1. NAME OF THE MEDICINAL PRODUCT

Sustanon® 250, 250 mg/ml solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sustanon 250 is a solution in oil. Each ampoule or vial contains 1ml arachis oil containing the following active substances :

- 30 mg testosterone propionate
- 60 mg testosterone phenylpropionate
- 60 mg testosterone isocaproate
- 100 mg testosterone decanoate

All four compounds are esters of the natural hormone testosterone. The total amount of testosterone per ml is 176 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

A clear, pale yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

- After castration,
- Eunuchoidism,
- Hypopituitarsim,
- Endocrine impotence,
- Male climacteric symptoms such as decreased libido and decreased mental and physical activity,
- Certain types of infertility due to disorders of spermatogenesis
  In female to male transsexuals:
- masculinization.

4.2 Posology and method of administration

Posology:

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

Adults (incl. elderly):

Usually, one injection of 1 ml per three weeks is adequate.

Paediatric population:

Safety and efficacy have not been adequately determined in children and adolescents.

Method of administration:

Sustanon should be administered by deep intramuscular injection.

4.3 Contraindications

- Known or suspected carcinoma of the prostate or breast (see section 4.4).
- Hypersensitivity to the active substance or to any of the excipients, including arachis oil. Sustanon is therefore contraindicated in patients allergic to peanuts or soya (see section 4.4.)

4.4 Special warnings and precautions for use

Sustanon 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.

There is limited experience on the safety and efficacy of the use of Sustanon 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.

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.

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 Sustanon before the start of treatment, at quarterly intervals for the first 12 months and yearly thereafter for the following parameters:

- Digital rectal examination (DRE) or 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:

- Tumours - Mammary carcinoma, hypernephroma, bronchial carcinoma and skeletal metastases. In these patients hypercalcemia may develop spontaneously, also during androgen therapy. The latter can be indicative of a positive tumour response to the hormonal treatment. Nevertheless, the hypercalcemia 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 characterized by edema 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 risk of deterioration of or reoccurrence of disease. In such cases treatment must be stopped immediately.
- Hypertension – Testosterone may cause a rise in blood pressure and Sustanon should be used with caution in men with hypertension.
- Diabetes mellitus - Androgens in general and Sustanon can improve glucose tolerance in diabetic patients (see section 4.5).
- Anti-coagulant therapy – Androgens in general and Sustanon can enhance the anticoagulant action of coumarin-type agents (see also section 4.5).
- 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.

There have been postmarketing reports of venous thromboembolic events, including deep vein thrombosis (DVT) and pulmonary embolism (PE), in patients using testosterone products. Evaluate patients who report symptoms of pain, oedema, warmth and erythema in the lower extremity for DVT and those who present with acute shortness of breath for PE. If a venous thromboembolic event is suspected, discontinue treatment with Sustanon and initiate appropriate workup and management.

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 minimise the individual VTE risk (*see Adverse Event*)

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.

Adverse events:
If androgen-associated adverse reactions occur (see section 4.8), treatment with Sustanon 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 Sustanon can interfere with anti-doping testing. The misuse of androgens to enhance ability in sports carries serious health risks and is to be discouraged.

Excipients:

Sustanon contains arachis oil (peanut oil) and should not be taken/ applied by patients known to be allergic to peanut. As there is a possible relationship between allergy to peanut and allergy to soya, patients with soya allergy should also avoid Sustanon (see section 4.3).

Sustanon contains 100 mg benzyl alcohol per ml solution and must not be given to premature babies or neonates. Benzyl alcohol may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old.

Paediatric Population:

In pre-pubertal children statural growth and sexual development should be monitored since androgens in general and Sustanon 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 Sustanon 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 interaction

Enzyme-inducing agents may decrease and enzyme-inhibiting drugs may increase testosterone levels. Therefore, adjustment of the dose of Sustanon 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 Sustanon treatment.

Anti-coagulant therapy:

High doses of androgens may enhance the anticoagulant 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.

4.6 Pregnancy, lactation and fertility

Pregnancy and lactation:

Sustanon is not indicated for treatment in women and therefore must not be used by pregnant or breast-feeding women. If used during pregnancy Sustanon poses a risk of virilization 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

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

4.8 Undesirable effects

Due to the nature of Sustanon, side effects cannot be quickly reversed by discontinuing medication. Injectables in general, may cause a local reaction at the injection site.

