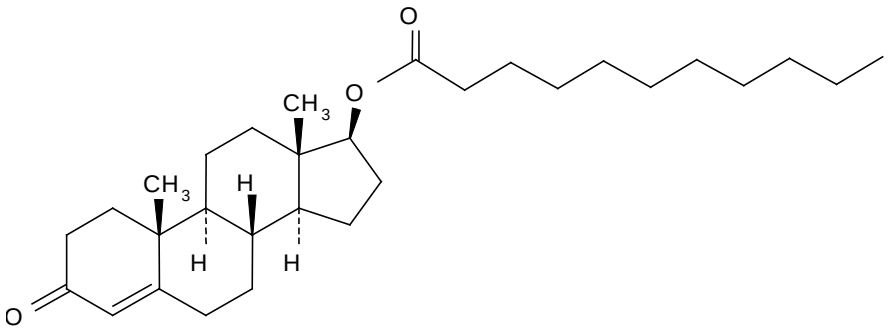
PRODUCT INFORMATION

REANDRON® 1000

NAME OF THE MEDICINE

Reandron 1000 is a hormonal preparation that contains 1000 mg testosterone undecanoate. The chemical name for testosterone undecanoate is (17β)-17-[(1-Oxoundecyl)oxy]-androst-4-en-3-one and has the following structural formula:



Molecular formula:	$C_{30}H_{48}O_3$
Molecular weight:	456.7
CAS Number:	5949-44-0

DESCRIPTION

Testosterone undecanoate is a white or off white crystalline substance. It is practically insoluble in water and soluble in methanol and ethanol and has a melting point of 58 - 64°C.

Reandron 1000 is a clear, yellowish oily solution for injection. Each glass ampoule/vial contains 1000 mg testosterone undecanoate and the excipients: benzyl benzoate and castor oil.

PHARMACOLOGY

Pharmacodynamics

Endogenous androgens, principally testosterone, secreted by the testes and its major metabolite dihydrotestosterone (DHT), are responsible for the development of the external and internal genital organs and for maintaining the secondary sexual characteristics (stimulating hair growth, deepening of the voice, development of the libido); for a general effect on protein anabolism; for development of skeletal muscle and body fat distribution; for a reduction in urinary nitrogen, sodium, potassium, chloride, phosphate and water excretion.

Testosterone does not produce testicular development: it reduces the pituitary secretion of gonadotropins.

The effects of testosterone in some target organs arise after peripheral conversion of testosterone to estradiol, which binds to estrogen receptors in the target cell nucleus e.g. the pituitary, fat, brain, bone and testicular Leydig cells.

Testosterone undecanoate is an ester of the naturally occurring androgen, testosterone. The active form, testosterone, is formed by cleavage of the side chain.

Pharmacokinetics

Absorption
Reandron 1000 is an intramuscularly administered depot preparation of testosterone undecanoate and thus circumvents the first-pass effect. Following intramuscular injection of testosterone undecanoate as an oily solution, the compound is gradually released from the depot and is almost completely cleaved by serum esterases into testosterone and undecanoic acid. An increase of serum levels of testosterone above basal values can already be measured one day after administration.

Distribution
In two separate studies, mean maximum concentrations of testosterone of 45 and 24 nmol/L were measured about 7 and 14 days, respectively, after single i.m. administration of 1000 mg of testosterone undecanoate to hypogonadal men. Post-maximum testosterone levels declined with an estimated half-life of about 53 days.

In serum of men, about 98% of the circulating testosterone is bound to sex hormone binding globulin (SHBG) and albumin. Only the free fraction of testosterone is considered as biologically active. Following intravenous infusion of testosterone to elderly men, an apparent volume of distribution of about 1.0 L/kg was determined.

Metabolism
Testosterone which is generated by ester cleavage from testosterone undecanoate is metabolised and excreted the same way as endogenous testosterone. The undecanoic acid is metabolised by ß-oxidation in the same way as other aliphatic carboxylic acids.

