual content, including substitution of different compounds, under-dosing, over-dosing, and contamination with other steroids or non-steroidal substances [6].

Investigators acquiring methasterone for legitimate research purposes should confirm compound identity and purity on every lot through:

- High-performance liquid chromatography area-percent purity (greater than 98 percent)
- Mass spectrometry confirmation of molecular weight (319.2637 for the protonated species $[M+H]^+$)
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) for structural confirmation
- Residual solvent analysis by gas chromatography
- Comparison against certified reference standards from accredited suppliers

Third-party analytical laboratories specializing in steroid analysis (Janoshik Analytical, Simec AG, Anabolic Lab) provide independent confirmation of vendor certificates of analysis. Given the controlled-substance status, all acquisition, possession, and use of methasterone for research purposes must comply with applicable federal, state, and institutional regulatory requirements, including DEA Schedule III registration where applicable [6, 23].

9. Reconstitution and Handling

Methasterone is supplied as a white to off-white crystalline powder (research-grade reference standard) or as capsules (grey-market product). The compound is stable as a solid at room temperature and at refrigerated conditions (2 to 8 degrees Celsius). Long-term storage should be at minus 20 degrees Celsius or below for maximum stability.

For in vitro research applications, stock solutions are typically prepared in dimethyl sulfoxide (DMSO) at concentrations of 10 to 100 mM, given the compound's limited aqueous solubility. DMSO stock solutions are stable at minus 20 degrees Celsius for at least 6 months. Working solutions for cell-based assays are prepared by dilution of the DMSO stock into culture medium, with final DMSO concentration maintained below 0.1 percent (v/v) to minimize solvent cytotoxicity.

For analytical reference applications, solutions are prepared in methanol or acetonitrile at concentrations of 0.1 to 1 mg/mL and are stable at 2 to 8 degrees Celsius for at least 30 days.

The compound is not formulated for parenteral administration. No injectable, transdermal, or intranasal preparations have been developed. The oral route (capsule) is the only route reported in the published use literature.

Light protection is not strictly required but is reasonable practice for long-term storage. The compound is chemically stable under standard laboratory handling conditions and is not hygroscopic, air-sensitive, or photolabile at typical exposure levels.

10. Stack Interactions and Combinations

Methasterone has been used in the non-medical performance-enhancement context in combination with numerous other compounds. The following interaction considerations are drawn from the pharmacological literature and from the published adverse-event case reports.

Aromatizable androgens (testosterone, methandrostenolone, boldenone): The combination of methasterone with aromatizable AAS is common in the non-medical use pattern, where methasterone provides a "dry" anabolic effect while the aromatizable component provides the androgenic and estrogenic support required to maintain libido, mood, and joint lubrication. No pharmacokinetic interaction is expected; the pharmacodynamic interaction is additive anabolic and additive HPG axis suppression [8, 20].

Other C17-alpha-alkylated oral AAS (oxymetholone, stanozolol, methandrostenolone, oxandrolone): The combination of two C17-alpha-alkylated oral AAS produces additive hepatotoxic stress. Multiple published case reports of methasterone hepatotoxicity document concurrent use of additional oral AAS, complicating causality attribution. The combination is strongly contraindicated from a hepatotoxicity perspective [12, 19].

Hepatotoxic supplements and drugs (acetaminophen, alcohol, kava, certain herbal preparations): Concurrent exposure to additional hepatotoxic agents during methasterone use is expected to increase the risk and severity of cholestatic liver injury. Several published case reports note concurrent alcohol consumption or supplement use as confounding factors [12].

Aromatase inhibitors (anastrozole, letrozole, exemestane): Because methasterone is non-aromatizable, aromatase inhibitors have no direct effect on methasterone pharmacology. However, in combination stacks where methasterone is used alongside aromatizable AAS, aromatase inhibitors are commonly co-administered to control estrogenic effects. No pharmacokinetic interaction with methasterone is expected.

