CLINICAL MONOGRAPH · HORMONE OPTIMIZATION

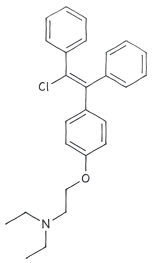
Clomiphene & Enclomiphene

Selective estrogen receptor modulator for fertility and HRT-alternative pathways

Clomiphene (sold as Clomid or Serophene) is an oral pill that has been used since the 1960s to help women with anovulatory infertility, most commonly women with polycystic ovary syndrome (PCOS), release an egg [asrm2013clomid]. It works by tricking the brain into thinking estrogen is low, which raises the hormones (FSH and LH) that drive ovulation.

The same brain-pituitary-gonadal mechanism that raises FSH and LH in women also raises LH and FSH in men. So for the past two decades, urologists and endocrinologists have used clomiphene off-label at lower doses (often 12.5, 25 mg every other day or daily) for men with secondary hypogonadism, low testosterone caused by a sluggish pituitary signal, particularly when the patient wants to preserve fertility (because exogenous testosterone shuts down sperm production) [moskovic2012; earl2019enclo].

Enclomiphene is the more active half of the clomiphene molecule, the pure antagonist that delivers most of the LH/FSH-raising effect. Repros Therapeutics tried to bring an enclomiphene-only product (Androxal) to FDA approval as a TRT alternative; the FDA did not approve it. RonanRx can compound clomiphene at non-standard strengths and as enclomiphene-isolate preparations on a patient-specific prescription when the manufactured 50 mg tablet does not fit the patient's clinical need [homburg2005; katz2012].



EVIDENCE POSTURE FDA APPROVED WELL STUDIED REVIEWED **2026-05-11**

State-licensed 503A | Pharmacist reviewed | Doctor led | Cold-chain ready | Patient choice preserved

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FOR CLINICIANS

Clomiphene citrate is a non-steroidal triphenylethylene SERM marketed as Clomid and Serophene (50 mg oral tablet) for ovulation induction in selected anovulatory women, the original 1967 FDA indication [asrm2013clomid] [katz2012; moskovic2012]. Mechanistically, clomiphene is a racemic 38:62 mixture of zuclomiphene (cis-isomer, mixed agonist/antagonist with a long terminal half-life) and enclomiphene (trans-isomer, pure ER antagonist with a short half-life and the dominant LH/FSH-raising effect) [mikkelson1986, ghobadi2009, adashi1984]. ER antagonism at hypothalamic estrogen receptors disinhibits GnRH pulsatility, raising pituitary LH and FSH; in anovulatory women this triggers folliculogenesis and ovulation, and in men it raises endogenous testosterone via the testicular axis with preservation of spermatogenesis [soares2018obesity; pelusi2022obesity].

Pivotal female-infertility evidence: PPCOS-I [legro2007ppcosi] compared clomiphene vs metformin vs combination in PCOS and demonstrated superior live-birth rates with clomiphene over metformin; PPCOS-II [legro2014ppcosii] subsequently demonstrated higher live-birth rates with letrozole vs clomiphene in PCOS, reorienting first-line ovulation induction toward letrozole while preserving clomiphene's established role [asrm2013clomid]. Cochrane evidence [brown2009cochrane] confirms ovulation and pregnancy benefit vs placebo in PCOS. Multi-gestation rate is the principal trade-off: approximately 5, 10% twin pregnancies in clomiphene-treated cycles, with higher-order multiples rare [bourdon2025]. Endometrial thinning from the cis-isomer's antiestrogenic effect on the uterus is a well-characterized but generally modest pharmacodynamic limitation [gonen1990endo, quaas2021endo] [krzastek2019].

Off-label male hypogonadism evidence: Guay 1995 [guay1995] reported the first systematic raising of endogenous testosterone in impotent men with secondary hypogonadism; subsequent case-series and observational evidence demonstrated durable testosterone increases (typically 200, 400 ng/dL baseline rising to 500, 800 ng/dL on 12.5, 25 mg/day or every-other-day dosing) with preservation of spermatogenesis, and a long-term safety profile (Krzastek 5-year follow-up) consistent with the short-term studies [earl2019enclo] [shabsigh2005]. The dedicated enclomiphene program, Kaminetsky 2013 phase 2 [kaminetsky2013enclo], Wiehle 2013 BJU pharmacodynamic study [wiehle2013enclo], Wiehle 2014 phase 2 head-to-head vs AndroGel [wiehle2014enclo], demonstrated testosterone restoration without the suppression of spermatogenesis that exogenous testosterone causes [mcbride2016recovery]; despite this evidence Androxal failed FDA review and no enclomiphene-isolated product is commercially available. AUA testosterone deficiency guideline [mulhall2018aua] and AUA/ASRM male infertility guideline [schlegel2021aua1, schlegel2021aua2] cite clomiphene/enclomiphene as evidence-based fertility-preserving alternatives for men who would otherwise receive testosterone replacement therapy.

Compounded clomiphene at non-standard strengths (12.5 mg, 25 mg, capsules vs tablet, troche or sublingual forms) and enclomiphene-isolate preparations occupy a legitimate, long-standing 503A niche distinct from copy-of-approved-product compounding: there is no manufactured 12.5 mg or 25 mg male-dosing tablet, no manufactured troche, and no FDA-approved enclomiphene-isolate product [homburg2005; fda503a; fda_essentially_a_copy]. Pharmacist review confirms patient-specific clinical rationale for any deviation from the manufactured 50 mg tablet. Pregnancy category X applies once pregnancy is confirmed; visual disturbances [purvin1995visual] are an uncommon but characteristic adverse event warranting discontinuation.

Why Personalized Clomiphene & Enclomiphene

The 50 mg clomiphene tablet that FDA reviewed in 1967 was calibrated for one job: inducing ovulation in selected anovulatory women over a five-day cycle. That dose was not picked for a 38-year-old man with secondary hypogonadism who wants to preserve fertility, and it was not picked for the patient whose body responds more to the longer-lived zuclomiphene isomer than to enclomiphene. Baseline testosterone, LH response, body weight, isomer sensitivity, side-effect tolerance (visual symptoms, mood, breast tenderness), and the goal of treatment (ovulation, testosterone restoration, post-cycle therapy under a prescriber) all sit outside what the original label was built around.

Compounding closes that gap. A 503A pharmacy can dispense 12.5 mg or 25 mg strengths that the manufactured 50 mg tablet cannot deliver without splitting, prepare an enclomiphene-isolated capsule that has no FDA-approved reference product on the market, or shift to a troche or sublingual form for a patient who reacts to the tablet excipients. The molecule is the same SERM that FDA reviewed for Clomid. The strength, the isomer ratio, and the dosage form are written for the individual on the prescription.

This is the older arrangement, the one that pre-dates mass-manufactured tablets. A licensed prescriber writes the order for a named patient. A licensed pharmacist prepares it and reviews it before it goes out. Modern state inspection and 503A rules keep that loop honest.

Quick Facts About Clomiphene & Enclomiphene

Category: Selective estrogen receptor modulator (SERM); mixture of two stereoisomers, enclomiphene (trans, pure ER antagonist) and zuclomiphene (cis, mixed agonist with longer half-life)

Active ingredient: Clomiphene citrate, a non-steroidal triphenylethylene SERM; clinical clomiphene citrate is the racemic 38:62 zuclomiphene-to-enclomiphene mixture. Compounded preparations include the racemate or enclomiphene-isolated isomer.

FDA-approved branded products: Clomid and Serophene (clomiphene citrate 50 mg oral tablets), originally FDA-approved in 1967 for ovulation induction in selected anovulatory women

Routes studied in humans: Oral (manufactured tablet; compounded capsule, troche/sublingual); the enclomiphene-only formulation Androxal was studied orally in phase 2 and phase 3 male hypogonadism trials by Repros Therapeutics but was not FDA-approved

Evidence posture: Strong evidence for FDA-approved use in female ovulation induction (PPCOS-I, PPCOS-II, Cochrane); well-studied off-label use in male secondary hypogonadism (Katz 2012, Moskovic 2012, Krzastek 2019, Soares 2018, Wiehle/Kaminetsky enclomiphene phase 2 trials, 2026 JCEM systematic review)

FDA-approval status: Clomid and Serophene (clomiphene citrate 50 mg tablets) are FDA-approved for ovulation induction in selected women with anovulatory infertility. Enclomiphene-isolated formulations (Androxal) are not FDA-approved. Compounded clomiphene and enclomiphene preparations are not FDA-approved.

Compounded under: 503A, patient-specific prescription only; legitimate compounding niche centers on lower male-hypogonadism doses (12.5, 25 mg) and enclomiphene-isolate forms not commercially available

Compounded role: Distinct from 'essentially-a-copy' territory: patient-specific compounding addresses (a) lower male-hypogonadism doses (12.5, 25 mg) than the 50 mg female-ovulation tablet, (b) enclomiphene-isolate dosage forms with no FDA-approved reference product, (c) troche/sublingual or non-tablet routes for patients who cannot tolerate the manufactured tablet excipients, and (d) custom strengths supporting individualized titration.

Schedule: Not a controlled substance under the Controlled Substances Act; prescription only. FDA pregnancy category X (contraindicated once pregnancy has been established).

SPECIALS: PATIENT-SPECIFIC PRESCRIPTION ONLY

Clomiphene & Enclomiphene described in this monograph is a 503A compounded preparation. Every dose is made on a prescription, for a named patient, by a licensed pharmacist. It is not a stocked, mass-manufactured product.

- **Made to order, not off a shelf.** No batch sits in a warehouse waiting for buyers. Your prescription triggers the prep.
- **Named-patient label.** The bottle carries one patient's name. The batch records carry one prescription.
- **Dose, strength, and route chosen for the patient.** A prescriber decides what gets compounded, not a manufacturer who set the strength for a trial population.
- **Licensed pharmacist on the hook.** A real person, with a license that can be pulled, signs off on every prep. State inspectors check the facility.
- **Compounded drugs are not FDA-approved.** They should not be evaluated using branded-drug trial data alone. Availability varies by state and prescribed medication.

How This Differs from a Research-Use-Only Website

A research-use-only website ships a vial from a warehouse. There is no prescription, no pharmacist, no facility inspection, and no way to recall the product if something is wrong with it. If the vial is mislabeled, contaminated, or under-potent, there is nobody whose license is at stake.

A 503A compounding pharmacy is the other thing. The doctor writes the prescription. A licensed pharmacist, whose name is on the label, prepares the medicine in a facility the state inspects. If something goes wrong, there is a person and a license on the hook, and a documented chain of custody on every lot. That accountability is what makes it safe.

