# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Restandol Testocaps 40 mg soft capsules

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect: Includes 0.07mg Sunset Yellow (E110) per capsule and propylene glycol monolaurate.
This medicine contains 117.2 mg propylene glycol monolaurate in each capsule. This quantity corresponds to 34.5 mg propylene glycol which is equivalent to 0.5 mg/kg.
Restandol Testocaps may contain trace amounts of soya lecithin.
For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Soft capsule. (Short term capsule)

Soft oval glossy capsule, transparent, orange in colour, with a yellow oily fill, with imprint 'Org DV3' in white.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Testosterone replacement therapy for male hypogonadism, when testosterone deificiency has been confirmed by clinical features and biochemical tests. In osteoporosis due to androgen deficiency in males.

### 4.2 Posology and method of administration

Initiation of testosterone therapy and its overall direction should only be carried out by specialists.
Testosterone therapy should only be used in male hypogonadism in which testosterone levels have been demonstrated to be low.

**Posology:**

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

Should be used only if hypogonadism (hyper- and hypogonadotrophic) has been demonstrated, and if other aetiology, responsible for the symptoms, has 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.) and confirmed by 2 separate blood testosterone measurements.

Dosage
Adults (incl. elderly):
The initial dosage required will usually be 120 - 160 mg daily for two to three weeks. Subsequent dosage (40 - 120 mg daily) should be based on the clinical effect obtained during the first weeks of therapy.

Paediatric population:
The safety and efficacy of Restandol Testocaps in children and adolescents has not been established. Pre-pubertal children treated with Restandol Testocaps should be treated with caution (see section 4.4).

Method of administration:
To ensure absorption, Restandol 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.

### 4.3 Contraindications

- Known or suspected carcinoma of the prostate or breast (see section 4.4).
- Use in patients with hypercalciuria, hypercalcaemia, nephrotic syndrome, ischaemic heart disease or untreated congestive heart failure.
- Restandol Testocaps may contain trace amounts of soya lecithin. If you are allergic to peanut or soya, do not use this medicinal product.
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 (see section 4.4).

**4.4 Special warnings and precautions for use**

Medical examination:

Testosterone level should be monitored at baseline and at regular intervals during treatment. Clinicians should adjust the dosage individually to ensure maintenance of eugonadal testosterone levels.

Physicians should consider monitoring patients receiving Restandol Testocaps 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 (see section 4.3),
- Hematocrit and haemoglobin to exclude polycythemia.

In patients receiving long-term androgen therapy, the following laboratory parameters should also be monitored regularly: haemoglobin and haematocrit liver function tests and lipid profile.

Conditions that need supervision:
Patients, especially the elderly, with the following conditions should be monitored for:

- Tumours – Patients with breast carcinoma, hypernephroma, lung carcinoma, and bone metastases can develop hypercalcaemia either spontaneously, (hypercalcaemia of malignancy) or during therapy with anabolic/androgenic steroids. Regular monitoring of serum calcium levels is recommended in these patients. Treatment must be stopped if hypercalcaemia occurs. Hypercalcaemia should first be adequately treated and only after restoration of normal calcium levels can androgen therapy can be continued (see section 4.3).
- Pre-existing conditions - In patients suffering from severe cardiac, hepatic or renal insufficiency or ischaemic heart disease, treatment with testosterone may cause severe complications characterized by oedema with or without congestive cardiac failure. In such cases treatment must be stopped immediately.

Patients who experienced myocardial infarction, cardiac-, hepatic- or renal insufficiency, hypertension, epilepsy, or migraine should be monitored due to the risk of deterioration of or reoccurrence of disease. In such cases treatment must be stopped immediately.
Testosterone may cause a rise in blood pressure and Restandol Testocaps should be used with caution in men with hypertension.

- Diabetes mellitus – Androgens in general and Restandol Testocaps can improve the glucose tolerance in diabetic patients (see section 4.5).
- Anti-coagulant therapy – Androgens in general and Restandol Testocaps can enhance the anti-coagulant action of coumarin-type agents (see section 4.5).

- Clotting disorders **–** Testosterone should be used with caution in patients with thrombophilia or risk factors for venous thromboembolism (VTE), as there have been post-marketing studies and reports of thrombotic events (e.g., deep-vein thrombosis, pulmonary embolism, ocular thrombosis) in these patients during testosterone therapy. In thrombophilic patients, VTE cases have been reported even under anticoagulation treatment, therefore continuing testosterone treatment after first thrombotic event should be carefully evaluated. In case of treatment continuation, further measures should be taken to minimize the individual VTE risk.

