# ANDROXAL

## (Enclomiphene Citrate) Capsules, for Oral Use

*Comprehensive Medication Guide & Investigational Product Information*

Repros Therapeutics development program • SERM • Not FDA-approved

**REGULATORY STATUS — READ FIRST**

ANDROXAL is the proposed brand name for enclomiphene citrate developed by Repros Therapeutics for secondary hypogonadism in men. An NDA was submitted; FDA issued a Complete Response Letter in 2015 and did not approve the product. The related EU application EnCyzix (enclomifene) received a CHMP negative opinion in 2018. ANDROXAL is not an FDA-approved marketed drug. This document is an educational insert-style summary of the development program, published trials, and class safety information. It is not a license to manufacture, compound, import, or use unapproved medicine.

**IMPORTANT DISCLAIMER**

Compiled from ClinicalTrials.gov records (e.g., ZA-301/ZA-302 programs), company releases, published enclomiphene papers, and clomiphene-class warnings. Always consult a licensed clinician and current law in your jurisdiction.

# HIGHLIGHTS OF PRODUCT INFORMATION

## PROPOSED INDICATION (NOT APPROVED)

ANDROXAL was developed to treat adult men with secondary (hypogonadotropic) hypogonadism — low morning testosterone with low or inappropriately normal LH — in order to restore testosterone into the eugonadal range while maintaining gonadotropins and sperm concentration.

## PROPOSED DOSAGE (TRIAL REGIMEN)

- 12.5 mg orally once daily.
- Up-titrate to 25 mg once daily if morning testosterone remains below approximately 300 ng/dL after about 6 weeks.
- Capsules in the development program; take at a consistent time, with or without food.

## DOSAGE FORMS STUDIED

Oral capsules 12.5 mg and 25 mg enclomiphene citrate.

## CONTRAINDICATIONS (PROPOSED / CLASS)

- Hypersensitivity to enclomiphene or clomiphene.
- Prostate cancer or male breast cancer (androgen-responsive disease requires evaluation).
- Pregnancy (class contraindication).
- Significant hepatic disease; untreated pituitary mass until evaluated.

## WARNINGS AND PRECAUTIONS

- Visual symptoms — stop and obtain eye exam (clomiphene-class).
- Thromboembolic risk theoretically associated with estrogen modulation.
- Monitor testosterone, LH, FSH, estradiol, hematocrit, PSA as appropriate.
- Not a treatment for primary testicular failure.

## ADVERSE REACTIONS

Headache, hot flush, nausea, mood change, visual disturbance, abdominal discomfort. Comparative series versus mixed clomiphene suggest fewer estrogenic complaints in some cohorts.

# FULL PRODUCT INFORMATION

## 1 DEVELOPMENT HISTORY AND PROPOSED USE

ANDROXAL (enclomiphene citrate) is the purified trans-(E)-isomer of clomiphene. Commercial clomiphene citrate (Clomid) is a mixture of enclomiphene (~62%) and zuclomiphene (~38%). Zuclomiphene is more estrogenic and persists longer in tissue. Isolating enclomiphene was intended to keep the antiestrogenic effect at the hypothalamus/pituitary while reducing estrogenic adverse effects.

Repros designed ANDROXAL for overweight or obese adult men with acquired secondary hypogonadism. The clinical rationale was that exogenous testosterone gel raises serum T but suppresses LH/FSH and can reduce sperm counts, whereas enclomiphene raises T by stimulating the man's own axis.

FDA did not approve the NDA. Public summaries of the 2015 Complete Response Letter cite trial-design and endpoint concerns and a request for additional data, including longer-term outcomes. Symptom benefit beyond laboratory testosterone restoration was a key review issue. Development of enclomiphene for this indication was later discontinued by the originator program.

## 2 DOSAGE AND ADMINISTRATION (AS STUDIED)

In phase 2b and phase 3 protocols, men received ANDROXAL 12.5 mg once daily. If morning total testosterone remained <300 ng/dL at about week 6, the dose could be increased to 25 mg once daily. No further titration was generally allowed. Treatment duration in pivotal protocols was typically 12–18 weeks, with semen analyses and 24-hour testosterone profiling in some studies.

These doses are investigational. They are not FDA-approved labeled doses.

## 3 DOSAGE FORMS AND STRENGTHS

Investigational ANDROXAL: oral capsules containing 12.5 mg or 25 mg enclomiphene citrate. (A related EU dossier, EnCyzix, proposed 8.5 mg and 17 mg hard capsules.)

## 4 CONTRAINDICATIONS

Based on class and protocol exclusions, ANDROXAL should not be used in pregnancy; hypersensitivity to enclomiphene/clomiphene; significant liver disease; untreated pituitary or intracranial lesion; and in men with known or suspected androgen-dependent prostate or breast cancer pending specialist evaluation.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Unapproved Status

There is no FDA-approved ANDROXAL label, REMS, or manufacturing standard for a finished brand product. Compounded "enclomiphene" products are not ANDROXAL and may differ in purity, isomer content, and dose accuracy.

### 5.2 Visual Symptoms

Clomiphene-class drugs can cause blurred vision, scotomata, and photophobia. Pivotal protocols included eye examinations. Stop the drug and obtain ophthalmology review if visual symptoms occur.

### 5.3 Thromboembolism

Estrogen-pathway modulators have been associated with thrombosis in other settings. Use caution in men with prior VTE or strong risk factors.

### 5.4 Laboratory Monitoring

Check morning total (and free, if indicated) testosterone, LH, FSH, estradiol, CBC/hematocrit, and PSA as age-appropriate at baseline and after 6–8 weeks.