What is Clomiphene & Enclomiphene?

Clomiphene citrate is a non-steroidal triphenylethylene molecule structurally related to tamoxifen and toremifene. It is a selective estrogen receptor modulator (SERM), a class of compounds that acts as an estrogen receptor antagonist in some tissues and a partial agonist in others. Commercial clomiphene citrate is a racemic mixture of two geometric isomers in an approximately 38:62 ratio: zuclomiphene (cis-clomiphene) and enclomiphene (trans-clomiphene) [asrm2013clomid]. The two isomers have distinct receptor pharmacology and pharmacokinetics: enclomiphene is a relatively pure estrogen receptor antagonist with a short half-life (hours to days) and is responsible for most of the acute LH/FSH-raising effect of the drug; zuclomiphene has mixed agonist activity, an extended terminal half-life (weeks because of enterohepatic recirculation), and accounts for much of the antiestrogenic side-effect burden including endometrial thinning and the long washout after discontinuation [mikkelson1986, ghobadi2009, adashi1984].

Clomid (originally manufactured by Merrell-Dow, now generic) and Serophene (clomiphene citrate 50 mg oral tablet) received FDA approval in 1967 for the treatment of ovulatory dysfunction in selected anovulatory women who wish to conceive [asrm2013clomid]. Generic clomiphene citrate 50 mg tablets are widely available. There is no FDA-approved enclomiphene-isolated product; Repros Therapeutics developed Androxal (enclomiphene citrate) and conducted phase 2 and phase 3 trials in male secondary hypogonadism through the 2010s but the FDA declined to approve the product in 2016, and Repros subsequently exited the market [earl2019enclo, hill2009enclo].

Compounded clomiphene preparations include lower-strength capsules (typically 12.5 mg or 25 mg, used for male hypogonadism off-label), enclomiphene-isolate capsules (chemically isolated trans-isomer with no FDA-approved reference product), and non-tablet dosage forms such as troches or sublingual preparations for patients who cannot tolerate manufactured tablet excipients [homburg2005].

How Clomiphene & Enclomiphene Works

Clomiphene acts at the estrogen receptor at multiple sites along the hypothalamic-pituitary-gonadal (HPG) axis [ghobadi2009]. The dominant clinically relevant action is competitive antagonism at hypothalamic estrogen receptors in the arcuate and preoptic nuclei. Normally, circulating estradiol exerts negative feedback on GnRH-producing neurons; clomiphene blocks this feedback, increases GnRH pulse frequency and amplitude, and disinhibits pituitary release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) [adashi1984] [katz2012; moskovic2012].

In anovulatory women, the resulting FSH rise drives folliculogenesis and the LH surge drives ovulation, the basis for clomiphene's FDA-approved use in ovulation induction [asrm2013clomid, brown2009cochrane] [mikkelson1986]. In men with secondary (hypogonadotropic) hypogonadism, the same disinhibition of LH and FSH stimulates Leydig-cell testosterone production and Sertoli-cell support of spermatogenesis, raising serum testosterone toward the eugonadal range while preserving (or improving) sperm parameters [guay1995; kaminetsky2013enclo; wiehle2013enclo].

The two isomers contribute differently to the clinical phenotype. Enclomiphene (the trans-isomer) is a relatively pure antagonist with a short half-life and is responsible for most of the acute LH/FSH-raising effect; zuclomiphene (the cis-isomer) is a partial agonist with a long half-life and contributes the residual antiestrogenic effects in peripheral tissues including the endometrium (endometrial thinning), the cervix (reduced cervical mucus quality), and possibly the retina (visual disturbances) [earl2019enclo; hill2009enclo]. The mixed isomer pharmacology, the slow zuclomiphene clearance, and the resulting compromise of endometrial receptivity have all been advanced as the rationale for an enclomiphene-only product [mulhall2018aua; gonen1990endo].

Biological Role of Clomiphene & Enclomiphene

The estrogen-receptor system is the central regulator of female reproductive physiology and a critical contributor to male reproductive, skeletal, and metabolic physiology. Estradiol from ovarian (women) or aromatized androgen (men) sources exerts negative feedback on the hypothalamus and pituitary to constrain LH and FSH release. This feedback loop is the operating principle of the HPG axis [mcbride2016recovery].

Pharmacologic interruption of estrogen negative feedback, by SERM (clomiphene, enclomiphene, tamoxifen) or by aromatase inhibition (letrozole, anastrozole), drives an iatrogenic rise in LH and FSH. In women with anovulatory infertility, this disinhibition recovers ovulatory cycles [schlegel2021aua1]. In men with secondary hypogonadism, the same disinhibition raises endogenous testosterone production without suppressing spermatogenesis, the pharmacologic basis for the clomiphene/enclomiphene approach to TRT-alternative therapy [adashi1984; asrm2013clomid; mulhall2018aua].

Detailed Mechanism of Clomiphene & Enclomiphene

Estrogen receptor pharmacology. Clomiphene and its isomers bind the estrogen receptor (ERα and ERβ) with affinity comparable to estradiol but with substantially slower dissociation kinetics. The ligand-receptor complex translocates to the nucleus and engages estrogen-response elements in target-gene promoters, but the conformational state induced by clomiphene differs from that induced by estradiol; the resulting altered coactivator/corepressor recruitment produces the tissue-selective antagonist/partial-agonist profile that defines SERMs. Zuclomiphene engages the receptor in a more agonist-like conformation in some tissues

(peripheral antiestrogenic effects); enclomiphene engages it predominantly in an antagonist conformation [adashi1984, mikkelson1986].

Hypothalamic-pituitary-gonadal disinhibition. The dominant therapeutic mechanism is at the hypothalamus. Estradiol normally restrains GnRH pulse generation in the arcuate nucleus through negative feedback. Clomiphene-mediated ER antagonism at the hypothalamus interrupts this feedback, GnRH pulse frequency and amplitude increase, and pituitary gonadotrophs release more LH and FSH. The increase is dose-dependent and isomer-dependent: enclomiphene's short half-life produces a sharper, more transient gonadotropin pulse pattern; zuclomiphene's long half-life produces a tonic background activity that persists weeks after discontinuation [adashi1984, ghobadi2009, wiehle2013enclo].

Ovarian response in women. The rise in FSH stimulates antral follicle recruitment and follicular maturation; the resulting estradiol surge eventually triggers an LH surge and ovulation. In women with PCOS, hyperandrogenism and disordered FSH/LH ratios make this response variable; approximately 75, 80% of clomiphene-treated PCOS cycles produce ovulation but only 30, 40% produce live birth per cycle [legro2007ppcosi, brown2009cochrane, asrm2013clomid]. The transition to letrozole as first-line therapy for PCOS infertility reflects the higher live-birth rate observed with letrozole in PPCOS-II [legro2014ppcosii], rather than failure of clomiphene's mechanism [katz2012; moskovic2012].

Testicular response in men. In men with secondary (hypogonadotropic) hypogonadism, typically characterized by total testosterone <300 ng/dL with inappropriately normal or low LH/FSH, clomiphene-mediated disinhibition raises pituitary LH, which in turn stimulates Leydig-cell testosterone synthesis [kaminetsky2013enclo]. Serum testosterone rises within 2, 4 weeks and stabilizes within 8, 12 weeks. Spermatogenesis is preserved or improved because the rise in FSH and intratesticular testosterone supports Sertoli-cell function, in contrast to exogenous testosterone therapy, which suppresses pituitary LH/FSH and shuts down spermatogenesis. Adjunctive hCG-based combination protocols have been used to accelerate spermatogenesis recovery in men coming off exogenous testosterone [wenker2015hcg], but clomiphene-only therapy avoids the initial spermatogenesis suppression altogether [mcbride2016recovery; mulhall2018aua].

Peripheral antiestrogenic effects. The cis-isomer (zuclomiphene), with its long half-life, produces measurable antiestrogenic effects in the endometrium (thinning that may impair implantation), the cervix (reduced midcycle mucus quality), and possibly the retina (the leading mechanistic hypothesis for clomiphene-associated visual disturbances). Gonen and Casper [gonen1990endo] documented sonographic endometrial thinning in clomiphene-stimulated cycles compared with natural or gonadotropin-stimulated cycles; Quaas 2021 [quaas2021endo] re-quantified endometrial thickness across clomiphene, letrozole, and gonadotropin cycles in the AMIGOS framework. Purvin's 1995 case series [purvin1995visual] characterized the visual disturbance (typically scintillating scotomata or after-images, generally reversible on discontinuation).

Pharmacokinetics. Single-dose PK in normal volunteers [mikkelson1986] established that the racemic preparation produces a peak plasma concentration within ~6 hours of oral dosing with a triphasic

disposition: an early distribution phase, an enclomiphene-dominated elimination phase over 1, 2 days, and a long terminal zuclomiphene tail extending weeks because of enterohepatic recirculation and tissue distribution. Ghobadi 2009 [ghobadi2009] characterized the differential isomer PK in anovulatory PCOS women and demonstrated that zuclomiphene concentrations remain detectable for >4 weeks after a single dose, while enclomiphene clears within days [wiehle2014enclo]. This kinetic asymmetry underlies the prolonged washout, the cumulative cycle-to-cycle exposure when the drug is given for multiple cycles, and the rationale for enclomiphene-isolated preparations [schlegel2021aua1; schlegel2021aua2].

Clomiphene & Enclomiphene Research History

Clomiphene was synthesized by Frank Palopoli and colleagues at the William S. Merrell Company in the late 1950s and demonstrated to induce ovulation in women with anovulatory infertility in the early 1960s. The compound, initially designated MRL-41, received FDA approval as Clomid (clomiphene citrate 50 mg tablet) for ovulation induction in 1967. Serophene (Merck Serono) is the second major branded clomiphene citrate product; generic clomiphene citrate 50 mg tablets are widely available. The original FDA approval predates modern controlled-trial standards; subsequent decades of accumulated trial data have refined the indication framing without changing the labeled use [asrm2013clomid, homburg2005].

Mechanistic dissection through the 1970s and 1980s. The recognition that commercial clomiphene citrate is a racemic mixture of two isomers with distinct pharmacology, enclomiphene (trans, pure antagonist, short half-life) and zuclomiphene (cis, mixed agonist/antagonist, long half-life), emerged from the binding and clinical pharmacology work of the 1970s and was synthesized by Adashi in his 1984 Fertility and Sterility review [adashi1984] [tomao2014ovarian; tomao2014breast]. Mikkelson 1986 [mikkelson1986] characterized single-dose pharmacokinetics in healthy volunteers; Ghobadi 2009 [ghobadi2009] extended the isomer-level PK analysis into anovulatory PCOS women and confirmed the asymmetric clearance [reigstad2017].