- Sleep Apnoea – 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 patients with risk factors such as adiposity or chronic lung diseases.

Adverse events:
If androgen-associated adverse reactions occur (see section 4.8), treatment with Restandol Testocaps should be discontinued and, upon resolution of complaints resumed with a lower dose.

The treatmentregimen should avoid undue stimulation on either physical or mental capacity of the patient. Evidence of excessive sexual stimulation requires discontinuance of therapy.

(Mis) use in sports:
Patients who participate in competitions governed by the World Anti-Doping Agency (WADA) should consult the WADA-code before using this product as Restandol Testocaps can interfere with anti-doping testing. The misuse of androgens to enhance ability in sports carries serious health risks and is to be discouraged.

Drug abuse and dependence:
Testosterone has been subject to abuse, typically at doses higher than recommended for the approved indication(s) and in combination with other anabolic androgenic steroids. Abuse of testosterone and other anabolic androgenic steroids can lead to serious adverse reactions including: cardiovascular (with fatal outcomes in some cases), hepatic and/or psychiatric events. Testosterone abuse may result in dependence and withdrawal symptoms upon significant dose reduction or abrupt discontinuation of use. The abuse of testosterone and other anabolic androgenic steroids carries serious health risks and is to be discouraged.

Excipients:
Restandol Testocaps contains Sunset Yellow (E110, FD&C Yellow no. 6) which may cause allergic reactions.
Restandol Testocaps may contain trace amounts of soya lecithin. If you are allergic to peanut or soya, do not use this medicinal product.

Paediatric Population:
In pre-pubertal children statural growth and sexual development should be monitored since androgens in general and Restandol Testocaps in high dosages may accelerate epiphyseal closure and sexual maturation.

Older People:
There is limited experience on the safety and efficacy of the use of Restandol Testocaps in patients over 65 years of age. Currently, there is no consensus about age specific testosterone reference values. However, it should be taken into account that physiologically testosterone serum levels are lower with increasing age.

**4.5 Interaction with other medicinal products and other forms of interactions**

Enzyme-inducing agents (like e.g. barbiturates and phenylbutazone) may decrease and enzyme-inhibiting drugs may increase testosterone levels. Therefore adjustment of the dose of Restandol Testocaps may be required.

Insulin and other anti-diabetic medicines:
Androgens may improve glucose tolerance and decrease the need for insulin or other anti-diabetic medicines in diabetic patients (see section 4.4). Patients with diabetes mellitus should therefore be monitored especially at the beginning or end of treatment and at periodic intervals during Restandol Testocaps treatment.

Anti-coagulant therapy

High doses of androgens may enhance the anti-coagulant action of coumarin-type agents (see section 4.4). Therefore close monitoring of prothrombin time, and if necessary a dose reduction of the anti-coagulant is required during therapy.

ACTH or corticosteroids:
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 (see section 4.4).

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.

Restandol Testocaps must be taken with a meal to establish appropriate plasma testosterone levels (see section 4.2).

**4.6 Fertility, pregnancy and lactation**

Pregnancy and lactation:
Restandol Testocaps are not indicated for treatment in women and therefore must not be used in pregnant or breastfeeding women. If used during pregnancy Restandol Testocaps pose a risk of virilisation of the fetus.

Fertility
In men treatment with androgens can lead to fertility disorders by repressing sperm-formation (see section 4.8).

**4.7 Effects on ability to drive and use machines**

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

**4.8 Undesirable effects**

The following adverse reactions have been associated with androgen therapy in general. The most appropriate MedDRA term to describe a certain adverse event is listed.

All adverse reactions are listed by system organ class and frequency: common (≥1/100 to <1/10) and not known (cannot be estimated from the available data).

