

NEW ZEALAND DATA SHEET

TESTOSTERONE IMPLANTS

Testosterone 100mg and 200mg Implants

Presentation

White to pale yellow, opaque or translucent cylinder with a diameter of 4.5mm and a length of 6mm and containing 100mg of testosterone.

White to pale yellow, opaque or translucent cylinder with a diameter of 4.5mm and a length of 12mm and containing 200mg of testosterone.

Uses

Actions

Pharmacotherapeutic group: Androgens. ATC code G03B A03.

TESTOSTERONE IMPLANT inserted once every 5-6 months delivers plasma levels of testosterone and dihydrotestosterone in the normal physiological range of healthy males. In males with primary (hypergonadotropic) hypogonadism, treatment with TESTOSTERONE IMPLANT results in a normalization of gonadotropin levels.

In hypogonadal men, treatment with TESTOSTERONE IMPLANT results in an improvement of testosterone deficiency symptoms. Moreover, treatment increases bone mineral density and lean body mass, and decreases body fat mass. Treatment also improves sexual function, including libido and erectile function. Treatment decreases serum LDL-C, HDL-C and triglycerides, increases haemoglobin and haematocrit, whereas no clinically relevant changes in liver enzymes and PSA have been reported. Treatment may result in an increase in prostate size, but no adverse effects on prostate symptoms have been observed. In hypogonadal diabetic patients, improvement of insulin sensitivity and/or reduction in blood glucose have been reported with androgens. In boys with constitutional delay of growth and puberty, treatment with testosterone accelerates growth and induces development of secondary sex characteristics.

Pharmacokinetics

Absorption

Absorption of testosterone from 100mg and 200mg implants closely approximates zero-order kinetics throughout the effective life of the implants and exhibits an absorption half-time of 2.5 months with an almost complete absorption after 6-10 months. During the first few days an initial burst may occur. After a single dose of 600, 800 or 1200mg, testosterone levels of about 20, 25, or 35 nmol/L, respectively are reached after about 3 weeks followed by a gradual decline to low normal testosterone levels by 4-10 months.

The estimated rate of release of testosterone is 1.2-1.3mg per day per 200mg implant and 0.65mg per day per 100mg implant. The bioavailability of testosterone is virtually complete.

Distribution

Testosterone displays a high (over 97%) non-specific binding to plasma proteins and sex hormone binding globulin in *in-vitro* tests.

Biotransformation

Testosterone is metabolized to dihydrotestosterone and oestradiol, which are further metabolized via the normal pathways.

Elimination

Serum testosterone gradually declines to low normal testosterone levels after 4-10 months. The apparent terminal elimination half-life ($t_{1/2}$) is about 2.5 months. Excretion mainly takes place via the urine as conjugates of etiocholanolone and androsterone.

Pre-clinical Safety Data Pre-clinical data with androgens in general reveal no hazards.

Indications

Testosterone replacement therapy in males for conditions associated with primary and secondary hypogonadism, either congenital or acquired.

Dosage and Administration

Dosage

600-1200mg depending on the individual requirements; in most hypogonadal men, a dose of 800mg maintains the plasma testosterone levels within the normal male physiological range for 4-5 months. Safety and efficacy have not been determined in children.

Administration

TESTOSTERONE IMPLANT should be inserted subcutaneously into an area where there is relatively little movement or blood supply, such as the lower abdominal wall or the buttock. Insertion is made under local anaesthesia, using a trocar and a cannula. The wound is closed either with an adhesive dressing or a fine suture. The implants should be inserted subcutaneously to facilitate removal if necessary. In the rare event that removal of the implant should be necessary, the implant may be located by palpation. After localization, the implant can be removed after a small incision under local anaesthetic.

Full aseptic 'no touch' technique should be adopted.

In general, the dose should be adjusted according to the response of the individual patient.

Contraindications

History or presence of prostate or breast cancer.

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

Warnings and Precautions

Physicians should consider subjects receiving TESTOSTERONE IMPLANT for monitoring before the start of treatment, at quarterly intervals for the first 12 months and yearly thereafter for the following parameters:

- digital rectal examination (DRE) of the prostate and PSA to exclude benign prostate hyperplasia or a sub-clinical prostate cancer
- haematocrit and haemoglobin to exclude polycythemia

In patients with pre-existing cardiac, renal or hepatic disease androgen treatment may cause complications characterized by oedema with or without congestive heart failure.