PCOS ovulation induction evidence consolidates 2007, 2014. PPCOS-I (Legro et al., NEJM 2007) [legro2007ppcosi] randomized 626 women with PCOS to clomiphene, metformin, or both for up to six cycles and reported a substantially higher live-birth rate with clomiphene (22.5%) than metformin (7.2%), with the combination not significantly better than clomiphene alone, establishing clomiphene as first-line for PCOS-related anovulatory infertility. The aromatase-inhibitor era then began: Mitwally and Casper 2001 [mitwally2001] introduced letrozole for ovulation induction; Casper 2007 [casper2007letrozole] reviewed the emerging evidence; and PPCOS-II (Legro et al., NEJM 2014) [legro2014ppcosii] randomized 750 women with PCOS to letrozole vs clomiphene and reported a significantly higher live-birth rate with letrozole (27.5%) than clomiphene (19.1%). The 2009 Cochrane review by Brown et al. [brown2009cochrane] integrated the older clomiphene-vs-placebo and clomiphene-vs-other-SERM evidence; the 2013 ASRM Practice Committee opinion on clomiphene [asrm2013clomid] codified its use position in the post-PPCOS era. International evidence-based PCOS recommendations

[pena2025adolescents] continue to incorporate letrozole as preferred first-line ovulation induction in PCOS while retaining clomiphene as a second-line option.

Off-label male hypogonadism literature builds 1995, 2020s. Guay 1995 [guay1995] demonstrated that raising endogenous testosterone with clomiphene in impotent men with secondary hypogonadism produced symptom benefit. Shabsigh 2005 [shabsigh2005] characterized the testosterone-to-estradiol ratio shift with clomiphene in male hypogonadism. Katz 2012 [katz2012] reported outcomes of clomiphene citrate in young hypogonadal men, demonstrating durable testosterone increases at 25 mg every other day and 50 mg daily without major toxicity. Moskovic 2012 [moskovic2012] documented long-term safety and efficacy in a urology cohort. Krzastek 2019 [krzastek2019] extended observational follow-up to five years and reported sustained efficacy and a safety profile consistent with the shorter-term studies. Patel 2016 [patel2016review] synthesized hormone-based treatments in subfertile males and positioned clomiphene/enclomiphene as evidence-based fertility-preserving alternatives. Soares 2018 [soares2018obesity] reported the first dedicated RCT of clomiphene vs placebo in male obesity-associated hypogonadism, and Pelusi 2022 [pelusi2022obesity] extended these findings to sexual-function endpoints in dysmetabolic obese men. The 2026 systematic review by Konnyu et al. [konnyu2026meta] consolidated hormonal treatment efficacy in normo-gonadotropic male infertility.

Enclomiphene-only development arc, 2009, 2019. The pharmacologic rationale for an enclomiphene-only preparation, preserving the LH/FSH-raising antagonist activity while avoiding the long zuclomiphene tail and its peripheral antiestrogenic effects, was articulated by Hill, Arutchelvam, and Quinton in 2009 [hill2009enclo]. Repros Therapeutics developed Androxal (enclomiphene citrate) and reported the foundational phase 2 trials: Kaminetsky 2013 [kaminetsky2013enclo] demonstrated stimulation of endogenous testosterone and sperm counts in men with secondary hypogonadism; Wiehle 2013 (BJU International) [wiehle2013enclo] characterized testosterone restoration pharmacodynamics; Wiehle 2014 (Fertility and Sterility) [wiehle2014enclo] reported the randomized head-to-head trial of enclomiphene vs AndroGel in secondary hypogonadism, demonstrating testosterone restoration with preserved sperm counts (vs AndroGel-induced suppression). Despite this evidence, FDA review concluded the phase 3 program did not establish a clinical benefit-risk profile suitable for approval as a TRT alternative, and Repros discontinued the program. Earl and Kim 2019 [earl2019enclo] reviewed the development history and clinical rationale. No enclomiphene-isolated product is currently FDA-approved.

Long-term cancer safety, 1992, 2017. The earliest signal of an association between fertility drugs and ovarian cancer came from Whittemore 1992 [whittemore1992] (collaborative case-control analysis) and Rossing 1994 (NEJM) [rossing1994], which reported elevated risks in nulligravid women treated with clomiphene [rossing2004casecontrol]. Subsequent larger analyses have, on balance, found no consistent excess risk of ovarian, breast, or endometrial cancer attributable to clomiphene exposure independent of underlying infertility, particularly when stratified by parity status [brinton2004ovarian; brinton2013endo; brinton2014breast]. The current ASRM committee opinion on clomiphene [asrm2013clomid] integrates this evidence into the labeled risk-benefit framing.

Compounded clomiphene niche [rossing2004casecontrol]. Compounded clomiphene at non-standard strengths (12.5 mg, 25 mg) and as enclomiphene-isolate preparations occupies a long-standing 503A niche distinct from copy-of-approved-product compounding: there is no manufactured 12.5 mg or 25 mg tablet, no manufactured troche or sublingual preparation, and no FDA-approved enclomiphene-isolate product. The male-hypogonadism literature consistently uses these lower strengths that are not commercially available.

Clomiphene & Enclomiphene Timeline

1956 • Frank Palopoli and colleagues at William S. Merrell Company synthesize MRL-41 (clomiphene citrate), a non-steroidal triphenylethylene SERM

1961 • Greenblatt and colleagues report first clinical use of MRL-41 (clomiphene) for ovulation induction in anovulatory women

1967 • FDA approves Clomid (clomiphene citrate 50 mg oral tablet) for ovulation induction in selected anovulatory women [asrm2013clomid; homburg2005]

1984 • Adashi publishes 'Clomiphene citrate: mechanism(s) and site(s) of action, a hypothesis revisited' in Fertility and Sterility, synthesizes the SERM mechanism and the isomer-dependent pharmacology [adashi1984]

1986 • Mikkelson et al [mikkelson1986]. characterize single-dose pharmacokinetics of clomiphene citrate in normal volunteers, demonstrating the asymmetric isomer clearance (fast enclomiphene, slow zuclomiphene)

1990 • Gonen and Casper publish sonographic determination of clomiphene's adverse effect on endometrial development, characterizes the peripheral antiestrogenic effect on the uterus [gonen1990endo]

1992 • Whittemore et al [whittemore1992]. publish collaborative case-control analysis of ovarian cancer risk and fertility drugs (Am J Epidemiol), first major signal of cancer-risk question with clomiphene

1994 • Rossing et al [rossing1994]. (NEJM) report elevated ovarian cancer risk in nulligravid women treated with clomiphene, pivotal signal that drove subsequent long-term cohort follow-up

1995 • Guay et al [guay1995]. (JCEM) demonstrate that raising endogenous testosterone with clomiphene in impotent men with secondary hypogonadism produces clinical benefit, opens the off-label male hypogonadism literature

1995 • Purvin (Arch Ophthalmol) publishes case series characterizing visual disturbances secondary to clomiphene citrate, establishes the clinical pattern that warrants discontinuation [purvin1995visual]

2001 • Mitwally and Casper introduce letrozole as an alternative aromatase-inhibitor pathway for ovulation induction in patients with inadequate clomiphene response [mitwally2001]

2004 • Brinton et al [brinton2004ovarian]. (Obstet Gynecol) publish ovarian cancer risk after ovulation-stimulating drugs, initiates the modern long-term cohort follow-up that ultimately did not confirm a consistent independent ovarian cancer signal

2005 • Homburg publishes 'Clomiphene citrate, end of an era?' mini-review (Hum Reprod), anticipates the letrozole transition [homburg2005]

2005 • Shabsigh et al [shabsigh2005]. (J Sex Med) characterize clomiphene's effect on the testosterone/estradiol ratio in male hypogonadism, clarifies the endocrine signature in men

2007 • PPCOS-I (Legro et al., NEJM), randomized 626 women with PCOS to clomiphene, metformin, or both; clomiphene superior to metformin for live birth, establishing clomiphene as first-line ovulation induction in PCOS [legro2007ppcosi]

2009 • Brown et al [brown2009cochrane]. publish Cochrane review of clomiphene and antiestrogens for ovulation induction in PCOS, quantitative synthesis of pre-PPCOS-II evidence base

2009 • Hill, Arutchelvam, and Quinton (IDrugs) review enclomiphene as an ER antagonist for testosterone deficiency, articulates the rationale for an isomer-isolated product [hill2009enclo]

2009 • Ghobadi et al [ghobadi2009]. publish isomer-level single-dose pharmacokinetic study of clomiphene in anovular PCOS women, confirms the asymmetric zuclomiphene/enclomiphene clearance in patients

2012 • Katz et al [katz2012]. (BJU Int) report outcomes of clomiphene citrate treatment in young hypogonadal men, durable testosterone increase at low doses, foundational urologic case series

2012 • Moskovic et al [moskovic2012]. (BJU Int) demonstrate clomiphene citrate is safe and effective for long-term management of hypogonadism, multi-year urology cohort

2013 • Kaminetsky, Werner, and Fontenot (J Sex Med) publish phase 2 trial of oral enclomiphene citrate in men with secondary hypogonadism, demonstrates testosterone restoration with preserved sperm counts [kaminetsky2013enclo]

2013 • Wiehle, Cunningham, Pitteloud et al [wiehle2013enclo]. (BJU Int) characterize pharmacodynamics of testosterone restoration by enclomiphene citrate in men with secondary hypogonadism

2013 • ASRM Practice Committee publishes 'Use of clomiphene citrate in infertile women: a committee opinion' (Fertility and Sterility), codifies the labeled-use framing after PPCOS-I [asrm2013clomid]

2013 • Brinton et al [brinton2013endo]. (Hum Reprod) report fertility drugs and endometrial cancer risk, extended infertility cohort follow-up does not confirm a clomiphene-attributable endometrial cancer signal

2014 • PPCOS-II (Legro et al., NEJM), randomized 750 women with PCOS to letrozole vs clomiphene; letrozole produced higher live-birth rates (27.5% vs 19.1%), reorienting first-line ovulation induction in PCOS toward letrozole [legro2014ppcosii]

2014 • Wiehle, Fontenot, Wike et al [wiehle2014enclo]. (Fertility and Sterility) report enclomiphene vs AndroGel head-to-head, testosterone restoration with sperm-count preservation (vs AndroGel-induced suppression)