| System Organ Class | Common | Not Known |
|---|---|---|
| Neoplasms benign, malignant and unspecified (incl. cysts and polyps) | | Prostatic cancer[1] |
| Blood and lymphatic system disorders | | Polycythaemia |
| Metabolism and nutrition disorders | Weight increased | Fluid retention |
| Psychiatric disorders | | Depression<br>Nervousness<br>Mood altered<br>Libido increased<br>Libido decreased |
| Vascular disorders | | Hypertension |
| Gastrointestinal disorders | | Nausea |
| Hepatobiliary disorders | | Abnormal Hepatic function |
| Skin and subcutaneous tissue disorders | | Pruritus<br>Acne |
| Musculoskeletal and connective tissue disorders | | Myalgia |
| Reproductive system and breast disorders | | Gynecomastia<br>Oligozoospermia<br>Priapism<br>Benign prostatic hyperplasia[2]<br>Ejaculation disorder |
| Investigations | Haematocrit increased<br>Red blood cell count increased<br>Haemoglobin increased | Abnormal Lipids [3]<br>PSA increased |
| [1] Progression of a sub-clinical prostatic cancer<br>[2] Prostatic growth (to normogonadal size)<br>[3] Decrease in serum LDL-C, HDL-C and triglycerides | | |

The terms used to describe the undesirable effects above are also meant to include synonyms and related terms.

During post marketing use of Restandol Testocaps, diarrhoea and abdominal pain has been reported.

Paediatric population:
The following undesirable effects have been reported in pre-pubertal children using androgens (see section 4.4): precocious sexual development, an increased frequency of erections, phallic enlargement and premature epiphyseal closure.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

**4.9 Overdose**

The acute oral toxicity of testosterone undecanoate is very low. High dosages of Restandol Testocaps may cause gastrointestinal complaints due to the oily solvent contained in the capsule. Treatment may consist of supportive measures.

**5 PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Androgens. ATC code G03B A03

Treatment of hypogonadal men with Restandol 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). Treatment dose-dependently decreases serum LDL-C, HDL-C and triglycerides, and increases haemoglobin 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 insulin-sensitivity and/or reduction in blood glucose have been reported with the use of androgens.
Restandol has effects on the growth and maturation of the male genital organs and structures (i.e. prostate, seminal vesicles, penis, and scrotum) male secondary sexual characteristics such as the development of male hair distribution, such as facial, pubic, chest, and auxiliary hair and other more general effects such as laryngeal enlargement, vocal chord thickening, and alterations in body musculature, bone mineral density and fat distribution.

**5.2 Pharmacokinetic properties**

Absorption:

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 partially circumventing the first-pass inactivation by the liver. Restandol 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 Restandol Testocaps leads to a clinically significant increase of total plasma testosterone with peak-levels of approximately 40 nmol/l ($C_{max}$), reached approximately 4-5h ($t_{max}$) 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 hydrolysed to yield the natural male androgen testosterone. Testosterone is further metabolized to dihydrotestosterone and estradiol, which are further metabolized via the normal pathways.

Elimination:

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 with androgens in general reveal no hazards for humans. The use of androgens in different species has been demonstrated to result in virilisation of the external genitals of female fetuses.

Toxicological studies with testosterone have only shown effects that can be explained by its hormone profile. Testosterone is not genotoxic. Studies in animals on the relation of testosterone and cancer, indicate on the possibility that high doses may promote the tumor growth in the genital organs, mammary glands and liver. The clinical relevance of this observation is not known. In view of the oral administration of Restandol Testocaps that the high probability of developing diarrhoea when taking large number of capsules due to the Castor oil, it is unlikely that such long lasting, high levels of testosterone can be obtained.

Reproduction studies with rodents and primates demonstrated that testosterone treatment may dose-dependently reduce the fertility by suppression of the spermatogenesis.

**6 PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Capsule content:
Each capsule contains 175.8 mg castor oil. In addition, this medicine contains 117.2 mg propylene glycol monolaurate (E477) in each capsule. This quantity corresponds to 34.5 mg propylene glycol which is equivalent to 0.5 mg/kg.
Capsule shell*:
Glycerin, Sunset Yellow FCF (E110) and gelatin.
* the capsules may contain traces of the excipients medium-chain triglycerides and lecithin.
Printing ink:
Opacode WB®.

**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 the original package and keep container in the original carton in order to protect from light.

**6.5 Nature and contents of container**

PVC/aluminium foil blister strips of 10 capsules, packed in an aluminium foil sachet.

3, 6, or 12 sachets are packed in an outer cardboard carton.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**

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

**7 MARKETING AUTHORISATION HOLDER**

Merck Sharp & Dohme Ireland (Human Health) Limited
Red Oak North
South County Business Park
Leopardstown
Dublin 18
Ireland

**8 MARKETING AUTHORISATION NUMBER**

PA1286/054/001

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 24th November 1978

Date of last renewal: 24th November 2008

**10 DATE OF REVISION OF THE TEXT**

February 2020