### 5.5 Fertility Counseling

Unlike testosterone gel, ANDROXAL was designed not to suppress spermatogenesis. Preservation of mean sperm concentration was a co-focus of phase 3 work. Individual men can still have adverse semen changes; obtain a semen analysis if conception is a goal.

### 5.6 Sport and Misuse

Anti-estrogenic agents are prohibited in many anti-doping codes (WADA S4). ANDROXAL is not a bodybuilding supplement.

## 6 ADVERSE REACTIONS

| System | Reported or Class Effects |
|---|---|
| Nervous system | Headache, dizziness, insomnia |
| Vasomotor | Hot flush |
| Gastrointestinal | Nausea, abdominal discomfort |
| Psychiatric | Mood lability, irritability |
| Ocular | Blurred vision, photophobia, scotomata |
| Reproductive / lab | Rise in T, LH, FSH; variable estradiol; breast tenderness uncommon vs mixed clomiphene |

## 7 DRUG INTERACTIONS

Formal interaction studies are limited. Exogenous testosterone, anabolic steroids, and GnRH analogues can override or blunt HPG-axis stimulation. Strong enzyme inducers or inhibitors may alter hormone levels. Monitor laboratories when concomitant drugs change.

## 8 USE IN SPECIFIC POPULATIONS

Pregnancy: contraindicated. Lactation: avoid. Pediatrics: not studied for this use. Geriatrics: pivotal programs focused on men often ≤60 years and frequently overweight (BMI ≥25 kg/m² in some protocols); data in older men are limited. Hepatic impairment: avoid significant liver disease.

## 10 OVERDOSAGE

No specific antidote. Provide supportive care for exaggerated SERM effects (vasomotor symptoms, visual change, gastrointestinal upset).

## 11 DESCRIPTION

Enclomiphene citrate is a nonsteroidal triphenylethylene SERM, the trans isomer of clomiphene.

**Free-base formula:** C26H28ClNO

ANDROXAL capsules in trials contained 12.5 mg or 25 mg of the citrate salt.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Enclomiphene blocks estrogen negative feedback at the hypothalamus and pituitary, increasing LH and FSH. LH stimulates Leydig-cell testosterone synthesis; FSH supports Sertoli-cell function and spermatogenesis.

### 12.2 Pharmacodynamics

In randomized trials, 12.5 mg and 25 mg daily raised morning and 24-hour average testosterone into the normal male range in a majority of intent-to-treat subjects with secondary hypogonadism. Company reports from ZA-301 noted that 79% of ITT ANDROXAL subjects had 24-hour average T in the normal range and that individual T values did not exceed the upper reference limit in that analysis. LH and FSH increased. Topical testosterone comparators raised T but reduced gonadotropins and sperm concentration.

### 12.3 Pharmacokinetics

Oral enclomiphene is absorbed and cleared more rapidly than zuclomiphene. Zuclomiphene accumulation is the pharmacokinetic rationale for a single-isomer product. Food-effect data are limited; once-daily dosing was used in trials.

## 14 CLINICAL STUDIES

ZA-301 and ZA-302 were multicenter, randomized, double-blind phase 3 studies in men with secondary hypogonadism (morning T typically <300 ng/dL, normal baseline sperm concentration in semen-focused protocols). ANDROXAL 12.5 mg (with optional up-titration to 25 mg) was compared with placebo and, in earlier/related work, with topical testosterone (Testim/AndroGel). Co-primary themes were (1) proportion of men whose testosterone Cavg entered the normal range and (2) lack of a clinically important drop in sperm concentration versus testosterone gel.

Published Wiehle/Kim program papers reported normalization of testosterone with preservation of mean sperm counts on enclomiphene, versus suppression on gel. FDA still declined approval, emphasizing that raising a laboratory value is not automatically sufficient without agreed clinical outcome evidence and additional safety follow-up.

## 16 HOW SUPPLIED

ANDROXAL was supplied only in clinical-trial packaging (12.5 mg and 25 mg capsules). It is not a commercially FDA-approved product. Store any legally prescribed compounded analog at room temperature, protected from moisture, out of reach of children — only if a licensed clinician and pharmacy have provided it lawfully.

## 17 PATIENT COUNSELING INFORMATION

Explain that ANDROXAL was never approved. Discuss vision warning, clot symptoms, need for blood and semen tests, and that internet “PCT” use is not an approved indication.

# PATIENT INFORMATION

**ANDROXAL (AN-drox-al) • enclomiphene citrate**

## What is the most important information I should know?

ANDROXAL is not an FDA-approved medicine. The company that developed it did not receive U.S. or EU marketing authorization. Do not buy unlabeled “Androxal” online.

Stop the medicine and get medical help if you have vision changes, chest pain, trouble breathing, or swelling of one leg. Do not take it if you are pregnant.

## What was ANDROXAL supposed to treat?

It was studied in adult men with secondary hypogonadism — low testosterone because the brain/pituitary signal to the testes is too low, not because the testes have completely failed. The idea was to raise the body’s own testosterone and keep sperm production working, unlike testosterone gel.

## How was it taken in studies?

- 12.5 mg capsule once a day, sometimes increased to 25 mg after about 6 weeks if testosterone was still low.
- Blood tests and, if fertility mattered, semen tests were required.

## What are possible side effects?

Headache, hot flashes, nausea, mood changes, stomach discomfort, and eye symptoms. Serious risks include blood clots and liver problems (uncommon).

## General information

This leaflet is educational. It does not authorize use of unapproved enclomiphene. Talk with a licensed clinician about approved options for hypogonadism and male infertility.

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**END OF DOCUMENT**

*Educational summary of the ANDROXAL investigational program. Not an approved label.*