2014 • Brinton et al [brinton2014breast]. (Cancer Epidemiol Biomarkers Prev), extended long-term cohort follow-up of ovulation-stimulating drugs and breast cancer risk: no consistent excess attributable to clomiphene

2014 • Tomao et al [tomao20140varian; tomao2014breast]. (J Ovarian Res and Curr Opin Obstet Gynecol) review fertility drugs in relation to ovarian and breast cancer risk, integrates the accumulated cohort evidence

2016 • Patel, Chandrapal, and Hotaling (Curr Urol Rep) review hormone-based treatments in subfertile males, positions clomiphene and enclomiphene as fertility-preserving alternatives to testosterone replacement [patel2016review]

2016 • FDA declines to approve Androxal (enclomiphene citrate, Repros Therapeutics) for secondary hypogonadism, no enclomiphene-isolated product reaches the US market [earl2019enclo]

2016 • McBride and Coward (Asian J Androl) characterize recovery of spermatogenesis following testosterone replacement, establishes the fertility-suppression rationale for SERM-based TRT alternatives [mcbride2016recovery]

2017 • Reigstad et al [reigstad2017]. (Cancer Epidemiol Biomarkers Prev), Norwegian registry-based cohort stratifies fertility-drug cancer risk by parity status, supporting the null association in clomiphene-exposed parous women

2018 • Mulhall et al [mulhall2018aua]. publish AUA Evaluation and Management of Testosterone Deficiency guideline, cites clomiphene and aromatase inhibitors as fertility-preserving alternatives

2018 • Bhasin et al [bhasin2018endo]. publish updated Endocrine Society clinical practice guideline on testosterone therapy in men with hypogonadism, discusses SERM-based fertility-preserving options

2018 • Soares et al [soares2018obesity]. (Int J Obes) report randomized double-blind placebo-controlled trial of clomiphene in male obesity-associated hypogonadism, testosterone restoration vs placebo

2019 • Krzastek et al [krzastek2019]. (J Urol) report long-term (5-year) safety and efficacy of clomiphene citrate for hypogonadism, durable testosterone increase with no major safety signal

2019 • Earl and Kim (Expert Rev Endocrinol Metab) review enclomiphene citrate as a fertility-preserving secondary hypogonadism treatment, consolidated rationale post-FDA non-approval [earl2019enclo]

2021 • AUA/ASRM publishes male infertility guidelines (Schlegel et al., parts I and II), SERM (clomiphene) listed among evidence-based options for hypogonadotropic hypogonadism with fertility goals [schlegel2021aua1; schlegel2021aua2]

2021 • Quaas et al [quaas2021endo]. (Fertility and Sterility), AMIGOS-framework endometrial thickness comparison across clomiphene, letrozole, and gonadotropin cycles in unexplained infertility

2022 • Pelusi et al [pelusi2022obesity]. report overall sexual function in dysmetabolic obese men with low testosterone treated with clomiphene, extends the Soares 2018 endpoint set to sexual function

2025 • Bourdon et al [bourdon2025]. (Fertility and Sterility) report nationwide impact of clomiphene citrate on multiple gestation births and perinatal outcomes

2025 • Khashaba et al [khashaba2025]. (Asian J Urol) publish systematic review of clomiphene citrate and tamoxifen on pregnancy rates in idiopathic male subfertility

2026 • Konnyu et al [konnyu2026meta]. (J Clin Endocrinol Metab) publish systematic review of hormonal treatment efficacy for reproductive outcomes in normo-gonadotropic male infertility

Clinical Contexts for Clomiphene & Enclomiphene

Ovulation induction in selected anovulatory women who wish to conceive FDA APPROVED

FDA-approved indication for manufactured Clomid and Serophene (clomiphene citrate 50 mg tablet). Modern guidance preferences letrozole as first-line in PCOS but retains clomiphene as a labeled second-line option.

Clomiphene citrate is FDA-approved (1967) for ovulation induction in selected anovulatory women. The Cochrane review [brown2009cochrane] confirmed superior ovulation and pregnancy rates vs placebo. PPCOS-I [legro2007ppcosi] established superiority over metformin (live-birth 22.5% vs 7.2%) and made clomiphene first-line for PCOS-related anovulatory infertility through 2014. PPCOS-II [legro2014ppcosii] subsequently demonstrated higher live-birth rates with letrozole (27.5%) than clomiphene (19.1%) in PCOS, reorienting first-line ovulation induction toward letrozole while preserving clomiphene's labeled role [homburg2005]. ASRM committee opinion [asrm2013clomid] codifies the use position. International evidence-based PCOS guidance [pena2025adolescents] preferences letrozole as first-line. Approximate 5, 10% multi-gestation rate (predominantly twins) is the principal trade-off [bourdon2025].

Branded product: Clomid / Serophene (clomiphene citrate 50 mg oral tablet)

Male secondary (hypogonadotropic) hypogonadism with fertility preservation goals WELL STUDIED

Off-label; well-studied across observational case series and a small number of randomized trials. Cited by AUA testosterone deficiency and AUA/ASRM male infertility guidelines as an evidence-based fertility-preserving alternative to testosterone replacement.

Men with secondary hypogonadism (total testosterone <300 ng/dL with inappropriately normal or low LH/FSH) who want to preserve fertility face a choice: testosterone replacement (suppresses spermatogenesis; recovery uncertain [mcbride2016recovery]) or SERM-based therapy that raises endogenous testosterone while preserving spermatogenesis [wiehle2013enclo; earl2019enclo]. Guay 1995 [guay1995], Shabsigh 2005 [shabsigh2005], Katz 2012 [katz2012], Moskovic 2012 [moskovic2012], and Krzastek 2019 [krzastek2019] demonstrated durable testosterone increases (from baseline 200, 400 ng/dL to 500, 800 ng/dL) on clomiphene 12.5, 25 mg every other day or daily, with long-term safety consistent with the short-term observational data. The enclomiphene-isolate program [kaminetsky2013enclo] added randomized evidence vs AndroGel showing testosterone restoration with preserved sperm counts vs AndroGel-induced suppression [wiehle2014enclo]. AUA testosterone deficiency guideline [mulhall2018aua] and AUA/ASRM male infertility guideline [schlegel2021aua1, schlegel2021aua2] cite SERM therapy as an evidence-based option. The 2026 systematic review [konnyu2026meta] consolidates the broader male-fertility evidence [patel2016review].

Male obesity-associated hypogonadism WELL STUDIED

Off-label; supported by a randomized trial [soares2018obesity] and an observational sexual-function endpoint extension [pelusi2022obesity]. Considered a reasonable option where preservation of fertility and avoidance of exogenous testosterone are clinical priorities.

Obesity-associated hypogonadism, low total testosterone in obese men, typically with low SHBG and a secondary-hypogonadism endocrine pattern, is increasingly common and is mechanistically distinct from classical primary or secondary hypogonadism. Soares et al. [soares2018obesity] randomized obese men with low testosterone to clomiphene 50 mg daily vs placebo and demonstrated testosterone restoration vs placebo. Pelusi 2022 [pelusi2022obesity] extended these findings to overall sexual function in dysmetabolic obese men. Use in this population must be paired with weight management; clomiphene does not address the underlying adiposity-driven aromatase activity but raises testosterone via the HPG axis [asrm2015obesity].

Idiopathic male subfertility (normo-gonadotropic) EMERGING

Off-label; the systematic-review evidence base is mixed and recent meta-analyses do not clearly support routine use. Use is generally restricted to selected cases under specialist supervision.

In men with idiopathic subfertility and normal baseline gonadotropins, clomiphene and tamoxifen have been used to raise testosterone and improve semen parameters. The recent systematic review by Khashaba et al. [khashaba2025] consolidated pregnancy-rate evidence; the 2026 JCEM systematic review [konnyu2026meta] reported that hormonal treatment effects on reproductive outcomes in normo-gonadotropic male infertility are limited and inconsistent across trials. AUA/ASRM male infertility guideline [schlegel2021aua1, schlegel2021aua2] does not recommend routine empirical use; clomiphene may be considered in selected cases where a documented endocrine abnormality (low normal testosterone, elevated estradiol-to-testosterone ratio) is present.

Off-Label Uses of Clomiphene & Enclomiphene

Male secondary hypogonadism with fertility preservation WELL STUDIED

Off-label; well-studied across observational case series and small randomized trials. Captured separately in the clinical_contexts section.

See the clinical_contexts entry above [katz2012; moskovic2012; krzastek2019]. Off-label use is supported by the AUA testosterone deficiency guideline [mulhall2018aua] and the AUA/ASRM male infertility guideline [schlegel2021aua1, schlegel2021aua2] as a fertility-preserving alternative to testosterone replacement.

Female low libido / hypoactive sexual desire dysfunction PRECLINICAL

Off-label; limited evidence. Not a recommended use; mentioned only because patients sometimes inquire.

Clomiphene has been investigated anecdotally and in small uncontrolled series for premenopausal low libido on the rationale that it raises endogenous testosterone modestly in women through similar HPG disinhibition [asrm2013clomid]. Evidence is insufficient to support routine use, and the manufactured 50 mg tablet is contraindicated in established pregnancy. Use for this purpose is not endorsed by RonanRx's pharmacist review.

FDA-Approved Uses of Clomiphene & Enclomiphene

Brand	Indication	Year	Route
Clomid	Ovulation induction in selected anovulatory women who wish to conceive, original FDA approval 1967 (clomiphene citrate 50 mg oral tablet)	1967	Oral tablet
Serophene	Ovulation induction in selected anovulatory women who wish to conceive (clomiphene citrate 50 mg oral tablet)	1967	Oral tablet

Clomid (originally Merrell-Dow, now generic) and Serophene (Merck Serono) are clomiphene citrate 50 mg oral tablets [homburg2005]. FDA-approved in 1967 for ovulation induction in selected anovulatory women who wish to conceive, typically women with World Health Organization Group II anovulation (normogonadotropic anovulation), with the largest evidence base in PCOS [asrm2013clomid, brown2009cochrane, legro2007ppcosi]. The labeled dosing for ovulation induction starts at 50 mg orally daily for 5 days beginning on cycle day 3, 4, or 5, with escalation to 100 mg or 150 mg in subsequent cycles if ovulation does not occur. Treatment is generally limited to a maximum of six ovulatory cycles because of the cancer-risk concerns historically associated with extended exposure (a concern that has not been confirmed in modern long-term cohort follow-up but is preserved in labeling and practice) [asrm2013clomid, brinton2014breast, reigstad2017].