Elimination
Testosterone undergoes extensive hepatic and extrahepatic metabolism. After the administration of radiolabelled testosterone, about 90% of the radioactivity appears in the urine as glucuronic and sulphuric acid conjugates and 6% appears in the faeces after undergoing enterohepatic circulation. Urinary products include androsterone and etiocholanolone.

Steady State Conditions
Following repeated i.m. injection of 1000 mg testosterone undecanoate to hypogonadal men using an interval of 10 weeks between two injections, steady-state conditions were achieved between the 3rd and the 5th administration. Mean C_{max} and C_{min} values of testosterone at steady-state were about 42 and 17 nmol/L, respectively. Post-maximum testosterone levels in the serum decreased with a half-life of about 90 days, which corresponds to the release rate from the depot.

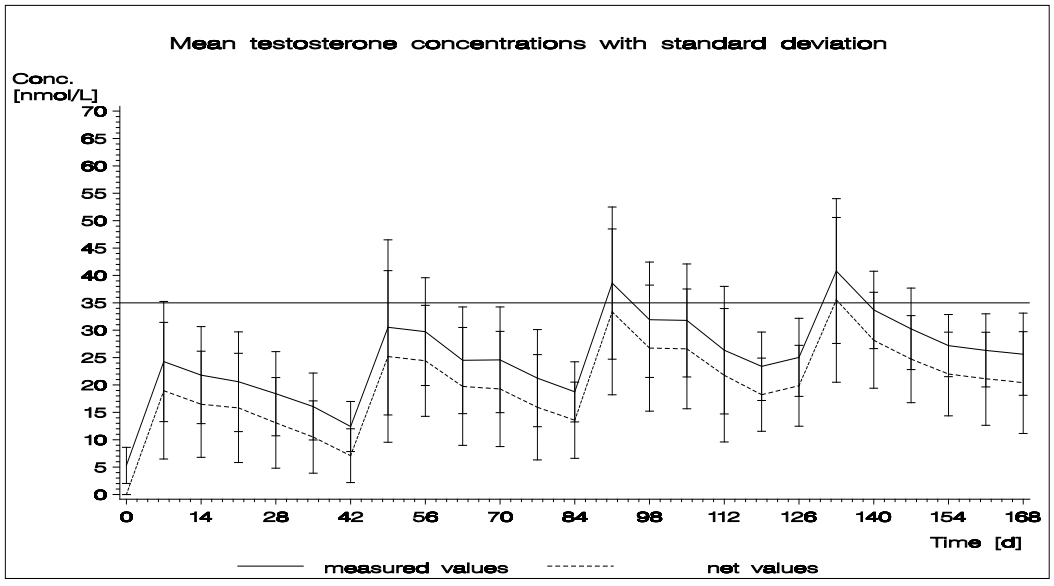
CLINICAL TRIALS

There were 4 pharmacokinetic studies, with 3 studies having open labelled extensions to support the dosage regimen, efficacy and safety of Reandron 1000 in the treatment of hypogonadism. The main pharmacokinetic and efficacy parameter was serum testosterone within the eugonadal range. The clinical studies included 72 men treated with Reandron 1000 (up to a maximum 36 weeks) while 60 men continued treatment longer term (range 18 –33 months). Initially, the dosage regimen investigated was 6 weeks between injections (injected into the gluteal muscle) however this time interval between injections was found to be too frequent and resulted in accumulation. An optimal injection interval has not been defined and injections were administered in the extension phase of the clinical trials at intervals between 10-12 weeks. The possibility exists that supraphysiological serum testosterone levels may be attained even at the prescribed dosage regimen and the dosing interval may need to be titrated accordingly. Results from the relevant clinical studies are summarised below.