Selective estrogen receptor modulators (tamoxifen, clomiphene): These are commonly used in post-cycle therapy (PCT) protocols following AAS cycles that include methasterone. No pharmacokinetic interaction with methasterone is expected. The pharmacodynamic rationale is stimulation of HPG axis recovery through estrogen receptor antagonism at the hypothalamic-pituitary level [8].

CYP450 inhibitors and inducers: The specific CYP450 isoforms responsible for methasterone hydroxylation have not been definitively characterized. By analogy with structurally related C17-alpha-alkylated AAS, CYP3A4 is the likely principal metabolizing enzyme. Strong CYP3A4 inhibitors (ketoconazole, itraconazole, ritonavir, clarithromycin) could increase methasterone exposure and hepatotoxic risk; CYP3A4 inducers (rifampin, carbamazepine, phenytoin, St. John's wort) could reduce exposure.

11. Adverse Events and Safety Signal

11.1 Hepatotoxicity

Hepatotoxicity is the dominant and most clinically significant adverse effect of methasterone. The pattern is bland cholestatic liver injury characterized by severe hyperbilirubinemia with modest aminotransferase elevation, distinct from the hepatocellular necrosis pattern observed with acetaminophen or idiosyncratic drug reactions. The clinical presentation, biochemical profile, histopathology, and outcomes are detailed in Section 7.2.

Key clinical features:

- Onset: typically 4 to 10 weeks after initiation of use (median 56 days)
- Paradoxical worsening: bilirubin continues to rise for approximately 2 to 4 weeks after discontinuation of the compound, peaking at a median of 28 days post-cessation
- Severity: median peak bilirubin 705 micromol/L (approximately 41 mg/dL), representing profound cholestasis
- Histopathology: marked canalicular and intrahepatocyte cholestasis with mild inflammatory infiltrate
- Recovery: median 90 days from peak bilirubin, with complete resolution in all published cases
- Mortality: zero deaths and zero liver transplantations in 52 published cases [10, 11, 12]

11.2 Renal injury

Acute kidney injury has been documented in 43 percent of published methasterone hepatotoxicity cases. The mechanism is principally bile cast nephropathy (accumulation of bile salts in renal tubules during severe cholestasis). Peak creatinine correlates with peak bilirubin; a bilirubin threshold of approximately 440 micromol/L predicts AKI development. Recovery is expected with resolution of the cholestatic injury. One case of IgA nephropathy has been reported [12, 14].

11.3 Cardiovascular effects

Methasterone, like all AAS, produces adverse cardiovascular effects including: suppression of high-density lipoprotein (HDL) cholesterol (the most sensitive lipid marker of AAS use, with reductions of 50 percent or greater reported with oral AAS); elevation of low-density lipoprotein (LDL) cholesterol; elevation of blood pressure; left ventricular hypertrophy with chronic use; and increased thrombotic risk through stimulation of erythropoiesis and platelet aggregation. These effects are class effects of AAS and are not specific to methasterone, though the hepatic first-pass exposure of oral C17-alpha-alkylated AAS produces more pronounced HDL suppression than injectable AAS at comparable androgenic doses [8, 18].

11.4 Endocrine effects

Suppression of the hypothalamic-pituitary-gonadal axis produces: reduced endogenous testosterone production; reduced spermatogenesis and potential infertility during use; testicular atrophy with prolonged use; and potential for prolonged hypogonadism following cessation (particularly after extended high-dose use). Because methasterone is non-aromatizable, it does not produce gynecomastia directly, though gynecomastia can occur during the post-cycle recovery period when the estrogen-to-androgen ratio is transiently elevated as endogenous production recovers [8, 18].

11.5 Dermatologic effects

The C2-alpha-methyl group and 5-alpha-reduced A-ring produce DHT-like effects on skin and hair follicles, including: acne (principally on the back, shoulders, and face); acceleration of androgenetic alopecia in genetically predisposed individuals; and oily skin. These effects are less pronounced than with non-dissociated androgens owing to the low androgenic rating, but are reported at typical usage doses [1, 8].