PPCOS-II [legro2014ppcosii] demonstrated higher live-birth rates with letrozole than with clomiphene in PCOS, and international evidence-based PCOS guidance [pena2025adolescents] preferences letrozole as first-line. Clomiphene retains a labeled role for selected women, particularly where letrozole is not appropriate or available [homburg2005]. Clomid is pregnancy category X, contraindicated once pregnancy has been established.

Compounded Clomiphene & Enclomiphene (503A)

Compounded clomiphene and enclomiphene are dispensed under 503A only on patient-specific prescriptions for documented clinical needs that the manufactured Clomid or Serophene 50 mg tablet

cannot meet [katz2012; kaminetsky2013enclo; wiehle2014enclo]. Three clinical scenarios drive the legitimate compounded niche:

(1) Male-hypogonadism dosing. The off-label male-hypogonadism literature consistently uses 12.5 mg, 25 mg, or low-dose daily-to-every-other-day regimens that are not available in the manufactured 50 mg tablet. Tablet splitting is not a satisfactory substitute because precision matters for hypogonadism titration and because the manufactured tablet is not scored for accurate quartering [wiehle2013enclo; earl2019enclo]. Compounded 12.5 mg or 25 mg capsules support these regimens.

(2) Enclomiphene-isolate preparations. There is no FDA-approved enclomiphene-isolated product. The phase 2 and phase 3 trial evidence base for enclomiphene in male hypogonadism demonstrated testosterone restoration with preserved sperm counts; clinicians who wish to translate that evidence into practice depend on compounded preparations because the manufactured racemate has the additional zuclomiphene-mediated antiestrogenic effects that the isomer-isolated formulation was designed to avoid [moskovic2012; krzastek2019; soares2018obesity].

(3) Alternative dosage forms [katz2012]. Compounded troche, sublingual, or oral-liquid preparations may be appropriate for selected patients who cannot tolerate the manufactured tablet, typically because of an excipient sensitivity or because a tablet form is impractical (e.g., gastric bypass with malabsorption, refusal of certain dyes).

Compounded clomiphene is not appropriate as a routine substitution for the manufactured 50 mg tablet for the FDA-labeled female ovulation-induction indication. Prescriptions that read as routine substitution for the manufactured product without a documented patient-specific clinical reason will not be filled. RonanRx's pharmacist review confirms patient-specific rationale, screens for contraindications, and verifies that the prescribed regimen is consistent with the documented evidence base [fda_essentially_a_copy, fda503a] [hill2009enclo].

Clomiphene & Enclomiphene Formulations and Routes

Form	Concentration	Description
Oral tablet (reference product)	Clomiphene citrate 50 mg	Manufactured Clomid and Serophene (clomiphene citrate 50 mg oral tablet); generic clomiphene citrate 50 mg tablets are widely available. FDA-approved for ovulation induction in selected anovulatory women.
Oral capsule (compounded)	Custom, typically 12.5 mg, 25 mg, or 50 mg	Compounded clomiphene citrate capsules at non-standard strengths support the male-hypogonadism literature dose range (12.5, 25 mg every other day or daily). Prepared under USP <795> standards.

Form	Concentration	Description
Oral capsule, enclomiphene isolate (compounded)	Custom, typically 6.25, 25 mg per capsule	Compounded enclomiphene citrate (trans-isomer isolated) capsules. No FDA-approved reference product; supports translation of the Kaminetsky/Wiehle phase 2 and phase 3 evidence base into practice.
Troche or sublingual tablet (compounded)	Custom	Compounded troche or sublingual preparation for selected patients who cannot tolerate manufactured tablet excipients or who require a non-tablet dosage form. Prepared under USP <795> standards.

Routes used in published literature: oral, sublingual, troche.

Clomiphene & Enclomiphene Dosing

Route	Population	Range	Duration	Study type
Oral	Adult women with anovulatory infertility (Clomid labeled regimen for ovulation induction)	50 mg once daily for 5 days beginning on cycle day 3, 4, or 5; if ovulation does not occur, escalate to 100 mg daily for 5 days in subsequent cycles, with a labeled maximum of 150 mg daily and a generally observed limit of six ovulatory cycles	Up to 6 ovulatory cycles per labeled use	FDA-approved labeled regimen
Oral	Adult men with secondary hypogonadism (off-label fertility-preserving regimen)	12.5, 25 mg every other day or daily; some series titrate to 50 mg every other day. Typical target: total testosterone in the mid-normal range with preservation of LH/FSH within or above the reference range and stable or improved semen parameters	Indefinite while clinically beneficial; long-term observational follow-up to 5 years (Krzastek 2019)	Off-label; observational case series and RCTs
Oral	Adult men with secondary hypogonadism, enclomiphene-isolate regimen (compounded)	Enclomiphene citrate 6.25, 25 mg daily, mirroring the Repros phase 2 and phase 3 program dose range (typically 12.5 or 25 mg daily)	Studied through 16 weeks in phase 2 RCTs; continued use as clinically indicated	Phase 2 and phase 3 RCTs of enclomiphene-isolate (Androxal), not FDA-approved

Female ovulation induction: 50 mg daily for 5 days beginning on cycle day 3, 5, with cycle-level monitoring of ovulation by serum mid-luteal progesterone, basal body temperature, or transvaginal ultrasound follicular monitoring. Escalation to 100 mg or 150 mg in subsequent cycles if ovulation does not occur. Treatment beyond six ovulatory cycles is not recommended on the labeled use. The 2014 PPCOS-II evidence supporting letrozole as first-line for PCOS-related anovulatory infertility [legro2014ppcosii] should be discussed with the patient [schlegel2021aua1]. Pregnancy must be excluded before initiation of each cycle; clomiphene is pregnancy category X once pregnancy has been established [asrm2013clomid] [katz2012; moskovic2012].

Male secondary hypogonadism (off-label, fertility-preserving): Most case series and the Krzastek 5-year observational cohort use 12.5, 25 mg every other day or daily, titrated by serum total testosterone after 4, 8 weeks to a target of mid-normal range [krzastek2019]. Higher doses (50 mg every other day) have been used but are not necessary in most patients; the dose-response relationship is shallow in the male-hypogonadism range. Baseline and on-therapy monitoring should include serum total testosterone, free testosterone or calculated bioavailable testosterone, LH, FSH, estradiol (which may rise modestly through preserved aromatization), and semen analysis when fertility is a clinical priority [kaminetsky2013enclo; wiehle2014enclo] [mulhall2018aua].

Enclomiphene-isolate (compounded): 6.25, 25 mg daily mirrors the Androxal phase 2/3 dose range; 12.5 or 25 mg daily are the most studied [wiehle2014enclo]. Pharmacist verification of API identity and quantitative analytical confirmation of isomer composition are particularly important for enclomiphene-isolate preparations because no FDA-approved reference product exists for cross-comparison.

Clomiphene & Enclomiphene Safety

Clomiphene's safety profile is well-characterized across nearly six decades of use [8]. The most common adverse events are vasomotor symptoms (hot flashes, in 10, 20% of treated cycles), abdominal discomfort, breast tenderness, nausea, and headache, all typically mild and self-limited. The most clinically significant safety considerations are: ovarian hyperstimulation syndrome (rare in clomiphene-treated cycles, more common with gonadotropin protocols); multiple gestation (predominantly twins, approximately 5, 10% of clomiphene-conceived pregnancies; higher-order multiples rare) [17]; visual disturbances [14]; endometrial thinning that may impair implantation [15][16]; and a historically discussed but not consistently confirmed long-term cancer-risk question.

Visual disturbances, typically scintillating scotomata, flashes, or after-images, are an uncommon but characteristic adverse event [8]. Purvin's 1995 case series [14] characterized the typical presentation and recovery pattern. Discontinuation is recommended when visual symptoms occur; most patients recover fully within days to weeks of stopping the drug. Persistent visual changes warrant ophthalmologic evaluation.

Pregnancy and lactation. Clomiphene is FDA pregnancy category X, contraindicated once pregnancy has been established. The drug is intended for use only during the periovulatory phase of a treatment cycle in women who are not yet pregnant [8]. Animal studies have shown teratogenicity at high doses [18]; congenital anomaly risk in clomiphene-conceived human pregnancies has been studied extensively and does not show a consistent independent excess attributable to the drug after adjustment for underlying maternal infertility [21].

Male-hypogonadism use. The off-label use literature reports a favorable short- and intermediate-term safety profile at the 12.5, 25 mg doses typically used in men. Krzastek's 5-year observational follow-up [32] reported sustained efficacy and no major safety signal; the most common reported adverse events are mild mood effects, breast tenderness, and (rarely) visual disturbances. Long-term randomized cardiovascular outcomes data specifically in men treated with clomiphene do not exist; clinicians should discuss this uncertainty explicitly with patients selecting clomiphene over testosterone replacement therapy [8 3031].

Cancer risk [2526]. The 1992 Whittemore collaborative analysis [19] and the 1994 Rossing NEJM cohort [20] generated initial signals of elevated ovarian cancer risk in clomiphene-exposed nulligravid women [27]. Subsequent extended cohort follow-up and parity-stratified registry analyses have not consistently confirmed an independent clomiphene-attributable excess of ovarian, breast, or endometrial cancer after adjustment for the underlying infertility population [222324]. Labeled use restricting clomiphene to a maximum of approximately six ovulatory cycles preserves the historically cautious posture [86 34].

Contraindications

Clomiphene is contraindicated in pregnancy (pregnancy category X, confirmed pregnancy must be excluded before each cycle), uncontrolled thyroid or adrenal dysfunction, hepatic disease or a history of hepatic dysfunction, abnormal uterine bleeding of undetermined origin (must be evaluated before initiation), ovarian cyst not due to PCOS (must be evaluated before initiation), and known hypersensitivity to clomiphene or any tablet excipient [8 2526].

Relative contraindications include uncontrolled depression or a history of visual disturbance on prior clomiphene exposure (clomiphene should not be re-initiated after a visual adverse event without an ophthalmologic clearance) [14]. Use in women with a personal or family history of estrogen-sensitive cancer (breast, endometrial) should be discussed against the long-term cohort evidence and individualized [8 2324].

Drug interactions

Clomiphene is metabolized primarily by hepatic CYP-mediated pathways; specific characterized drug-drug interactions are limited. Co-administration with other SERMs (tamoxifen, raloxifene) is not recommended because of the overlapping mechanism and absence of clinical-trial evidence for combination use. Co-administration with aromatase inhibitors (letrozole, anastrozole) has been studied in selected female ovulation-induction contexts and in male hypogonadism contexts as combination SERM + AI regimens; this is a specialist combination not warranted in routine use.