Research Report No. A00315

This was a pharmacokinetic study conducted with Reandron 1000 in 14 hypogonadal men. The dosage interval between injections was 6 weeks and 4 intramuscular injections were administered. The primary efficacy parameter was the maintenance of testosterone levels within the eugonadal range after the 4th injection. Other secondary parameters investigated were adverse events, local intramuscular tolerability, status of the prostate and urine flow and standard clinical chemistry parameters including serum lipids and prostate specific antigen (PSA). The pharmacokinetic outcomes are presented below as Figure 1.

Figure 1. Time course of mean serum testosterone concentration (measured and net values) with SD during treatment of 14 hypogonadal patients with 4 x 1000 mg Reandron 1000 i.m.



It was found that at the end of the treatment period, all men had serum testosterone levels above the lower limit of the eugonadal range. The 6 week time interval between injections resulted in accumulation of testosterone suggesting that a longer time interval between injections was required. The implication is that serum testosterone levels should be monitored

to determine the optimum interval between injections. Local tolerability at the injection site (gluteus medius muscle) was investigated with injection site pain reported 3 times at the time of injection and 3 times between injection intervals. Apart from injection site pain and leg pain associated with the injection, redness and tenderness at the injections site were also reported.

Research Report No. A01198

This was a comparative study with Reandron 1000 and testosterone enanthate (N = 20 per group) to investigate the efficacy and safety of treatment. Reandron 1000 was administered intramuscularly at 6 week intervals for the first 3 injections and then at a 9 week interval while testosterone enanthate was administered intramuscularly at 3 week intervals over the 30 week study duration. The primary efficacy variables investigated were erythropoiesis (haemoglobin, haematocrit) and grip strength, which were similar between the groups. Multiple secondary and safety parameters were investigated including serum testosterone levels and intramuscular tolerability (also see Adverse Effects). The pharmacokinetic results for both treatment groups are presented below in Figure 2. The greater fluctuation in serum testosterone for the group treated with testosterone enanthate could be due to the longer dosing interval (3 weeks) between injections.

An extension of this clinical study (Research Report No. A05965) was allowed whereby all patients (n = 36 initiated the extension and n = 32 completed the extension phase) were administered a further 8 intramuscular injections of Reandron 1000 (84 weeks). The pharmacokinetic results for serum testosterone in the extension phase are presented in Figure 3.

Figure 2. Mean serum testosterone levels in 2 treatment groups of 20 hypogonadal men each before and during administration of Reandron 1000 (TU) or testosterone enanthate (TE).