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, Haematocrit increased, Red blood cell count increased, Haemoglobin increased

Metabolism and nutrition disorders	Fluid retention, Weight gain
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
Investigations	Lipids abnormal[2],[1]PSA increased

[1] Progression of a sub-clinical prostatic cancer.

[2] 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.

Paediatric population

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

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[1], Psychotic disorder [1], Mania, Paranoia and Delusion
Cardiovascular disorders: Myocardial infarction[1], Cardiac failure[1], Cardiac failure chronic [1,2,] Cardiac arrest, Sudden cardiac death, Cardiac hypertrophy [1,2,] Cardiomyopathy [1], Ventricular arrhythmia, Ventricular tachycardia [1], Venous/arterial thrombotic and embolic events (including Deep Venous Thrombosis [1], Pulmonary Embolism [1], Coronary artery thrombosis, Carotid artery occlusion [1,2,] Intracranial venous sinus thrombosis [1,2]), Cerebrovascular accident and Ischaemic stroke
Hepatobiliary disorders: Peliosis hepatis [1], Cholestasis, Liver injury, Jaundice [1] and Hepatic failure
Skin and subcutaneous tissue disorders: Alopecia [1]
Reproductive system and breast disorders: Testicular atrophy, Azoospermia, Infertility (in males), Enlarged clitoris and Breast atrophy (in females)

[1] Has been reported with Sustanon

[2] With fatal outcomes in some cases

4.9 Overdose

The acute toxicity of testosterone is low.

If symptoms of chronic overdose occur (e.g. polycythemia, priapism) treatment should be discontinued and after disappearance of the symptoms, be resumed at a lower dosage.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Androgens. ATC code G03B A03.

Treatment of hypogonadal men with Sustanon results in a clinically significant rise of plasma concentrations of testosterone, dihydrotestosterone, estradiol and androstenedione, as well as a decrease of SHBG (sex hormone binding globulin). Lutenizing hormone (LH) and follicle-stimulating hormone (FSH) are restored to the normal range. In hypogonadal men, treatment with Sustanon 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 decreases serum LDL-C, HDL-C and triglycerides, and 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 insulin sensitivity and/or reduction in blood glucose have been reported with the use of androgens. In boys with constitutional delay of growth and puberty, treatment with Sustanon accelerates growth and induces development of secondary sex characteristics

In female-to-male transsexuals treatment with Sustanon induces masculinization.

5.2 Pharmacokinetic properties

Sustanon 250 contains four esters of testosterone with different durations of action. The esters are hydrolyzed into the natural hormone testosterone as soon as they enter the general circulation.

Absorption:

A single dose of Sustanon 250 leads to an increase of total plasma testosterone with peak levels of approximately 70 nmol/l (C_{max}), which are reached approximately 24-48 h (t_{max}) after administration. Plasma testosterone levels return to the lower limit of the normal range in males in approximately 21 days.

Distribution:

Testosterone displays a high (over 97%) non-specific binding to plasma proteins and sex hormone binding globulin in in vitro tests.

Biotransformation:

Testosterone is 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.

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 virilization of the external genitals of female fetuses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Arachis oil; benzyl alcohol.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf life of Sustanon, under the given storage conditions, is 3 years.

Sustanon may be used until the expiration date indicated on the package.

Since an opened ampoule or vial cannot be resealed in such a way to further guarantee the sterility of the contents, the solution should be used immediately.

6.4 Special precautions for storage

Store 8-30 °C; protect from light.

6.5 Nature and contents of container

Sustanon 250 ampoules :

Each colourless glass ampoule is filled with 1 ml of Sustanon 250. A box of Sustanon 250 contains 1 ampoule.

Sustanon 250 vials :

Each type I glass vial is filled with 1 ml of Sustanon 250.

A box of Sustanon 250 contains 1 vial.

6.6 Special precautions for disposal and other handling

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

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

7. DATE OF REVISION OF THE TEXT

April 2020

8. PRODUCT OWNER

Aspen Global Incorporated

Mauritius