Exogenous estrogens (combined oral contraceptives, hormone replacement therapy) may attenuate clomiphene's effect on the hypothalamus and are not used concurrently in patients receiving clomiphene for ovulation induction or male hypogonadism. Concomitant testosterone replacement defeats the purpose of clomiphene in male hypogonadism (the SERM raises endogenous testosterone; exogenous testosterone suppresses the same axis); these are alternatives, not combination therapy [8][4][3][4][1].

Adverse events

Common adverse events in female ovulation-induction trials and observational series include hot flashes (10, 20%), abdominal discomfort or bloating (5, 10%), breast tenderness, nausea, vomiting, and headache. Less common adverse events include visual disturbances (1, 2%), reversible alopecia, and mood changes. Vaginal bleeding and abnormal menses may occur during a treatment cycle [8][6] [4][1].

Multiple gestation rate in clomiphene-treated cycles is approximately 5, 10% (predominantly twins; higher-order multiples rare) [1][7]. Ovarian hyperstimulation syndrome is rare with clomiphene compared with gonadotropin protocols. Endometrial thinning [1][5][1][6] may impair implantation in a subset of cycles and is a known reason for switching to letrozole or gonadotropin protocols in patients with otherwise good ovulatory response.

Male-hypogonadism off-label use (12.5, 25 mg every other day or daily): the most common reported events across Katz, Moskovic, Krzastek, Soares, and the enclomiphene phase 2 program are mild mood changes, breast tenderness, transient visual disturbances, and occasional headache [3][8]. Sperm-count preservation distinguishes clomiphene from exogenous testosterone replacement [3][6][4][5]. Long-term cardiovascular outcomes specifically in men treated with clomiphene have not been studied in randomized trials [3][0][3][1][3][2].

Visual disturbances warrant discontinuation. Purvin 1995 [1][4] characterized the typical pattern (scintillating scotomata, flashes, after-images) and the generally reversible course after discontinuation.

Monitoring Clomiphene & Enclomiphene Therapy

Female ovulation induction: pre-treatment workup includes confirmation of patency of fallopian tubes and a recent semen analysis on the male partner. Baseline laboratory evaluation includes TSH, prolactin, AMH or antral follicle count, and any indicated PCOS workup. On therapy, ovulation is confirmed by mid-luteal progesterone, basal body temperature, urinary LH testing, or transvaginal ultrasound follicular monitoring. Pregnancy testing precedes each cycle. Treatment is limited to a maximum of approximately six ovulatory cycles per labeled and committee-opinion guidance [asrm2013clomid, asrm2021female] [schlegel2021aua1].

Male secondary hypogonadism (off-label): baseline workup includes total testosterone (confirmed on repeat morning measurement per AUA and Endocrine Society guidelines [mulhall2018aua, bhasin2018endo]), free or calculated bioavailable testosterone, LH, FSH, estradiol, prolactin, SHBG, PSA in age-appropriate men, hematocrit, and semen analysis when fertility is a clinical priority [krzastek2019].

On-therapy monitoring at 4, 8 weeks after initiation and every 6, 12 months thereafter: total testosterone (target mid-normal range), LH/FSH (should be within or above reference range), estradiol, semen analysis as indicated, hematocrit, and PSA in age-appropriate men. Visual symptoms warrant discontinuation and ophthalmologic evaluation.

Clomiphene & Enclomiphene in Special Populations

Clomiphene & Enclomiphene Evidence Quality

Evidence supporting the manufactured Clomid / Serophene 50 mg tablet for ovulation induction in selected anovulatory women is strong and longstanding: the Cochrane synthesis [brown2009cochrane], PPCOS-I [legro2007ppcosi], PPCOS-II [legro2014ppcosii], and the ASRM committee opinion [asrm2013clomid] integrate decades of randomized and observational data. The principal evolution in this evidence base over the past decade has been the demonstration of letrozole's superior live-birth rate in PCOS-related anovulatory infertility [legro2014ppcosii, pena2025adolescents], which reorients first-line therapy without invalidating clomiphene's labeled role [shabsigh2005]. Multi-gestation rate is the principal trade-off [bourdon2025]; long-term cancer-risk concerns have not been confirmed in modern parity-stratified cohort follow-up [brinton2013endo; moskovic2012].

Evidence supporting off-label use in male secondary hypogonadism is well-studied but uneven: a coherent body of observational case series and small-to-medium RCTs [guay1995] demonstrates durable testosterone restoration and acceptable short- and intermediate-term safety, and the AUA testosterone deficiency guideline [mulhall2018aua] and AUA/ASRM male infertility guideline [schlegel2021aua1, schlegel2021aua2] cite SERM therapy as an evidence-based fertility-preserving option [shabsigh2005]. The dedicated enclomiphene phase 2 and phase 3 program adds randomized evidence vs AndroGel for the isomer-isolated formulation; however, FDA non-approval of Androxal means no enclomiphene-isolated product is available as a manufactured reference [soares2018obesity; konnyu2026meta; kaminetsky2013enclo; earl2019enclo]. Long-term randomized cardiovascular outcomes data in men treated with clomiphene specifically do not exist; the parallel TRAVERSE evidence for testosterone replacement is not transferable [brinton2014breast; reigstad2017; tomao2014ovarian; hill2009enclo].

Evidence specifically supporting compounded preparations is absent, there is no parallel efficacy program for compounded clomiphene or enclomiphene [krzastek2019] [katz2012; pelusi2022obesity]. Compounded use is therefore an extrapolation from the manufactured-product evidence (for the racemic preparation) and from the Repros phase 2/3 program (for enclomiphene), justified case by case by patient-specific clinical factors that the manufactured 50 mg tablet cannot accommodate [tomao2014breast; wiehle2013enclo; wiehle2014enclo].

Major Clomiphene & Enclomiphene Clinical Studies

Study	Design	Participants	Duration	Finding
PPCOS-I (Legro et al., NEJM 2007)	Phase III randomized double-blind clinical trial of clomiphene vs metformin vs both in PCOS-related anovulatory infertility	626	Up to 6 ovulatory cycles	Clomiphene superior to metformin for live birth (22.5% vs 7.2%); combination not significantly better than clomiphene alone, established clomiphene as first-line ovulation induction in PCOS through 2014 [legro2007ppcosi]
PPCOS-II (Legro et al., NEJM 2014)	Phase III randomized double-blind clinical trial of letrozole vs clomiphene for infertility in PCOS	750	Up to 5 treatment cycles	Letrozole produced higher live-birth rate (27.5%) than clomiphene (19.1%), reorienting first-line ovulation induction in PCOS toward letrozole while preserving clomiphene's labeled role [legro2014ppcosii]
Brown et al. Cochrane review (2009)	Systematic review and meta-analysis of clomiphene citrate and antiestrogens vs placebo for ovulation induction in PCOS	—	Pooled across trials	Clomiphene produced higher ovulation and pregnancy rates than placebo; foundational quantitative synthesis pre-PPCOS-II [brown2009cochrane]
ASRM Practice Committee (Fertil Steril 2013)	Committee opinion synthesizing labeled use and evidence-based positioning of clomiphene for infertile women	—	—	Codified the labeled use, the six-cycle treatment limit, and the place of clomiphene in the post-PPCOS-I era. Subsequent letrozole transition reflects PPCOS-II but does not invalidate the committee opinion's framing [asrm2013clomid].
Adashi (Fertil Steril 1984), Mechanism review	Conceptual/ mechanistic review of clomiphene's site(s)	—	—	Established the SERM framing for clomiphene, the isomer-dependent pharmacology (enclomiphene pure antagonist

Study	Design	Participants	Duration	Finding
	and mechanism(s) of action			short half-life, zuclomiphene mixed agonist long half-life), and the hypothalamic-pituitary disinhibition mechanism [adashi1984]
Mikkelson et al. (Fertil Steril 1986), Single-dose PK	Pharmacokinetic study of clomiphene citrate in normal volunteers	—	—	Established the triphasic disposition with fast enclomiphene clearance (1, 2 days) and slow zuclomiphene tail (weeks), kinetic basis for the long washout and rationale for an enclomiphene-isolated product [mikkelson1986]
Ghobadi et al. (J Clin Pharmacol 2009), Isomer PK in PCOS	Single-dose PK study in anovular PCOS women, with isomer-level measurement	—	—	Confirmed the asymmetric isomer clearance in patients, zuclomiphene detectable >4 weeks after a single dose, enclomiphene cleared within days [ghobadi2009]
Purvin (Arch Ophthalmol 1995), Visual disturbances	Case series of visual disturbances attributed to clomiphene citrate	—	—	Characterized the typical presentation (scintillating scotomata, flashes, after-images) and the generally reversible course after discontinuation; established the discontinue-on-symptom recommendation [purvin1995visual]
Gonen and Casper (Hum Reprod 1990), Endometrial effect	Sonographic study of endometrial thickness and pattern in clomiphene-stimulated vs natural cycles	—	—	Demonstrated clomiphene's adverse effect on endometrial development, the peripheral antiestrogenic signature attributed to zuclomiphene [gonen1990endo]
Quaas et al. (Fertil Steril 2021), AMIGOS endometrial thickness	Comparison of endometrial thickness after ovarian stimulation with gonadotropin,	—	—	Endometrial thickness was lower in clomiphene cycles than in letrozole or gonadotropin cycles; clinically meaningful difference [quaas2021endo]

Study	Design	Participants	Duration	Finding
	clomiphene, or letrozole in unexplained infertility (AMIGOS substudy)			
Guay et al. (JCEM 1995), Original male-hypogonadism series	Open-label study of clomiphene-mediated testosterone restoration in impotent men with secondary hypogonadism	—	—	Demonstrated symptomatic and biochemical benefit; opened the off-label male-hypogonadism literature [guay1995]
Shabsigh et al. (J Sex Med 2005), T/E ratio in male hypogonadism	Observational characterization of clomiphene's effect on the testosterone-to-estradiol ratio in male hypogonadism	—	—	Established the endocrine signature of clomiphene therapy in men, testosterone rises faster than estradiol, T/E ratio increases [shabsigh2005]
Katz et al. (BJU Int 2012), Young hypogonadal men	Retrospective cohort of clomiphene citrate treatment outcomes in young hypogonadal men	86	Median 19 months	Durable testosterone increase from baseline ~250 ng/dL to ~610 ng/dL on 25 mg every other day to 50 mg daily; symptomatic improvement; favorable safety [katz2012]
Moskovic et al. (BJU Int 2012), Long-term hypogonadism safety	Multi-year urology cohort of clomiphene citrate for long-term management of hypogonadism	—	—	Sustained testosterone restoration and acceptable safety over multi-year follow-up; supports use as a long-term TRT alternative in selected men [moskovic2012]
Krzastek et al. (J Urol 2019), Five-year safety and efficacy	Retrospective cohort of long-term (up to 5-year) clomiphene citrate therapy for hypogonadism	—	—	Sustained efficacy and a safety profile consistent with short-term studies; longest observational follow-up in the male-hypogonadism literature [krzastek2019]
Soares et al. (Int J Obes 2018), Obesity-associated hypogonadism RCT	Randomized double-blind placebo-controlled trial of clomiphene in male	—	—	Clomiphene produced clinically meaningful testosterone restoration vs placebo; first