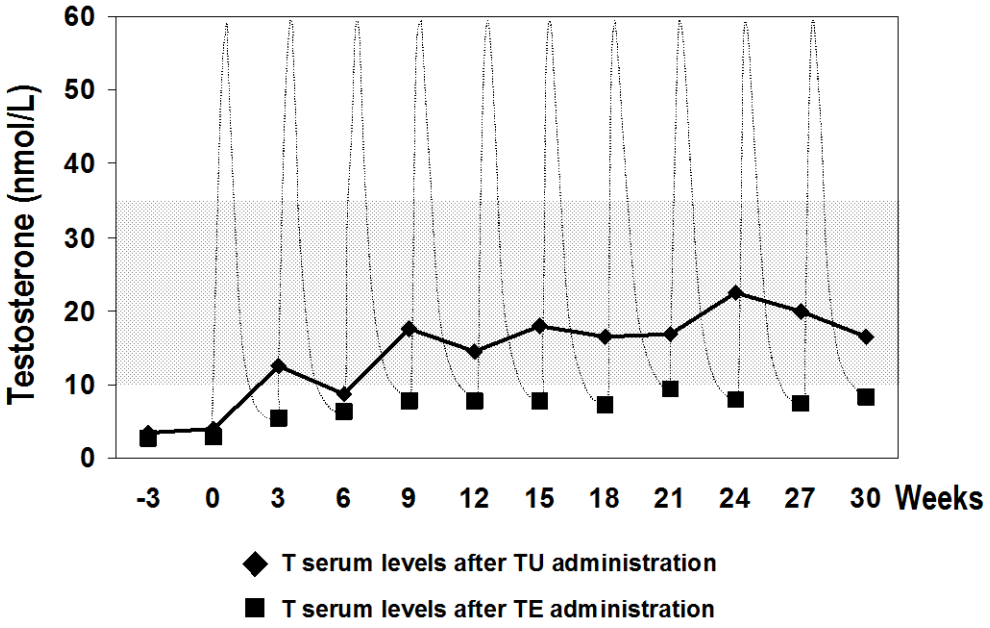
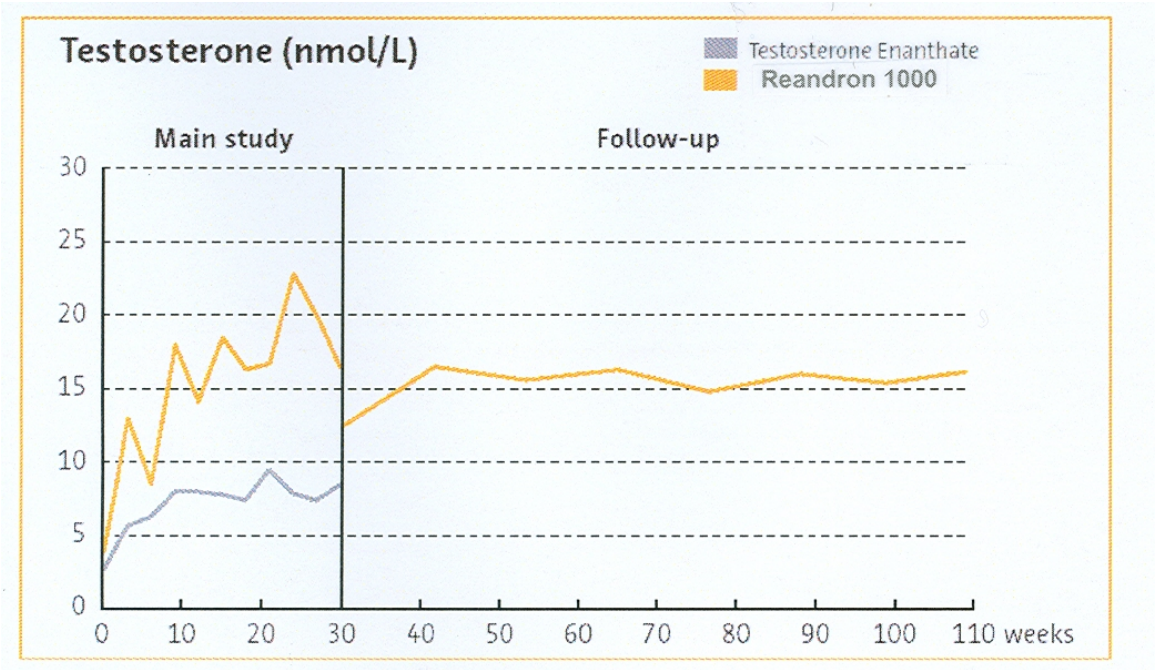


Figure 3. Serum testosterone levels following multiple injections of Reandron 1000



INDICATIONS

Testosterone replacement in primary and secondary male hypogonadism.

CONTRAINDICATIONS

The use of Reandron 1000 is contraindicated in men with:

- androgen-dependent carcinoma of the prostate or of the male mammary gland;
- hypercalcaemia accompanying malignant tumours;
- hypersensitivity to the active substance or to any of the excipients;
- past or present liver tumours

The use of Reandron 1000 in women is contraindicated.

