SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Restandol® Testocaps™ 40mg capsule, soft.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains Testosterone Undecanoate 40.0mg which is equivalent to 25.3mg testosterone.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Oval, glossy capsules, transparent, orange in colour, with a yellow oily fill.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Clinical Indications
Testosterone replacement therapy in male hypogonadal disorders, for example:

after castration;
eunuchoidism;
hypopituitarism;
endocrine impotence;
male climacteric symptoms like decreased libido and decreased mental and physical activity;
certain types of infertility due to disorders of spermatogenesis

Testosterone therapy may also be indicated in osteoporosis due to androgenic deficiency.

4.2 Posology and method of administration

Dosage

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.

Elderly Patients
It should be noted that smaller and less frequent doses may achieve the same response.

Children
Safety and efficacy has not been determined in children and adolescents.

Administration

Oral.
To ensure absorption, Restandol Testocaps must be taken with a normal meal, if necessary with a little fluid, and be 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. If an uneven number of capsules is taken daily, the greater part should be taken in the morning.

4.3 Contraindications

Pregnancy
Breast feeding
Known or suspected prostatic or mammary carcinoma;
History of liver tumours
Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Physicians should consider patients receiving Restandol 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 in men over the age of 45 years, to exclude prostate cancer (see section 4.3)
- hematocrit and hemoglobin to exclude polycythemia. In case of severe polycythemia, treatment with Restandol Testocaps should be stopped or the dosage should be lowered.

Patients, especially the elderly, with the following conditions should be monitored:

In patients with pre-existing cardiac, renal or hepatic disease androgen treatment may cause complications charecterized by oedema with or without congestive heart failure. In such case, treatment must be stopped immediately. Patients after myocardial infarction, cardiac, hepatic or renal insufficiency, hypertension, epilepsy, or migraine should be monitored due to the risk of deterioration or reoccurance. In addition to discontinuation of the drug, diuretic therapy may be required.

Mammary carcinoma, hypernephroma, bronchial carcinoma, and skeletal metastases, since these conditions may produce hypercalcaemia or hypercalciuria which may in turn be exacerbated by androgen therapy. If hypercalcaemia or hypercalciuria develops treatment should be discontinued.

Androgens should be used cautiously in prepubertal boys to avoid premature epiphyseal closure or precocious sexual development.

Caution is required when administering with anticoagulants and anti-diabetic agents, since androgens in general can affect glucose tolerance and the action of anticoagulants (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.

Androgen therapy should only be used in male hypogonadism in which testosterone levels have been demonstrated to be low.

In treating males, stimulation to the point of increasing nervous, mental and physical activities beyond the patient's cardiovascular capacity should be avoided.

Tumours and other histological abnormalities and disturbances of liver function have been reported in patients subjected to prolonged treatment with some testosterone derivatives. Most of these compounds were 17-alpha alkyl derivatives but a smaller number of cases have occurred with certain 17-beta esters of testosterone. The possibility that such changes result from the use of Restandol Testocaps has not been excluded.

If undesirable effects occur, administration of Restandol Testocaps should be discontinued and/or resumed at a lower dose.

Restandol Testocaps contains Sunset Yellow (E110, FD&C Yellow no. 6) which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent administration of liver enzyme inducing drugs such as rifampicin, barbiturates, carbamazepine, dichloralphenazone, phenylbutazone, phenytoin or primidone may decrease the effect of Restandol Testocaps.

Androgens may improve glucose tolerance and decrease the need for insulin or other anti-diabetic medicines in diabetic subjects. Patients on insulin or other anti-diabetic medication should be closely monitored, with therapy adjusted as appropriate (See also section 4.4).

High doses of androgens may enhance the anticoagulant action of coumarine type agents and additional monitoring of INR and adjustment of anticoagulant dose may need to be considered.

Restandol Testocaps must be taken with a normal meal to ensure absorption.

The concurrent administration of testosterone with ACTH or corticosteroids may enhance oedema formation: thus these active substances should be administered cautiously, particularly in patients with cardiac or hepatic disease or in patients predisposed to oedema.

Laboratory test interactions: Androgens may decrease levels of thyroxine-binding globulin resulting in decreased total T4 serum levels and increased resin uptake of T3 and T4. Free thyroid hormone levels remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.

4.6 Fertility, pregnancy and lactation

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

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

4.7 Effects on ability to drive and use machines

Restandol Testocaps has no influence on the ability to drive or use machines.