11.6 Psychological and neurobehavioral effects

AAS use, including methasterone, is associated with mood alterations including increased aggression, irritability, and in some individuals anxiety or depressive symptoms during use or upon cessation. These effects are class effects mediated by

AR activation in the central nervous system and by HPG axis perturbation. Dose-response data specific to methasterone are not available [8, 18].

11.7 Pregnancy and lactation

No data exist on methasterone use in pregnancy or lactation. All exogenous androgens are contraindicated in pregnancy owing to the risk of virilization of female fetuses. Methasterone should be considered absolutely contraindicated in pregnancy.

12. Comparative Assessment

This section presents a structured comparative assessment of five alternative oral anabolic-androgenic steroids against methasterone (Superdrol), evaluated on five competency standards: anabolic potency, androgenic dissociation, hepatotoxicity, clinical validation, and overall risk-benefit profile. The five comparators were selected as the principal oral AAS with substantial clinical or research-community use history and published pharmacological and toxicological data.

12.1 Oxandrolone (Anavar)

Structural class: 17-alpha-alkylated 2-oxa-5-alpha-androstan-3-one derivative. The replacement of the C2 carbon with oxygen (the 2-oxa modification) is the distinctive structural feature.

Anabolic potency: Q-ratio approximately 10 in rat bioassays (anabolic activity approximately 322 to 633 percent of methyltestosterone, androgenic activity approximately 24 percent). Lower than methasterone's Q-ratio of 20 but still highly dissociated [13, 24].

Androgenic dissociation: High. The 2-oxa modification reduces androgenic activity similarly to methasterone's 2-alpha-methyl modification, though by a different structural mechanism.

Hepatotoxicity: Mild to moderate at therapeutic doses (2.5 to 20 mg daily). Oxandrolone is generally considered the least hepatotoxic of the C17-alpha-alkylated AAS, with published clinical trials at doses of 20 mg daily for 12 weeks demonstrating only modest transaminase elevations. Cases of serious cholestatic hepatitis are rare at therapeutic doses but have been reported at higher doses used in the non-medical context. Substantially less hepatotoxic than methasterone at equi-effective anabolic doses [24, 25].

Clinical validation: Oxandrolone is FDA-approved for adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infections, and severe trauma, and for relief of bone pain accompanying osteoporosis. It has

extensive clinical trial data in burn recovery, HIV-associated wasting, Turner syndrome growth promotion, and constitutional delay of growth. It is the most clinically validated oral AAS in current pharmaceutical use [24, 25].

Overall risk-benefit: Favorable. Oxandrolone offers a substantially better hepatotoxicity profile than methasterone, extensive clinical validation, and maintained pharmaceutical manufacturing quality. Anabolic potency is lower than methasterone in preclinical assays, but the safety margin is wider.

Comparison to methasterone: Methasterone has higher anabolic potency and a higher Q-ratio in preclinical bioassays. Oxandrolone has vastly superior clinical validation, a milder hepatotoxicity profile, and the advantage of pharmaceutical-grade availability as a registered medicine. Oxandrolone is the clear preferred choice when a clinically validated oral anabolic agent is required.

12.2 Oxymetholone (Anadrol)

Structural class: 17-alpha-alkylated 2-hydroxymethylene-5-alpha-androstan-3-one derivative. The 2-hydroxymethylene group is the distinctive structural modification.

Anabolic potency: High. Q-ratio approximately 9 in rat bioassays. Oxymetholone produces dramatic weight gain (principally through both lean mass accretion and substantial water retention) at the therapeutic dose of 1 to 5 mg/kg daily [13, 26].

Androgenic dissociation: Moderate. Androgenic effects are more pronounced than with methasterone or oxandrolone, with virilization a dose-limiting concern in female patients.

Hepatotoxicity: Severe. Oxymetholone is associated with cholestatic hepatitis, peliosis hepatis (blood-filled hepatic cysts), and hepatocellular carcinoma on prolonged use. The hepatotoxicity profile is among the most severe of the C17-alpha-alkylated AAS. Published case reports document fatal hepatic complications. The hepatotoxicity burden is comparable to or greater than that of methasterone, though the patterns differ (peliosis hepatis and hepatocellular carcinoma are more characteristic of prolonged oxymetholone use, while acute bland cholestasis is more characteristic of methasterone) [19, 26].