PRECAUTIONS

Reandron 1000 should be used only if hypogonadism (hyper- and hypogonadotrophic) has been demonstrated and if other aetiologies responsible for the symptoms have been excluded before treatment is started. Testosterone insufficiency should be clearly demonstrated by clinical features (regression of secondary sexual characteristics, change in body composition, asthenia, reduced libido, erectile dysfunction etc.), confirmed by biochemical tests (2 separate blood testosterone measurements) and according to contemporary diagnostic criteria established by endocrine societies. Currently, there is no consensus about age specific testosterone reference values. However, it should be taken into account that physiologically testosterone serum levels fall with increasing age.

Due to variability in laboratory values, all measures of testosterone should be carried out in the same laboratory.

Prior to testosterone initiation, all patients must undergo a detailed examination in order to exclude the risk of pre-existing prostatic cancer. Careful and regular monitoring of the prostate gland and breast must be performed in accordance with recommended methods (digital rectal examination and estimation of serum PSA) in patients receiving testosterone therapy at least once yearly and twice yearly in elderly patients and at risk patients (those with clinical or familial factors).

Androgens may accelerate the progression of sub-clinical prostatic cancer and benign prostatic hyperplasia.

Improved insulin sensitivity may occur in patients treated with androgens who achieve normal testosterone plasma concentrations following replacement therapy.

Haemoglobin and haematocrit should be checked periodically in patients on long-term androgen therapy to detect cases of polycythaemia (see ADVERSE EFFECTS).

In general, the use of intramuscular injections in patients with acquired or inherited bleeding disorders is not recommended due to the risk of bleeding. Testosterone and its derivatives have been reported to increase the activity of coumarin-derived oral anticoagulants (see also INTERACTIONS WITH OTHER MEDICINES).

Testosterone should be used with caution in patients with thrombophilia, as there have been post-marketing studies and reports of thrombotic events in these patients during testosterone therapy.

Deep intramuscular injection of testosterone undecanoate is not advisable in men with any form of bleeding or coagulation disorder, including those using anti-coagulants because of the risk of haematoma. Either alternative non-injectable testosterone products should be used or expert advice sought from a haematologist (see “Interactions with other medicines”).

Cases of benign and malignant liver tumours have been reported in users of hormonal substances, such as androgen compounds. A hepatic tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in men using Reandron 1000.

Caution should be exercised in patients predisposed to oedema. e.g. in case of severe cardiac, hepatic, or renal insufficiency or ischaemic heart disease, as treatment with androgens may result in increased retention of sodium and water. In case of severe complications characterised by oedema with or without congestive heart failure, treatment must be stopped immediately (see ADVERSE EFFECTS).

Caution must be taken in patients who have had elevated blood pressure, disturbance in renal function, epilepsy or migraine. The product may elevate blood pressure. The product is not recommended for patients with cardiac insufficiency.

Pre-existing sleep apnoea may be potentiated.

Androgens are not suitable for enhancing muscular development in healthy individuals or for increasing physical ability.

Using Reandron 1000 might result in a positive finding in doping tests.

As with all oily solutions, Reandron 1000 must be injected strictly intramuscularly and very slowly. Pulmonary microembolism of oily solutions can in rare cases lead to signs and symptoms such as cough, dyspnoea, malaise, hyperhydrosis, chest pain, dizziness, paraesthesia, or syncope. These reactions may occur during or immediately after the injection and are reversible. Treatment is usually supportive, e.g. by administration of supplemental oxygen.

Suspected anaphylactic reactions after Reandron 1000 injection have been reported.

Certain clinical signs: irritability, nervousness, weight gain, prolonged or frequent erections may indicate excessive androgen exposure requiring dosage adjustment. Periodic testosterone measurements should be made during treatment, particularly when considering dose adjustment.

Carcinogenicity and Mutagenicity

The potential carcinogenicity of testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, the implant induced cervical uterine tumours, which metastasised in some cases. There is suggestive evidence that injection of testosterone in some strains of female mice increases their susceptibility to hepatoma. Testosterone is known to act as a tumour promoter and has been shown to increase carcinomas in the liver of rats. There are rare reports of hepatocellular carcinoma in patients receiving long term therapy with androgens in high doses. 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. Elderly patients treated with androgens may be at an increased risk for the development of prostatic hyperplasia and prostatic cancer.