Androgens in general and TESTOSTERONE IMPLANT can improve the glucose tolerance and the anticoagulant action (see also **Interactions**).

There is insufficient evidence for a recommendation regarding the safety of treatment with testosterone esters in men with sleep apnoea. Good clinical judgement and caution should be employed in subjects with risk factors such as adiposity or chronic lung diseases.

In pre-pubertal children statural growth and sexual development should be monitored since androgens in general and TESTOSTERONE IMPLANT in high dosages may accelerate epiphyseal closure and sexual maturation.

If androgen associated adverse reactions occur, treatment with TESTOSTERONE IMPLANT should be discontinued and upon resolution of the complaints resumed with lower dosages.

The misuse of androgens to enhance ability in sports carries serious health risks and is to be discouraged.

Use During Pregnancy and Breastfeeding

There are no adequate data for the use of TESTOSTERONE IMPLANT in pregnant women. In view of the risk of virilization of the foetus, TESTOSTERONE IMPLANT should not be used during pregnancy. Treatment with TESTOSTERONE IMPLANT should be discontinued when pregnancy occurs.

There are no adequate data for the use of TESTOSTERONE IMPLANT during lactation. Therefore, TESTOSTERONE IMPLANT should not be used during lactation.

Effects on Ability to Drive and Use Machines

As far as is known TESTOSTERONE IMPLANT has no effect on alertness and concentration.

Adverse Effects

Experience in the market situation has shown that the most frequent adverse events with TESTOSTERONE IMPLANT are extrusion, infection and bruising or bleeding.

Due to the nature of TESTOSTERONE IMPLANT, side effects cannot be quickly reversed by discontinuing medication.

The following adverse reactions have been associated with androgen therapy in general.

System Organ Class	MedDRA term*
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Prostatic cancer ¹
Blood and lymphatic system disorders	Polycythaemia
Metabolism and nutrition disorders	Fluid retention
Psychiatric disorders	Depression, nervousness, mood disturbances, libido increased, libido decreased
Musculoskeletal and connective tissue disorders	Myalgia

Vascular disorders	Hypertension
Gastrointestinal disorders	Nausea
Skin and subcutaneous tissue disorders	Pruritis, acne
Reproductive system and breast disorders	Gynaecomastia, oligozoospermia, priapism, prostatic disorder ²
Investigations	Hepatic function abnormal, lipids abnormal ³ , PSA increased

MedDRA version 7.1

¹ Progression of a sub-clinical prostatic cancer

² Prostatic growth (to eugonadal state)

³ Decrease in serum LDL-C, HDL-C and triglycerides

Interactions

Enzyme-inducing agents may decrease and enzyme-inhibiting agents may increase testosterone levels. Therefore, adjustment of the dose of TESTOSTERONE IMPLANT may be required.

Androgens may improve glucose tolerance and decrease the need for insulin or other anti-diabetic medicines (see **Warnings and Precautions** section).

High doses of androgens may enhance the anticoagulant action of coumarin-type agents allowing a reduction of the dose of these agents.

Overdosage

The acute toxicity of testosterone is low.

If symptoms of chronic overdose occur (e.g. polycythemia or priapism) the implant(s) should be removed and after disappearance of the symptoms, be resumed at a lower dosage.

Pharmaceutical Precautions

List of excipients

None (TESTOSTERONE IMPLANT consists of pure testosterone without any excipients).

Incompatibilities

Not applicable.

Shelf-life

5 years.

TESTOSTERONE IMPLANT may be used until the expiration date indicated on the package.

Special precautions for storage

Store below 30°C.

Store in original package and keep container in the outer carton.

Medicine Classification

Prescription Medicine.

Package Quantities

Each sterile implant is supplied singly in a sealed glass tube, positioned between plugs of non-absorbent wool.

Name and Address

Merck Sharp & Dohme (NZ) Ltd

P O Box 99 851

Newmarket

Auckland 1149

Tel: 0800 500 673

Date of Preparation

20 January 2011

(RA 1530 OS S1 (Ref 2.0) dated June 2006)