Clinical validation: FDA-approved for the treatment of anemias caused by deficient red cell production, including aplastic anemia, myelofibrosis, and hypoplastic anemias. Clinical use has been substantially reduced by the availability of erythropoiesis-stimulating agents (epoetin alfa, darbepoetin). Clinical trial data are available but limited in scope relative to oxandrolone [26].

Overall risk-benefit: Unfavorable for most applications. High hepatotoxicity, moderate androgenic dissociation, and substantial water retention limit the utility. The clinical niche (refractory anemia) is narrow and largely superseded by safer alternatives.

Comparison to methasterone: Both compounds produce severe hepatotoxicity. Oxymetholone produces substantially more water retention and androgenic side effects. Methasterone has a higher Q-ratio and a "drier" anabolic profile. Oxymetholone has the advantage of FDA approval and pharmaceutical-grade availability. Neither compound offers an acceptable safety profile for elective anabolic use.

12.3 Stanozolol (Winstrol)

Structural class: 17-alpha-alkylated pyrazol-fused 5-alpha-androstane derivative. The pyrazole ring fused to the A-ring is the distinctive structural feature.

Anabolic potency: High. Q-ratio approximately 6 in rat bioassays (anabolic activity approximately 320 percent of methyltestosterone, androgenic activity approximately 30 percent). Lower Q-ratio than methasterone [13, 27].

Androgenic dissociation: Moderate to high. Androgenic effects are more pronounced than methasterone but less than testosterone.

Hepatotoxicity: Moderate to severe. Stanozolol produces cholestatic hepatitis and has been associated with peliosis hepatis on prolonged use. The hepatotoxicity profile is intermediate between oxandrolone (mild) and oxymetholone (severe). Published case reports of cholestatic jaundice exist but are less numerous and generally less severe than the methasterone case literature [19, 27].

Clinical validation: Stanozolol has been used clinically for hereditary angioedema prophylaxis (where it stimulates hepatic synthesis of C1-esterase inhibitor) and historically for treatment of anemia and osteoporosis. The hereditary

angioedema indication remains current in some jurisdictions. Clinical data are available but narrower in scope than oxandrolone [27].

Overall risk-benefit: Moderate. The hereditary angioedema indication provides a specific clinical niche. Hepatotoxicity is significant but generally less severe than methasterone at common use doses.

Comparison to methasterone: Methasterone has a higher Q-ratio and a more potent anabolic profile per milligram. Stanozolol has clinical validation for hereditary angioedema, a longer track record, and a generally (though not uniformly) less severe hepatotoxicity profile. Stanozolol is available in both oral and injectable (aqueous suspension) forms; the injectable form avoids hepatic first-pass exposure.

12.4 Methyltestosterone

Structural class: 17-alpha-methylated testosterone. The simplest of the C17-alpha-alkylated AAS, differing from testosterone only by the addition of the 17-alpha-methyl group.

Anabolic potency: The reference standard (Q-ratio = 1 by definition in the Hersherberger bioassay). Anabolic and androgenic potencies are approximately equal, with no meaningful tissue dissociation [13].

Androgenic dissociation: None. Methyltestosterone is fully androgenic and fully aromatizable, producing the complete spectrum of androgenic and estrogenic effects.

Hepatotoxicity: Moderate. Cholestatic hepatitis has been reported. The hepatotoxicity profile is generally considered moderate within the C17-alpha-alkylated AAS class, less severe than oxymetholone or methasterone at common clinical doses (10 to 50 mg daily) [19].

Clinical validation: Historically approved for male hypogonadism and delayed puberty. Clinical use has been largely supplanted by transdermal and injectable testosterone formulations, which avoid hepatic first-pass exposure and the associated hepatotoxicity. Methyltestosterone remains available in some combination products (with esterified estrogens for menopausal vasomotor symptoms) in some jurisdictions [28].

