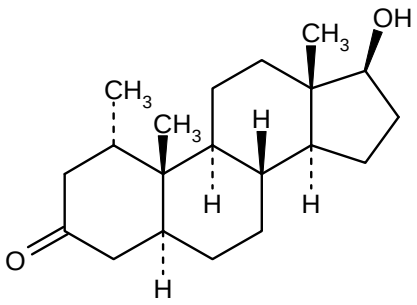
PRODUCT INFORMATION

PROVIRON®

NAME OF THE MEDICINE

Mesterolone is a white to yellowish crystalline powder and is practically insoluble in water.
The chemical name for mesterolone is 17 beta-Hydroxy-1 alpha-methyl-5 alpha-androstan-3-one and has the following structural formula:



Molecular formula	$C_{20}H_{32}O_2$
Molecular weight	304.47
Melting point	205 - 211°C
CAS Number	001424-00-6

DESCRIPTION

Proviron is a hormonal preparation and contains 25 mg mesterolone.

Each small white tablet contains mesterolone 25 mg and the excipients: lactose, starch-maize, povidone, methyl hydroxybenzoate, propyl hydroxybenzoate and magnesium stearate.

PHARMACOLOGY

Pharmacodynamics

Mesterolone (Proviron) has androgenic properties. Early studies suggested oral mesterolone did not usually suppress gonadotrophins or endogenous testosterone production. A later single dose study suggests there may be a central suppression effect at doses of 75-100 mg daily.

Pharmacokinetics

Following oral ingestion mesterolone is rapidly absorbed. In a study in 18 men the intake of Proviron 25 mg generated maximum serum drug levels of 3.1 ± 1.1 ng/mL after 1.6 ± 0.6 hours. Thereafter, drug levels in serum decrease with a terminal half-life of 12 - 13 hours. Mesterolone is bound to serum proteins by 98 %. Binding to albumin accounts for 40 % and binding to SHBG (sex hormone binding globulin) to 58 %.

Mesterolone is rapidly metabolised. The metabolic clearance rate from serum accounts for 4.4 ± 1.6 $mL \cdot min^{-1} \cdot kg^{-1}$. Renal excretion of unchanged drug has not been detected. In a study of C14 labelled mesterolone in two men, up to 2% of mesterolone was excreted as the conjugated form in the urine. The main metabolite has been identified as 1α-methyl-androsterone, which - in conjugated form - accounts for 55 - 70 % of renally excreted metabolites. The ratio of conjugated main metabolite glucuronide to sulfate detected in urine was about 12:1. As a further metabolite 1α-methyl-5α-androstane-3α,17β-diol has been recognized, which accounted for about 3 % of renally eliminated metabolites. Mesterolone was excreted in the form of metabolites. Within 7 days approximately 80% of the labelled doses were recovered in the urine and up to 13% in the faeces. Half of the labelled doses were excreted in the urine within 24 hours.

The absolute bioavailability of mesterolone was determined to be about 3 % of the oral dose.

INDICATIONS

- Hypogonadism

Androgen replacement for male hypogonadism, where there is androgen deficiency confirmed by clinical and biochemical testing (See ‘Precautions’ and ‘Dosage and Administration’).

CONTRAINDICATIONS

Carcinoma of the prostate, previous or existing liver tumours, breast cancer, hypercalcaemia.

Hypersensitivity to the active substance or to any of the excipients.

PRECAUTIONS

Androgens are not suitable for enhancing muscular development in healthy individuals or for increasing physical ability (See Adverse Effects).

The diagnosis of hypogonadism in males requires full endocrinological assessment including clinical history and physical examination, expert interpretation of serial measurements of serum testosterone, LH and FSH, additional tests as required to identify underlying disorders, and evaluation of the general health of the patient. See Dosage and Administration.

Prostate disease should be excluded prior to commencement, and regular examinations of the prostate should be carried out prophylactically.

Hepatic impairment (monitoring of hepatic function is recommended).

Conditions aggravated by fluid overload from sodium or fluid retention, such as cardiovascular disorders or renal impairment, hypertension, epilepsy or migraine.

In older men, urinary obstruction may be precipitated. Increased libido may occur.

Use in puberty may cause premature closure of the epiphyses and stop linear growth.

Diabetes mellitus, androgen-sensitive polycythaemia or sleep apnoea may be exacerbated.