Study	Design	Participants	Duration	Finding
	obesity-associated hypogonadism			dedicated RCT in this population [soares2018obesity]
Pelusi et al. (Endocr Metab Immune Disord Drug Targets 2022), Sexual function in obese men	Observational extension to overall sexual function in dysmetabolic obese men with low testosterone treated with clomiphene	—	—	Sexual function improved alongside testosterone restoration; supports the obesity-hypogonadism use case [pelusi2022obesity]
Kaminetsky et al. (J Sex Med 2013), Enclomiphene phase 2	Phase 2 randomized study of oral enclomiphene citrate vs testosterone gel in men with secondary hypogonadism	—	—	Enclomiphene stimulated endogenous testosterone production and preserved sperm counts; testosterone gel suppressed sperm counts as expected [kaminetsky2013enclo]
Wiehle et al. (BJU Int 2013), Enclomiphene pharmacodynamics	Randomized double-blind dose-finding pharmacodynamic study of enclomiphene citrate in men with secondary hypogonadism	—	—	Characterized the dose-response and pharmacodynamic time course of testosterone restoration by enclomiphene-isolate; mechanistic foundation for the phase 3 program [wiehle2013enclo]
Wiehle et al. (Fertil Steril 2014), Enclomiphene vs AndroGel	Phase 2 randomized comparator trial of enclomiphene citrate vs AndroGel in men with secondary hypogonadism	—	—	Enclomiphene restored testosterone while preventing oligospermia; AndroGel restored testosterone but suppressed sperm counts, fertility-preservation rationale [wiehle2014enclo]
Earl and Kim (Expert Rev Endocrinol Metab 2019), Enclomiphene review	Review of enclomiphene citrate development and clinical rationale for secondary hypogonadism	—	—	Synthesizes the phase 2/3 program, the FDA non-approval, and the case for an isomer-isolated SERM in men who want to preserve fertility [earl2019enclo]
		—	—	

Study	Design	Participants	Duration	Finding
Schlegel et al. (Fertil Steril 2021), AUA/ ASRM male infertility guideline	Joint AUA/ASRM clinical practice guideline parts I and II covering diagnosis and treatment of male infertility			Cites SERM (clomiphene) and aromatase inhibitor therapy as evidence-based options for selected men with hypogonadotropic hypogonadism and fertility goals; reserves routine empirical use [schlegel2021aua1; schlegel2021aua2]
Mulhall et al. (J Urol 2018), AUA testosterone deficiency guideline	AUA clinical practice guideline on evaluation and management of testosterone deficiency	—	—	Recognizes clomiphene and aromatase inhibitor therapy as fertility-preserving alternatives to testosterone replacement in selected men [mulhall2018aua]
Bhasin et al. (JCEM 2018), Endocrine Society guideline	Endocrine Society clinical practice guideline on testosterone therapy in men with hypogonadism	—	—	Discusses SERM-based fertility-preserving options in the context of TRT decision-making [bhasin2018endo]
Bourdon et al. (Fertil Steril 2025), Nationwide multi-gestation analysis	Nationwide registry analysis of clomiphene citrate-conceived pregnancies and multi-gestation births	—	—	Quantifies the contemporary multi-gestation and perinatal-outcome impact of clomiphene-driven ovulation induction [bourdon2025]
Brinton et al. (Hum Reprod 2013), Endometrial cancer follow-up	Extended infertility-cohort follow-up of fertility drugs and endometrial cancer risk	—	—	Did not confirm an independent clomiphene-attributable endometrial cancer signal after adjustment for the underlying infertility population [brinton2013endo]
Brinton et al. (Cancer Epidemiol Biomarkers Prev 2014), Breast cancer follow-up	Long-term follow-up of ovulation-stimulating drugs and breast cancer risk	—	—	No consistent excess breast cancer risk attributable to clomiphene independent of underlying infertility [brinton2014breast]
		—	—	

Study	Design	Participants	Duration	Finding
Reigstad et al. (Cancer Epidemiol Biomarkers Prev 2017), Parity-stratified cancer risk	Norwegian registry-based cohort stratifying fertility-drug cancer risk by parity status			Supports the null association in clomiphene-exposed parous women; partially explains the historical Whittemore/Rossing signals as residual confounding by infertility/parity [reigstad2017]
Konnyu et al. (JCEM 2026), Male infertility systematic review	Systematic review of hormonal treatment efficacy for reproductive outcomes in normo-gonadotropic male infertility	—	—	Effects of SERM, aromatase inhibitor, and gonadotropin therapy on reproductive outcomes in normo-gonadotropic men are limited and inconsistent across trials; supports cautious patient-by-patient framing [konnyu2026meta]
Khashaba et al. (Asian J Urol 2025), Idiopathic male subfertility SR	Systematic review of clomiphene citrate and tamoxifen efficacy on pregnancy rates in idiopathic male subfertility	—	—	Pooled SERM effect on pregnancy rates in idiopathic male subfertility is modest; specialist-level individualization remains required [khashaba2025]

Clomiphene & Enclomiphene Pharmacokinetics & Pharmacodynamics

Pharmacokinetics

Clomiphene citrate is rapidly absorbed after oral administration; peak plasma concentrations of the racemic mixture occur within ~6 hours. The molecule is metabolized primarily by hepatic CYP-mediated pathways and excreted in feces with extensive enterohepatic recirculation. The defining pharmacokinetic feature is the asymmetric isomer clearance: enclomiphene (trans-isomer) clears within 1, 2 days; zuclomiphene (cis-isomer) has an extended terminal half-life on the order of weeks because of enterohepatic recirculation and tissue distribution [mikkelson1986, ghobadi2009].

Single-dose PK in healthy volunteers [mikkelson1986] established the triphasic disposition. Ghobadi 2009 [ghobadi2009] extended the isomer-level analysis to anovular PCOS women and confirmed that zuclomiphene concentrations remain detectable for >4 weeks after a single oral dose. This kinetic asymmetry underlies the prolonged washout, the cumulative cycle-to-cycle exposure across multi-cycle ovulation induction, and the pharmacologic rationale for enclomiphene-isolated preparations.

Compounded preparations may differ from the manufactured tablet in dissolution and absorption characteristics depending on capsule excipients and dosage form (capsule vs troche vs sublingual); cross-product PK equivalence cannot be assumed without local stability and absorption data.

Pharmacodynamics

Pharmacodynamic effects on the HPG axis are dose-dependent. In ovulation-induction dosing (50, 150 mg daily for 5 days), serum FSH and LH rise during and shortly after the treatment days; ovulation typically occurs 5, 10 days after the last treatment day [katz2012]. In male-hypogonadism dosing (12.5, 25 mg every other day or daily), serum LH and FSH rise within 2, 4 weeks; total testosterone follows and stabilizes within 8, 12 weeks [wiehle2014enclo]. Estradiol may also rise modestly through preserved aromatization of the additional testosterone; routine monitoring of estradiol is recommended in men on long-term therapy [moskovic2012; krzastek2019; kaminetsky2013enclo].

Peripheral pharmacodynamic effects, endometrial thinning, cervical mucus quality, occasional visual disturbances, are attributable primarily to the zuclomiphene isomer and its extended residence time at peripheral ER sites [gonen1990endo, quaas2021endo, purvin1995visual]. Enclomiphene-isolated preparations were developed specifically to dissociate the LH/FSH-raising central effect from these peripheral antiestrogenic effects [hill2009enclo, earl2019enclo].

↓↑ Comparing Clomiphene & Enclomiphene Formulations

Manufactured Clomid and Serophene (and their generics) are clomiphene citrate 50 mg oral tablets containing the racemic 38:62 zuclomiphene:enclomiphene mixture [asrm2013clomid; mikkelson1986; ghobadi2009]. There is no manufactured product at lower strengths or in non-tablet dosage forms.

Compounded preparations vary in strength (typical compounded male-hypogonadism strengths are 12.5 mg or 25 mg capsules), in isomer composition (compounded enclomiphene-isolate capsules contain only the trans-isomer), and in dosage form (capsule, troche, sublingual). PK and pharmacodynamic equivalence to the manufactured tablet cannot be assumed across these differences. Pharmacist verification of API identity and quantitative analytical confirmation of isomer composition are particularly important for enclomiphene-isolate preparations because no FDA-approved reference product exists for cross-comparison [earl2019enclo].

🌡 Clomiphene & Enclomiphene Storage and Handling

Manufactured Clomid and Serophene tablets are stored at controlled room temperature (20, 25°C / 68, 77°F) in the original container, protected from light and moisture. Compounded clomiphene capsules, troches, and sublingual preparations are stored per the pharmacy's stability data and beyond-use date

assignment under USP <795>; controlled room temperature storage is typical for nonsterile oral preparations [usp_795].

Clomiphene & Enclomiphene Compounding & Operations

503A compounding

Compounded clomiphene and enclomiphene preparations are prepared under 503A on patient-specific prescriptions in state-licensed compounding pharmacies. RonanRx prepares nonsterile oral capsules, troches, and sublingual preparations per USP General Chapter <795>, the official compendial standard for nonsterile pharmaceutical compounding, with documented active ingredient sourcing, gravimetric verification, and lot traceability [fda503a; usp_795].

Beyond-use dating, ingredient identity verification, and stability assessment follow USP <795> requirements. Each compounded batch is documented per state board of pharmacy retention rules with full traceability from API lot through dispensing. Enclomiphene-isolate preparations require additional analytical verification of isomer composition because no FDA-approved reference product exists for cross-comparison.

Pharmacist review

Each prescription for compounded clomiphene or enclomiphene undergoes pharmacist review prior to dispensing [kaminetsky2013enclo]. The review confirms: a documented patient-specific clinical reason that the manufactured 50 mg tablet is not appropriate (male-hypogonadism dose individualization at 12.5, 25 mg, enclomiphene-isolate for fertility preservation, or alternative dosage form for excipient sensitivity); absence of contraindications (confirmed-pregnancy status in women, active hepatic disease, abnormal uterine bleeding of undetermined origin, prior visual adverse event without ophthalmologic clearance); appropriate concomitant medication review; and a prescribed regimen consistent with the documented evidence base for the population [asrm2013clomid; mulhall2018aua; schlegel2021aua1].