Testosterone undecanoate was not genotoxic, as assessed *in vitro* for reverse gene mutations and chromosomal aberrations. An *in vivo* assay of chromosomal damage (micronucleus test in mice) was also negative.

Use in Pregnancy (Category D)

Reandron 1000 is for use in men only and must not be used in women. Androgenic substances may have a virilising effect on the female fetus and are contraindicated during pregnancy (see CONTRAINDICATIONS).

Use in Lactation

Reandron 1000 must not be used in women and is contraindicated during lactation (see CONTRAINDICATIONS).

Paediatric use

Clinical trials with Reandron 1000 have not been conducted in children or adolescents under the age of 18 and use in this population is not recommended.

In addition to causing masculinisation in children, testosterone can cause accelerated growth, bone maturation, and premature epiphyseal closure, thereby reducing the final height. The appearance of common acne is also expected.

Use in the Elderly

Limited data does not suggest the need for a dosage adjustment in elderly patients.

Use in Patients with Hepatic Impairment

No formal studies have been performed in patients with hepatic impairment. The use of Reandron 1000 is contraindicated in men with past or present liver tumours.

Use in Patients with Renal Impairment

No formal studies have been performed in patients with renal impairment.

Effect on Laboratory Tests

Androgens may decrease levels of thyroxine binding globulin, resulting in decreased T_4 serum concentrations and in increased resin uptake of T_3 and T_4. Free thyroid hormone levels, however, remain unchanged and there is no clinical evidence of thyroid insufficiency.

INTERACTIONS WITH OTHER MEDICINES

Androgens may enhance blood sugar levels reducing the effects of insulin. The dosage of the hypoglycaemic agent may need to be lowered.

Interactions can occur with drugs that induce microsomal enzymes, which can result in increased clearance of testosterone (e.g. barbiturates).

Androgens may interfere with the metabolism of other drugs. Accordingly, plasma and tissue concentrations may be affected e.g. increased oxyphenbutazone serum levels have been reported. The metabolism of cyclosporin might be slowed.

Moreover, testosterone and derivatives have been reported to increase the activity of coumarin-derived oral anticoagulants, possibly requiring dose adjustment. Independently of this finding, the use of intramuscular injections in patients with acquired or inherited bleeding disorders is not recommended due to the risk of bleeding (see PRECAUTIONS).

Theoretically, any substance which affects liver function should not be taken with testosterone. Examples of herbal products include: angelica dahurica, chapparal, comfrey, eucalyptus, germander tea, Jin Bu Huan, kava, penny royal oil, skullcap, and valerian.

ADVERSE EFFECTS

The most frequently reported adverse effects during treatment with Reandron 1000 are acne and injection site pain.

Regarding adverse effects associated with the use of androgens, please also refer to PRECAUTIONS.

Table 1 below shows adverse drug reactions (ADRs) classified by MedDRA System Organ Classes (MedDRA SOCs)* reported with Reandron 1000. The frequencies are based on clinical trial data and are defined as:

Common ≥1/100 to <1/10
Uncommon ≥1/1000 to <1/100

The following ADRs were reported in six clinical trials with over 400 patients, with a suspected relationship to Reandron 1000.