4.8 Undesirable effects

If Restandol Testocaps are used in children precocious sexual development and cessation of the bone growth may occur by premature and irreversible epiphyseal closure.

In women, androgens have been described to cause symptoms of virilisation such as hirsutism, acne and voice changes (deepening, hoarsening). The voice changes may be irreversible.

Other adverse drug reactions of testosterone treatments that have been reported are (see also Section 4.4):

Prostatic growth, progression of a sub-clinical prostatic cancer, PSA increased, urinary obstruction, gynaecomastia, pruritis, nausea, cholestatic jaundice, changes in liver function tests, increased or decreased libido, depression, nervousness, mood disturbances, myalgia.

With high doses and prolonged treatment electrolyte changes (sodium, potassium, calcium, inorganic phosphate and water retention), hypertension, oligozospermia, or azospermia, priaprism, changes in lipid metabolism, polycythaemia, oligo- or amenorrhoea.

In a few patients diarrhoea and abdominal pain or discomfort have been reported during use of Restandol Testocaps.

4.9 Overdose

High doses of Restandol Testocaps may cause gastrointestinal complaints due to the castor oil present in the capsule. Treatment consists of supportive measures.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Androgens. ATC code G03B A03

Restandol Testocaps, after oral administration, delivers physiological amount of testosterone in the circulation. Treatment of hypogonadal men also results in a clinically significant rise of plasma concentrations of dihydrotestosterone and oestradiol, as well as a decrease of SHBG (sex hormone binding globulin). Treatment of males with primary (hypergonadotropic) hypogonadism results in a normalization of gonadotropin levels.

Endogenous androgens, principally testosterone, secreted by the testes and its major metabolite 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.

Androgens are also responsible for the growth spurt of adolescence and for the eventual termination of linear growth and stimulate the production of red blood cells by enhancing erythropoietin production.

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

Exogenous administration of androgens inhibits endogenous testosterone release. With large doses of exogenous androgens, spermatogenesis may be suppressed.

5.2 Pharmacokinetic properties

Absorption
Restandol Testocaps must be taken with a normal meal or breakfast to ensure absorption. Food enhances the absorption of Restandol Testocaps: In healthy volunteers the AUC of testosterone was increased more than 12 –fold compared with fasted conditions when Restandol Testocaps was taken with a normal meal. No differences were found in the AUC of testosterone when Restandol Testocaps was taken with a normal meal (containing 18.8 grams of fat) as compared to a high fat meal (containing 44.1 grams of fat). The absorption is about 7%. Following oral administration of Restandol 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 circumventing the first pass inactivation by the liver.

Distribution
From the lymphatic system testosterone undecanoate is released into the plasma. Single administration of 20-80 mg Restandol Testocaps to postmenopausal women leads to peak-levels of total plasma testosterone of approximately 1.5-2.0, 2.5-5.5 and 5.2-10.3ng/ml after a dose of 20, 40 and 80 mg Restandol Testocaps, respectively. These levels are reached approximately 5-6 h (t_{max}) after administration. Plasma testosterone levels remain elevated for at least 8 hours. In Japanese women the testosterone levels are about two fold higher.

During steady state after 28 days of administration plasma levels of total testosterone in hypogonadal men were increased after administration of 40 mg t.i.d, 40 b.i.d+80 mg, 80 mg b.i.d and 80 mg t.i.d. The dose of 80 mg b.i.d or 80 mg t.i.d. resulted in levels in the male physiological range for a considerable proportion of the time during the day. 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 oestradiol.

Elimination
Testosterone, oestradiol 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 20-240 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
Castor oil
Propylene glycol laurate (E477)

Capsule shell
Glycerin
Sunset Yellow (E110)
Gelatin

Printing ink
Opacode WB® white

Auxiliary substances
Medium-chain triglycerides
Lecithin

6.2 Incompatibilities

None

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30 °C.
Do not refrigerate or freeze.
Keep the blister in the outer carton.

6.5 Nature and contents of container

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

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements
See also “Special precautions for storage” (section 6.4) and “Posology and method of administration” (section 4.2)

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
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Hoddesdon
Hertfordshire
EN11 9BU
UK

8. MARKETING AUTHORISATION NUMBER(S)

MA058/03301

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30th August 2006

10. DATE OF REVISION OF THE TEXT

September 2013

11. LEGAL CATEGORY

Prescription Only Medicine