NEW ZEALAND DATA SHEET

1 PRODUCT NAME

ANDRIOL TESTOCAPS® 40 mg

Liquid filled capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 40 mg testosterone undecanoate, equivalent to 25.3 mg testosterone dissolved in a mixture of castor oil and propylene glycol monolaurate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Soft, oval (No. 6), glossy capsule, transparent, orange in colour, with a yellow, oily fill, coded ORG DV3 in white.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

In the male
Testosterone replacement therapy for primary or secondary hypogonadal disorders (either congenital or acquired) when testosterone deficiency has been confirmed by clinical features and biochemical tests, for example:

- after castration
- eunuchoidism
- hypopituitarism
- endocrine impotence
- male climacteric symptoms such as decreased libido and decreased feeling of general well-being and fitness
- certain types of infertility due to spermatogenesis disorders.

Moreover, in men testosterone therapy may be indicated in osteoporosis due to androgen deficiency.

4.2 Dose and method of administration

Adults including elderly
In general, dosage should be adjusted according to the response of the individual patient. Usually, an initial dosage of 120-160mg daily for 2-3 weeks is adequate, followed by a maintenance dosage of 40-120mg daily based on the clinical effect obtained during the first weeks of therapy.

Method of Administration
ANDRIOL TESTOCAPS must be taken with a meal, with some 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. If an uneven number of capsules is to be taken, the larger dose should be taken in the morning.

Paediatric population
Safety and efficacy have not been adequately determined in children and adolescents. Pre-pubertal children treated with ANDRIOL TESTOCAPS should be treated with caution.

4.3 Contraindications

- Known or suspected prostatic carcinoma or breast carcinoma in the male
- Pregnancy
- Breast-feeding
- Hypersensitivity to the active substance or to any of the excipients.

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 ANDRIOL 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 hemoglobin to exclude polycythemia.

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

- **Tumours** – Mammary carcinoma, hypernephroma, bronchial carcinoma and skeletal metastases. In these patients hypercalcaemia may develop spontaneously, also during androgen therapy. The latter can be indicative of a positive tumour response to the hormonal treatment. Nevertheless, the hypercalcaemia should first be treated appropriately and after restoration of normal calcium levels, hormone therapy can be resumed.
- **Pre-existing conditions** – In patients with pre-existing cardiac, renal or hepatic insufficiency/disease androgen treatment may cause complications characterised by oedema with or without congestive heart 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.
- **Diabetes mellitus** – Androgens in general and ANDRIOL TESTOCAPS can improve the glucose tolerance in diabetic patients.
- **Anti-coagulant therapy** – Androgens in general and ANDRIOL TESTOCAPS can enhance the anti-coagulant action of coumarin-type agents.
- **Sleep Apnea** –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 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 ANDRIOL TESTOCAPS should be discontinued and, upon resolution of complaints, resumed with a lower dose.

(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 ANDRIOL 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. (See section 4.8.)

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

Elderly People
There is limited experience on the safety and efficacy of the use of Andriol 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.

The use of steroids may influence the results of certain laboratory tests.

Androgens should be used with caution in men suffering from benign prostatic hypertrophy.

Excipients
ANDRIOL TESTOCAPS contains Sunset Yellow (E110, FD&C Yellow No. 6) which may cause allergic reactions.

4.5 Interaction with other medicines and other forms of interaction

Enzyme-inducing agents may exert decreasing effects on the testosterone levels. Enzyme-inhibiting drugs may increase testosterone levels. Therefore adjustment of dose for ANDRIOL 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. Patients with diabetes mellitus should therefore be monitored especially at the beginning or end of treatment and at periodic intervals during ANDRIOL TESTOCAPS treatment.

Anti-coagulant therapy:
High doses of androgens may enhance the anti-coagulant action of coumarine-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.

ANDRIOL 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 Breastfeeding
ANDRIOL TESTOCAPS are contraindicated in pregnancy and lactation. Androgenic substances may have a virilising effect on the female foetus and should be avoided during pregnancy.