Table 1. Categorised relative frequency of ADRs by MedDRA SOCs based on pooled clinical trial data**

System Organ Class	Common	Uncommon
Blood and lymphatic system disorders	Polycythaemia	Haematocrit increased Red blood cell count increased Haemoglobin increased
Gastrointestinal disorders		Diarrhoea Nausea
Immune system disorders		Hypersensitivity
Metabolism and nutrition disorders	Weight increased	Increased appetite Glycosylated haemoglobin increased Hypercholesterolaemia Blood triglycerides increased Blood cholesterol increased
Musculoskeletal and connective tissue disorders		Arthralgia Pain in extremity Muscle spasm Muscle strain Myalgia Musculoskeletal stiffness Blood creatine phosphokinase increased
Nervous system disorders		Headache Migraine Tremor
Psychiatric disorders		Depression Emotional disorder

System Organ Class	Common	Uncommon
		Insomnia Restlessness Aggression Irritability
Respiratory, thoracic and mediastinal disorders		Bronchitis Sinusitis Cough Dyspnoea Snoring Dysphonia
Hepatobiliary disorders		Liver function test abnormal Aspartate aminotransferase increased
Skin and subcutaneous tissue disorders	Acne	Alopecia Erythema Rash Rash papular Pruritus Dry skin
Renal and urinary disorders		Urine flow decreased Urinary retention Urinary tract disorder Nocturia Dysuria
Reproductive system and breast disorders	Prostate specific antigen increased Prostate examination abnormal Benign prostate hyperplasia	Prostatic intraepithelial neoplasia Prostate induration Prostatitis Prostatic disorder Libido increased Libido decreased Testicular pain Breast induration Breast pain Gynaecomastia Estradiol increased Blood testosterone free increased Blood testosterone increased
Vascular disorders	Hot flush	Cardiovascular disorder Hypertension Blood pressure increased Dizziness
General disorders and administration site conditions	Various kinds of injection site reactions***	Fatigue Asthenia Hyperhidrosis Night sweats

* The most appropriate MedDRA term to describe a certain adverse reaction is listed. Synonyms or related conditions are not listed, but should be taken into account as well.

** N=302 hypogonadal men treated with i.m. injections of 4 mL and N=120 of 3 mL of testosterone undecanoate 250 mg/mL

***Various kinds of injection site reaction: Injection site pain, Injection site discomfort, Injection site pruritis, Injection site erythema, Injection site haematoma, Injection site irritation, Injection site reaction.

Pulmonary microembolism of oily solutions can in rare cases lead to signs and symptoms such as cough, dyspnoea, malaise, hyperhidrosis, chest pain, dizziness, paraesthesia, or syncope. These reactions may occur during or immediately after the injections and are reversible. Cases suspected by the company or the reporter to represent pulmonary oily microembolism have been reported rarely in clinical trials (in ≥ 1/10,000 and < 1/1,000 injections) as well as from postmarketing experience (see PRECAUTIONS).

Suspected anaphylactic reactions after Reandron 1000 injection have been reported.

In addition to the above mentioned ADRs, nervousness, hostility, sleep apnoea, various skin reactions including seborrhoea, increased hair growth, increased frequency of erections and in very rare cases jaundice have been reported under treatment with testosterone containing preparations.

Therapy with high doses of testosterone preparations commonly reversibly interrupts or reduces spermatogenesis, thereby reducing the size of the testicles; testosterone replacement therapy of hypogonadism can in rare cases cause persistent, painful erections (priapism). High-dosed or long-term administration of testosterone occasionally increases the occurrences of water retention and oedema.

The following adverse events were noted during treatment in the comparative clinical study of Reandron 1000 (testosterone undecanoate) with testosterone enanthate [Report No. A01198].

Table 2. Adverse events reported in the clinical study of Reandron 1000 with testosterone enanthate [Report No. A01198]

Reandron 1000	Testosterone enanthate
Upper respiratory infection (x4), headache (x2), hot flashes, injection site pain, joint disorder, respiratory disorder, rhinitis, weight gain.	Upper respiratory disorder (x3), acne (x2), flu syndrome (x2), dry skin, hair disorder, injection site pain, muscle cramps, pain.

In the literature, the following ADRs from testosterone containing preparations have been reported.