Androgens are considered to be unsafe in patients with porphyria.

In rare cases benign and in even rarer cases malignant liver tumours leading in isolated cases to life-threatening intra-abdominal haemorrhage have been observed after the use of hormonal substances such as the one contained in Proviron. Peliosis hepatis has been reported in patients who received high doses over a prolonged period. Upper abdominal complaints should be reported to the doctor.

Carcinogenicity, mutagenicity and impairment of fertility

The carcinogenic potential of mesterolone has not been investigated in long term studies. However, sex steroids are known to promote the growth of certain hormone dependant tissues and tumours. There are rare reports of hepatocellular carcinoma in patients receiving long term therapy with androgens

at high doses. Withdrawal of the drugs did not lead to regression of the tumour in all cases. Chronic androgen deficiency is a protective factor for prostatic disease and hypogonadal men receiving androgen replacement therapy require surveillance for prostate disease similar to that recommended for eugonadal men of comparable age. Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hyperplasia and prostatic cancer.

The genotoxic potential of mesterolone has not been investigated.

The effects of mesterolone on fertility and early embryonic development have not been investigated. Proviron is for use in male patients only.

Mesterolone was shown to inhibit spermatogenesis in animals following oral administration. Fertility studies on the effect on sperm cells in humans have not been carried out with Proviron.

Use in pregnancy: Category X

Proviron is for use in male patients only.

Interactions with other medicines

Drug interactions which result in an increased clearance of sex hormones can lead to decreased therapeutic efficacy. This has been established with many hepatic enzyme inducing drugs (Including phenobarbital and phenytoin).

Androgens have been reported to enhance the activity of a number of drugs, with resulting increases in toxicity. Drugs affected include cyclosporin, antidiabetics, thyroxine and anticoagulents such as warfarin. Resistance to the effects of neuromuscular blockers has also been reported.

Effects on laboratory tests

Androgens may interfere with a number of clinical laboratory tests such as those for glucose tolerance and thyroid function.

ADVERSE EFFECTS

There is little information available on reported adverse events for Proviron.

If, in individual cases, frequent or persistent erections occur, the dose should be reduced or the treatment discontinued in order to avoid injury to the penis.

Headache has been reported.

The following adverse effects have been reported for androgens in general:

Fluid retention, impaired glucose tolerance, altered lipids and haematological parameters, abnormal liver function tests.

Gynaecomastia, prostate hyperplasia, virilization, priapism, increased libido, hirsutism, acne, precocious sexual development.

Premature epiphyseal closure.

Neoplasms including liver and prostate (See Contraindications and Precautions).
Psychiatric disturbances including mania, hypomania, depression, aggression and emotional lability have been described.

DOSAGE AND ADMINISTRATION

The tablets are to be swallowed whole with some liquid.

Unless otherwise prescribed by the doctor the following dosages are recommended:

- Hypogonadism: Before commencing therapy the diagnosis of hypogonadism should be unequivocally established; see Precautions.
For development of secondary male sex characteristics 1-2 Proviron tablets 3 times per day for several months.

-As maintenance dose 1 Proviron tablet 2-3 times per day will often be sufficient.

OVERDOSAGE

There have been no reports of ill-effects from acute overdosage.

Excess use of androgens has been associated with adverse effects including liver abnormalities, neoplasms, atherogenic blood lipid profile, increased risk of cardiovascular disease, reduced glucose tolerance, hypogonadal states, gynaecomastia, virilization, early closure of epiphyses, psychiatric disturbances, acute withdrawal syndrome, gastrointestinal bleeding and tendon damage.

Symptomatic treatment should be undertaken based on individual clinical assessment.

PRESENTATION AND STORAGE CONDITIONS

50 white tablets contained in either a glass bottle or blister strips.

AUST R 10712 (bottle)
AUST R 136196 (blister)

Store all medicines properly and keep them out of reach of children.
For storage conditions and expiry date see the pack.

NAME AND ADDRESS OF THE SPONSOR

Bayer Australia Limited
ABN 22 000 138 714
875 Pacific Highway
Pymble
NSW 2073
Australia

POISON SCHEDULE OF THE MEDICINE

PRESCRIPTION ONLY MEDICINE

DATE OF APPROVAL: 30 April 2007

Date of most recent amendment: 7 December 2009

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