RonanRx does not fill prescriptions that read as routine substitution of compounded clomiphene for the manufactured 50 mg tablet for the FDA-labeled female ovulation-induction indication, consistent with FDA guidance on compounded copies of commercially available drugs [fda_essentially_a_copy] [krzastek2019].

Quality and traceability

Active pharmaceutical ingredients (clomiphene citrate racemate and enclomiphene citrate isomer-isolated) are sourced from FDA-registered facilities with documented certificates of analysis. Enclomiphene-isolate API requires analytical confirmation of isomer composition because no FDA-approved reference product exists. Each batch is recorded with lot numbers traceable to API source, compounding date, beyond-use date, and dispensing pharmacist of record. Finished product lot records are retained per state board of pharmacy retention requirements.

Cold chain

Clomiphene and enclomiphene preparations are not cold-chain products. Manufactured tablets and compounded capsules, troches, and sublingual preparations are stored at controlled room temperature. Routine shipping does not require temperature-controlled transport.

Frequently Asked Questions About Clomiphene & Enclomiphene

Is compounded clomiphene the same as Clomid?

No. Clomid and Serophene are the FDA-approved manufactured clomiphene citrate 50 mg tablets [asrm2013clomid]. Compounded clomiphene is pharmacy-prepared on a patient-specific prescription and is not bioequivalent to the manufactured tablet. Compounded drugs are not FDA-approved [fda_essentially_a_copy]. RonanRx compounds clomiphene only when the prescriber documents a clinical reason that the manufactured 50 mg tablet does not fit the patient, for example, a non-standard strength (12.5 mg or 25 mg for male hypogonadism), an enclomiphene-isolated preparation, or an alternative dosage form [fda503a].

Why would a man take clomiphene?

Off-label, men with low testosterone caused by an under-active pituitary signal (secondary hypogonadism) may take clomiphene at low doses (12.5, 25 mg daily or every other day) to raise their endogenous testosterone while preserving sperm production [moskovic2012; krzastek2019]. Conventional testosterone replacement (gel, injection, patch) suppresses the pituitary signal and therefore shuts down sperm production [mcbride2016recovery]. The AUA testosterone deficiency guideline and the AUA/ASRM male infertility guideline recognize SERM therapy (clomiphene, enclomiphene) as a fertility-preserving alternative in selected men [mulhall2018aua; schlegel2021aua1; katz2012].

What is enclomiphene and why isn't it FDA-approved?

Clomiphene citrate is a mixture of two isomers, enclomiphene (the trans isomer, a pure estrogen receptor antagonist with a short half-life) and zuclomiphene (the cis isomer, a mixed agonist with a long half-life) [hill2009enclo]. Enclomiphene delivers most of the LH/FSH-raising effect; zuclomiphene contributes the long washout and most of the peripheral antiestrogenic effects (endometrial thinning, occasional visual side effects). Repros Therapeutics developed an enclomiphene-only product called Androxal and conducted phase 2 and phase 3 trials in male secondary hypogonadism [earl2019enclo]. The FDA did not approve Androxal, and Repros exited the market. Compounded enclomiphene citrate capsules support clinicians who wish to translate the Repros evidence base into practice, because no FDA-approved enclomiphene-isolated product exists [kaminetsky2013enclo; wiehle2013enclo; wiehle2014enclo].

How does clomiphene compare with letrozole for PCOS?

PPCOS-II (Legro et al., NEJM 2014) randomized 750 women with PCOS to letrozole vs clomiphene and found a higher live-birth rate with letrozole (27.5% vs 19.1%), letrozole is now preferred first-line for PCOS-related anovulatory infertility, including in the international evidence-based PCOS guidance [legro2014ppcosii; pena2025adolescents; asrm2013clomid]. Clomiphene retains a labeled FDA role and is appropriate where letrozole is not, but it is no longer the first choice for PCOS.

What are the most common side effects?

Women on labeled ovulation-induction doses: hot flashes (10, 20%), abdominal discomfort or bloating, breast tenderness, nausea, and headache, usually mild and self-limited [asrm2013clomid]. Visual disturbances (1, 2%) warrant discontinuation. Multiple gestation (predominantly twins) occurs in approximately 5, 10% of treated cycles [bourdon2025]. Men on off-label doses (12.5, 25 mg): mild mood changes, breast tenderness, occasional visual disturbance, generally well tolerated in observational follow-up out to 5 years [purvin1995visual; katz2012; krzastek2019].

Does clomiphene cause cancer?

Early signals from the 1992 Whittemore collaborative analysis and the 1994 Rossing NEJM cohort suggested elevated ovarian cancer risk in clomiphene-exposed nulligravid women [whittemore1992; rossing1994; tomao2014ovarian]. Modern long-term cohort follow-up, Brinton 2013 (endometrial cancer), Brinton 2014 (breast cancer), Reigstad 2017 (parity-stratified registry), and the Tomao 2014 reviews, has not consistently confirmed an independent excess attributable to the drug after adjustment for the underlying infertility population [brinton2013endo; brinton2014breast; reigstad2017]. The historic six-cycle treatment limit in labeled use remains the cautious practice [tomao2014breast].

Can I take clomiphene during pregnancy?

No. Clomiphene is FDA pregnancy category X, contraindicated once pregnancy has been established. The drug is used only during a treatment cycle in women who are not yet pregnant [asrm2013clomid]. Pregnancy testing precedes each cycle [elizur2008safety].

Does RonanRx sell compounded clomiphene or enclomiphene directly to patients?

No. Compounded clomiphene and enclomiphene require a patient-specific prescription written by a licensed doctor for an identified patient with a documented clinical reason that the manufactured Clomid 50 mg tablet is not appropriate, plus pharmacist review before dispensing [fda_essentially_a_copy]. RonanRx is not a direct-to-consumer storefront [fda503a].

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How to Access Clomiphene & Enclomiphene

Compounded Clomiphene & Enclomiphene is dispensed under 503A on a patient-specific prescription. Depending on your role, the next step looks different.

FOR PRESCRIBING CLINICIANS

Offer this medication

A pharmacist will follow up within two business days. We'll cover state availability, supported formulations, and what integration looks like for your clinic.

ronanrx.com/request-partnership-call

PATIENT WITH A DOCTOR

Receive your prescription

If your doctor has prescribed Clomiphene & Enclomiphene, sign up so we can prepare and ship your medication. The signup wizard collects intake and connects you to the prescribing workflow.

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PATIENT WITHOUT A DOCTOR

Find a partner clinic

RonanRx prescribes through partner clinics — we don't initiate prescriptions on this site. Read how the referral process works and how to find a partner clinic in your state.

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Other compounds RonanRx makes

This monograph is one of many in the RonanRx formulary. Every compound below is prepared under 503A on a patient-specific prescription. Browse the full catalog at ronanrx.com/medications and ronanrx.com/peptides, or scan the codes at right for each index.

Medications

Peptides

MEDICATIONS (40)

Alpha-Lipoic Acid (ALA) — Antioxidant & mitochondrial
Coenzyme Q10 (CoQ10) — Antioxidant & mitochondrial
Glutathione — Antioxidant & mitochondrial
NAD+ / NMN — Antioxidant & mitochondrial
Compounded Topical Anesthetics (BLT, LET) — Dermatology
Topical Minoxidil — Dermatology
Topical Tretinoin — Dermatology
Compounded Magnesium — Energy & nutritional
Cyanocobalamin — Energy & nutritional
High-Dose Vitamin D — Energy & nutritional
Hydroxocobalamin — Energy & nutritional
Iron (Compounded) — Energy & nutritional
L-Carnitine — Energy & nutritional
Methylcobalamin (B12) — Energy & nutritional
Methylfolate — Energy & nutritional
Anastrozole — Hormone optimization
Clomiphene & Enclomiphene — Hormone optimization
DHEA — Hormone optimization
Estradiol — Hormone optimization
Estriol — Hormone optimization
Human Chorionic Gonadotropin (HCG) — Hormone optimization
Pregnenolone — Hormone optimization
Progesterone — Hormone optimization
Testosterone — Hormone optimization
Compounded Metformin — Metabolic & weight
Compounded Semaglutide — Metabolic & weight
Compounded Tirzepatide — Metabolic & weight
Lipotropic Injection (MIC, MICC) — Metabolic & weight
Low-Dose Naltrexone (LDN) — Metabolic & weight
Naltrexone-Bupropion Combination — Metabolic & weight
Topiramate — Metabolic & weight
Bremelanotide / PT-141 — Sexual health
Compounded Sildenafil — Sexual health
Compounded Tadalafil — Sexual health
Trimix Injection — Sexual health
Compounded Gabapentin — Sleep & recovery
Compounded Melatonin — Sleep & recovery
Compounded T3 (Liothyronine) — Thyroid
Compounded T3/T4 Combinations — Thyroid
Compounded T4 (Levothyroxine) — Thyroid

PEPTIDES (21)

Sermorelin — Available now

Tesamorelin — Available now

AOD-9604 — Growth-hormone axis (under FDA review)

CJC-1295 — Growth-hormone axis (under FDA review)

GHRP-2 / GHRP-6 — Growth-hormone axis (under FDA review)

Hexarelin — Growth-hormone axis (under FDA review)

Ipamorelin — Growth-hormone axis (under FDA review)

MK-677 / Ibutamoren — Growth-hormone axis (under FDA review)

5-Amino 1MQ — Metabolic & longevity (under FDA review)

Epitalon / Epithalon — Metabolic & longevity (under FDA review)

MOTS-C — Metabolic & longevity (under FDA review)

Thymosin Alpha-1 / Thymalin — Metabolic & longevity (under FDA review)

DSIP, Delta Sleep-Inducing Peptide — Neuro & cognitive (under FDA review)

Selank — Neuro & cognitive (under FDA review)

Semax — Neuro & cognitive (under FDA review)

Vasoactive Intestinal Peptide (VIP) — Neuro & cognitive (under FDA review)

BPC-157 — Tissue repair (under FDA review)

KPV — Tissue repair (under FDA review)

LL-37 — Tissue repair (under FDA review)

Pentadeca Arginate (PDA) — Tissue repair (under FDA review)

TB-500 / Thymosin Beta-4 — Tissue repair (under FDA review)