Overall risk-benefit: Unfavorable for anabolic applications. The absence of anabolic-androgenic dissociation means that anabolic doses produce full androgenic and estrogenic effects. The compound is obsolescent for most indications.

Comparison to methasterone: Methasterone has a dramatically higher Q-ratio (20 versus 1), is non-aromatizable, and produces a qualitatively different (more anabolic, less androgenic) effect profile. Methyltestosterone has the advantage of pharmaceutical availability and some remaining clinical indications. The two compounds represent opposite ends of the anabolic-androgenic dissociation spectrum among oral AAS.

12.5 Epistane (2-alpha,3-alpha-epithio-17-alpha-methyl-5-alpha-androstan-17-beta-ol)

Structural class: 17-alpha-alkylated 2,3-epithio-5-alpha-androstane derivative. The 2,3-epithio (sulfur bridge) group across the A-ring is the distinctive structural feature. Also known as methepitiostane or Havoc.

Anabolic potency: Moderate to high. Preclinical Q-ratio data are limited, as the compound was characterized principally in the designer steroid era rather than in the classical Hershberger bioassay literature. User reports suggest moderate anabolic potency with low androgenic activity, qualitatively similar to but less potent than methasterone [29].

Androgenic dissociation: High. The epithio group produces substantial anabolic-androgenic dissociation.

Hepatotoxicity: Moderate. As a C17-alpha-alkylated AAS, epistane produces hepatotoxic stress, but published case reports of severe cholestatic injury are substantially less frequent than with methasterone. The apparently lower hepatotoxicity may reflect lower potency (requiring shorter cycles at lower doses for equivalent anabolic effect), differences in bile salt transporter inhibition, or both [29].

Clinical validation: None. Epistane has never been developed as a pharmaceutical and has no clinical trial data. Like methasterone, it was marketed as a designer steroid supplement and is now a controlled substance in the United States under the Designer Anabolic Steroid Control Act of 2014 [16, 29].

Overall risk-benefit: Poor validation but moderate empirical safety profile relative to methasterone. The absence of any clinical data and the controlled-substance status limit any assessment.

Comparison to methasterone: Both are designer steroids of the DHT structural class with no pharmaceutical pedigree. Methasterone appears more potent per milligram but also more hepatotoxic. Epistane offers a less potent but apparently safer (in terms of hepatotoxicity severity) alternative within the same regulatory and quality-control limitations.

12.6 Comparator summary

The five comparators span the range of oral AAS from the clinically validated (oxandrolone, with FDA approval and extensive trial data) to the designer and unvalidated (epistane, with no clinical data). **Oxandrolone** represents the gold standard for risk-benefit among oral AAS: moderate anabolic potency, high dissociation, mild hepatotoxicity, and extensive clinical validation. **Oxymetholone** provides the highest raw mass-building potency but at the cost of severe hepatotoxicity, water retention, and androgenic effects. **Stanozolol** occupies an intermediate position with a specific clinical niche in hereditary angioedema. **Methyltestosterone** is the reference standard but is pharmacologically undissociated and clinically obsolescent. **Epistane** is the closest structural and pharmacological analog to methasterone among the designer steroids, with apparently lower potency and lower hepatotoxicity.

Methasterone occupies a distinctive position: it has the highest Q-ratio of any characterized oral AAS, it is non-aromatizable, and it produces potent lean-tissue anabolic effects without estrogenic side effects. These pharmacological attributes are offset by the most severe and best-documented hepatotoxicity profile in the designer steroid class, the complete absence of clinical validation, the absence of pharmaceutical-grade supply, and the Schedule III controlled-substance status. No clinical context exists in which methasterone would be preferred over oxandrolone (for validated anabolic indications) or over injectable testosterone (for androgen replacement). The compound's persistence in the non-medical performance-enhancement context reflects its potent anabolic effects and its historical availability as an over-the-counter supplement, rather than any evidence-based advantage over safer alternatives.

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