Table 3. Adverse effects reported from testosterone containing preparations

System Organ Class	Adverse effects
Blood and the lymphatic system disorders	Rare cases of polycythaemia
Metabolism and nutrition disorders	Weight gain
Musculoskeletal system	Muscle cramps
Nervous system	Nervousness, hostility, depression
Respiratory system	Sleep apnoea
Hepatobiliary disorders	In very rare cases jaundice and liver function test abnormalities

Skin and appendages	Various skin reactions may occur including acne, seborrhoea, and balding
Reproductive system and breast disorders	Libido changes, increased frequency of erections, therapy with high doses of testosterone preparations commonly reversibly interrupts or reduces spermatogenesis, thereby reducing the size of the testicles, testosterone replacement therapy of hypogonadism can in rare cases cause persistent, painful erections (priapism)
General disorders and administration site conditions	High-dosed or long-term administration of testosterone occasionally increases the occurrences of water retention and oedema, injection site reactions and hypersensitivity reactions may occur

DOSAGE AND ADMINISTRATION

Reandron 1000 (1 ampoule/vial corresponding to 1000 mg testosterone undecanoate) is injected every 10 to 14 weeks for testosterone replacement, where testosterone deficiency has been confirmed by clinical features and biochemical tests. Injections with this frequency are capable of maintaining sufficient testosterone levels and do not lead to accumulation.

The injections must be administered very slowly. Care should be taken to inject Reandron 1000 deeply into the gluteal muscle (the only site for which clinical experience has been obtained) following the usual precautions for intramuscular administration. Reandron 1000 is strictly for intramuscular injection. Special care must be taken to avoid intravenous injection and injections must not be given subcutaneously. See Instructions for use/handling to avoid injury when opening.

Start of Treatment

Serum testosterone levels should be measured before start of treatment and during initiation of treatment. Depending on serum testosterone levels and clinical symptoms, the first injection interval may be reduced to a minimum of 6 weeks as compared to the recommended range of 10 to 14 weeks for maintenance. With this loading dose, sufficient steady-state testosterone levels may be achieved more rapidly.

Individualisation of Treatment

The injection interval should remain within the recommended range of 10 to 14 weeks. It is advisable to measure and monitor testosterone serum levels regularly, particularly if the dosage regimen is changed or if there is clinical concern about the adequacy or excessiveness of testosterone replacement. Measurements should be performed at the end of an injection interval and clinical symptoms considered. Serum levels below normal range would indicate the need for a shorter injection interval. In case of high serum levels an extension of the injection interval may be considered or administration of a smaller volume could also be considered (i.e. could result in a shorter injection interval).

Reandron 1000 contains no antimicrobial agent. Reandron 1000 is for single use in one patient only. Discard any residue.

Instructions for use/handling

Handling the One-Point-Cut (OPC) ampoule:
There is a pre-scored mark beneath the coloured point on the ampoule eliminating the need to file the neck. Prior to opening, ensure that any solution in the upper part of the ampoule flows down to the lower part. Use both hands to open; while holding the lower part of the ampoule in one hand, use the other hand to break off the upper part of the ampoule in the direction away from the coloured point.

Handling the vial:
Flip off the protective cap (A) from the vial and aseptically clean the rubber stopper. Do not remove the metal ring (B) or the crimp cap (C).

OVERDOSAGE

No special therapeutic measure apart from termination of therapy with the drug or dose reduction is necessary after overdosage.

PRESENTATION AND STORAGE CONDITIONS

Each 5 mL glass ampoule or 6 mL glass vial contains 4 mL oily solution with 1000 mg testosterone undecanoate. Not all presentations may be marketed.

Store Reandron 1000 below 30ºC and keep out of reach of children. Storage conditions and expiry date are provided on the packaging.

NAME AND ADDRESS OF THE SPONSOR

Bayer Australia Ltd
ABN 22 000 138 714
875 Pacific Highway

Pymble NSW 2073

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE ARTG

26 October 2005

DATE OF MOST RECENT AMENDMENT

19 July 2017

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