1. NAME OF THE MEDICINAL PRODUCT

Andriol® Testocaps® 40 mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 40.0 mg testosterone undecanoate, which is equivalent to 25.3 mg testosterone.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Soft oval glossy capsules, transparent, orange in color, coded ORG DV3 in white (***for porcine***) black (***for bovine***) containing a yellow oily fill.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Adults:

The initial dosage required will usually be 120-160 mg daily for 2-3 weeks. Subsequent dosage (40-120 mg daily) should be based on the clinical effect obtained during the first weeks of therapy.

Children:

Safety and efficacy have not been adequately determined in children.

To ensure absorption, Andriol Testocaps must be taken with a meal, if necessary with a little fluid and swallowed whole without chewing. It is preferable that half of the daily dose be taken in the morning and the other half in the evening.

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

4.3 Contraindications

History or presence of prostate cancer or breast cancer

Hypersensitivity to the active substance or to any of the excipients

4.4 Special warnings and precautions for use

Physicians should consider subjects receiving Andriol Testocaps 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,
- hematocrit and hemoglobin to exclude polycythemia.

In patients with preexisting cardiac, renal or hepatic disease androgen treatment may cause complications characterized by edema with or without congestive heart failure.

Androgens in general and Andriol Testocaps can improve the glucose tolerance and the anticoagulant action (see also section 4.5).

There is insufficient evidence for a recommendation regarding the safety of treatment with testosterone esters in men with sleep apnea. Good clinical judgment 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 Andriol Testocaps in high dosages may accelerate epihyseal closure and sexual maturation.

If androgen associated adverse reactions occur, treatment with Andriol Testocaps should be discontinued and/or resumed with a lower dose.

4.5 Interaction with other medicinal products and other forms of interaction

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

Androgens may improve glucose tolerance and decrease the need for insulin or other anti-diabetic medicines (see section 4.4).

Androgens may enhance the anticoagulant action of coumarine type agents allowing a reduction of the dose of these agents.

Andriol Testocaps must be taken with a meal to ensure absorption.

4.6 Pregnancy and lactation

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

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

4.7 Effects on ability to drive and use machines

As far as is known Andriol Testocaps has no effect on alertness and concentration.

4.8 Undesirable effects

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	Pruritus, 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 normogonadal size)

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

4.9 Overdose

The acute toxicity of testosterone is low.

An overdose of Andriol Testocaps may cause gastrointestinal complaints due to castor oil; treatment consists of supportive measures.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Androgens. ATC code G03B A03

5.1 Pharmacodynamic properties

Treatment of hypogonadal men with Andriol Testocaps dose-dependently restores serum total and bioavailable testosterone to levels within the normal range. Treatment also results in an increase of serum concentrations of dihydrotestosterone (DHT) and estradiol (E_2), as well as in a decrease of sex hormone-binding globulin (SHBG), luteinizing hormone (LH) and follicle-stimulating hormone (FSH). In both young and aging hypogonadal men, treatment with Andriol Testocaps 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 dose-dependently decreases serum LDL-C, HDL-C and triglycerides, increases hemoglobin and hematocrit, 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 insuline sensitivity and/or reduction in blood glucose have been reported. In boys with constitutional delay of growth and puberty, treatment with Andriol Testocaps first accelerates growth and induces development of secondary sex characteristics. In oophorectomized women on estrogen-only therapy, addition of Andriol Testocaps improves libido and increases bone mineral density and lean body mass. In female-to-male transsexuals, treatment with Andriol Testocaps induces masculinization.

5.2 Pharmacokinetic properties

Absorption:

Following oral administration of Andriol Testocaps, an important part of the active substance testosterone undecanoate is co-absorbed with the lipophilic solvent from the intestine into the lymphatic system, thus partially

circumventing the first-pass inactivation by the liver. Andriol Testocaps must be taken with a normal meal or breakfast to ensure absorption. The bioavailability is about 7%.

Distribution:

From the lymphatic system testosterone undecanoate is released into the plasma and hydrolyzed to testosterone.

Single administration of 80-160 mg Andriol Testocaps leads to a clinically significant increase of total plasma testosterone with peak-levels of approximately 40 nmol/l (C_{max}), reached approximately 4-5 h (t_{max}) after administration. Plasma testosterone levels remain elevated for at least 8 hours. Testosterone and testosterone undecanoate display a high (over 97%) non-specific binding to plasma proteins and sex hormone binding globulin in in vitro tests.

Biotransformation:

In plasma and tissues testosterone undecanoate is hydrolyzed to yield the natural male androgen testosterone. Testosterone is further metabolized to dihydrotestosterone and estradiol.

Elimination:

Testosterone, estradiol and dihydrotestosterone are metabolized via the normal pathways. Excretion mainly takes place via the urine as conjugates of etiocholanolone and androsterone.

Linearity:

Dose-linearity has been demonstrated for a dose range of 40-240 mg/day.

5.3 Preclinical safety data

Preclinical data reveal no hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each capsule contains about 293 mg of a mixture of castor oil and propylene glycol monolaurate (E477). Capsule shell ingredients are glycerin, Sunset Yellow (E110, FD&C Yellow no. 6) and gelatin

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30 °C; do not refrigerate or freeze.

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

6.5 Nature and contents of container

A box of Andriol Testocaps contains either 3, 6 or 12 sachets, each containing a blister with 10 capsules.

6.6 Instructions for use and handling <and disposal>

Any unused product or waste material should be disposed of in accordance with local requirements.

See also "Special precautions for storage" and "Posology and method of administration".

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

October 2005