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

As far as is known ANDRIOL TESTOCAPS have no adverse 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 altered, libido increased, libido decreased
Musculoskeletal and connective tissue disorders	Myalgia
Vascular disorders	Hypertension
Gastrointestinal disorders	Nausea

Hepatobiliary disorders	Hepatic function abnormal
Skin and subcutaneous tissue disorders	Pruritus, acne
Reproductive system and breast disorders	Gynaecomastia, oligozoospermia, priapism, , benign prostatic hyperplasia[2]
Investigations	Lipids abnormal[3], PSA increased
	Haematocrit increased
	Red blood cell count increased
	Haemoglobin increased

[1] Progression of a sub-clinical prostatic cancer
[2] Prostatic growth (to normogonadal size)
[3] Decrease in serum LDL-C, HDL-C and triglycerides

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

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

Drug abuse and dependence:

Testosterone, often in combination with other anabolic androgenic steroids (AAS), has been subject to abuse at doses higher than recommended for the approved indication (see section 4.4). The following additional adverse reactions have been reported in the context of testosterone/AAS abuse:

Endocrine disorders: Secondary hypogonadism[1]

Psychiatric disorders: Hostility, Aggression, Psychotic disorder, Mania, Paranoia and Delusion

Cardiovascular disorders: Myocardial infarction, Cardiac failure, Cardiac failure chronic[1,2], Cardiac arrest, Sudden cardiac death[1], Cardiac hypertrophy[1,2], Cardiomyopathy[1], Ventricular arrhythmia, Ventricular tachycardia, Venous/arterial thrombotic and embolic events (including Deep Venous Thrombosis, Pulmonary Embolism, Coronary artery thrombosis, Carotid artery occlusion[1,2], Intracranial venous sinus thrombosis[1,2]), Cerebrovascular accident, Ischaemic stroke

Hepatobiliary disorders: Peliosis hepatis, Cholestasis[1], Liver injury, Jaundice, Hepatic failure

Skin and subcutaneous tissue disorders: Alopecia

Reproductive system and breast disorders: Testicular atrophy, Azoospermia, Infertility (in males), Enlarged clitoris and Breast atrophy (in females)

[1] Has been reported with Andriol
[2] With fatal outcomes in some cases

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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

The acute oral toxicity of testosterone undecanoate is low. High dosages of ANDRIOL TESTOCAPS may cause gastrointestinal complaints due to the oily solvent contained in the capsule. Treatment consists of supportive measures.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Androgens. ATC code G03B A03

Testosterone is the principal endogenous hormone essential for normal growth and development of the male sex organs and male secondary sex characteristics. During adult life testosterone is essential for the functioning of the testes and accessory structures, and for the maintenance of libido, sense of well-being, erectile potency, prostate and seminal vesicle function.
Treatment of hypogonadal men with ANDRIOL TESTOCAPS results in a clinically significant rise of plasma concentrations of testosterone, dihydrotestosterone and androstenedione, as well as a decrease of SHBG (sex hormone binding globulin). In males with primary (hypergonadotropic) hypogonadism treatment with ANDRIOL TESTOCAPS results in a normalization of gonadotropin levels.

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.
Single administration of 80-160mg ANDRIOL TESTOCAPS leads to a clinically significant increase of total plasma testosterone with peak-levels of approximately 40 nmol/L (Cmax) reached approximately 4-5 hours (tmax) 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 metabolised to dihydrotestosterone and estradiol.

Elimination:
Testosterone, estradiol and dihydrotestosterone are metabolised 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 293mg 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

Shelf-life 36 months when stored below 30°C.

6.4 Special precautions for storage

Do not refrigerate or freeze. Keep blister in outer carton in order to protect from light.

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 Special precautions for disposal

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

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

Merck Sharp & Dohme (NZ) Ltd
P O Box 99 851
Newmarket
Auckland 1149
Tel: 0800 500 673

9 DATE OF FIRST APPROVAL

23 November 2001

10 DATE OF REVISION OF THE TEXT

27 July 2017

SUMMARY TABLE OF CHANGES

Section changed	**Summary of new information**
All sections	Conversion to new Data Sheet format
4.4 Special warnings and precautions for use	Addition of subsection related to potential for drug abuse and dependence.
4.8 Undesirable effects	Addition of subsection related to reported adverse events in the context of testosterone abuse and dependence.

S-CCDS-MK3033-CP-052017