Prescribing Information

Androgel 16.2 mg/g Gel
(Testosterone)

Composition
One gram of gel contains 16.2 mg testosterone. One pump actuation delivers 1.25 g of gel containing 20.25 mg of testosterone. Other ingredients: Carbomer 980, isopropyl myristate, ethanol 96 %, sodium hydroxide and purified water.

Product Description
Androgel 16.2 mg/g Gel is a transparent or slightly opalescent colourless gel.

Pharmacological properties

Pharmacodynamics

Pharmacotherapeutic class: Androgens, ATC Code: G03B A03

Endogenous androgens, mainly testosterone, secreted by the testes and its main metabolite, DHT, are responsible for the development of external and internal genital organs and for the maintenance of secondary sexual characteristics (hair growth, deepening of the voice, development of libido). Androgens also have an effect on protein anabolism, development of skeletal muscle and body fat distribution, and also reduce urinary excretion of nitrogen, sodium, potassium, chlorides, phosphorus, and water.

Testosterone reduces pituitary gland secretion of gonadotropins.

The effects of testosterone on some target organs occur only after conversion at the peripheral level of the testosterone to estradiol, which then binds to the target cell oestrogen nuclear receptors, for example, in the pituitary gland, the adipose tissue, the brain, the bone, and the Leydig cells in the testicle.

Pharmacokinetics

The percutaneous absorption of testosterone after administration of ANDROGEL 16.2 mg/g, gel varies between 1% and 8.5%. After percutaneous through the skin, testosterone diffuses into the general circulation at relatively constant levels during a diurnal cycle.

Blood testosterone concentration increases from the first hour after application to reach a steady state from the second day. The daily changes in testosterone levels are then similar in amplitude to those observed during the circadian rhythm of the endogenous testosterone. The percutaneous route thus avoids the blood distribution peaks induced by injections. It does not cause any supraphysiological hepatic concentrations of the steroid, unlike oral androgen therapy.

The administration of 5 g of ANDROGEL 16.2 mg/g, gel produces a mean increase in plasma

testosterone levels of approximately 2.3 ng/mL (8.0 nmol/L).

When treatment is stopped, testosterone levels start decreasing about 2 hours after the last administration. Levels return to baseline within approximately 72 to 96 hours of the last administration.

The main active metabolites of testosterone are dihydrotestosterone and oestradiol.
Testosterone is primarily excreted in the urine as conjugated metabolites, with a small amount being excreted unchanged in the faeces.

In the phase III double-blind study, at the end of a 112-day treatment period, during which the dose of ANDROGEL 16.2 mg/g gel could be determined based on total testosterone concentrations, 81.6% (CI 75.1-87.0%) of men had total testosterone concentration in the normal range of young eugonadal men (300 - 1,000 ng/dL). In patients taking a daily dose of ANDROGEL 16.2 mg/g, gel, the mean (±SD) daily testosterone concentration on Day 112 (Cav) was 561 (±259) ng/dL, mean Cmax was 845 (±480) ng/dL, and mean Cmin was 334 (±155) ng/dL. The corresponding concentrations at Day 182 (double-blind period) were Cav 536 (±236) ng/dL, mean Cmax 810 (±497) ng/dL, and mean Cmin 330 (±147) ng/dL.

In the phase III open-label study, at the end of a 364-day treatment period, during which the dose of ANDROGEL 16.2 mg/g gel could be determined based on total testosterone concentrations, 77.9% (CI 70.0, 84.6) of men had total testosterone concentration in the normal range of young eugonadal men (300 - 1,000 ng/dL).

In patients taking a daily dose of ANDROGEL 16.2 mg/g, gel, the mean (±SD) daily testosterone concentration on Day 266 (Cav) was 459 (±218) ng/dL, mean Cmax was 689 (±414) ng/dL, and mean Cmin was 305 (±121) ng/dL. The corresponding concentrations on Day 364 (open-label period extension) were Cav 454 (±193) ng/dL, mean Cmax 698 (±382) ng/dL, and mean Cmin 302 (±126) ng/dL.

Pre-clinical safety data

Testosterone was found to be non-mutagenic in vitro, based on the model for reverse mutations (Ames test) or for hamster ovary cells. In studies in laboratory animals, a link was found between treatment with androgens and certain cancers. Experimental data in rats showed an increased incidence of prostate cancer after testosterone treatment.

Sex hormones are known to facilitate the development of certain tumours induced by known carcinogens. The importance of these findings and the real risk to humans is unclear.

It has been reported that the administration of exogenous testosterone suppressed spermatogenesis in rats, dogs and non-human primates, which was reversible upon discontinuation of treatment.

Indication

ANDROGEL 16.2 mg/g gel is indicated in adults as replacement therapy for male

hypogonadism when testosterone deficiency has been clinically and biologically confirmed.

Recommended Dosage

Adult and elderly populations

The recommended dose is two pump actuations (i.e. 40.5 mg of testosterone) applied once daily at approximately the same time, preferably in the morning. The daily dose will be adjusted by the doctor based on the clinical or laboratory response of each patient, not exceeding four pump actuations or 81 mg testosterone per day. The dose should be adjusted in increments by one press on the pump.

The dose should be determined based on morning blood testosterone concentrations prior to dosing. Steady state blood testosterone concentrations are reached from approximately the second day of treatment with ANDROGEL 16.2 mg/g, gel. The dosage is adjusted based on blood testosterone levels measured in the morning before application of the product, after steady state is reached. Testosterone blood levels should be evaluated periodically. The dosage may be reduced if the blood testosterone levels exceed the desired level. If the concentration is low, the dosage may be increased stepwise up to 81 mg of testosterone (four pump actuations).

Treatment should be discontinued if blood testosterone levels consistently exceed the normal range at the lowest daily dose of 20.25 mg (1.25 g gel, i.e. one pump actuation) or if normal blood testosterone levels are not achieved at the highest dose of 81 mg (5 g gel, i.e. four pump actuations).

Paediatric population

The safety and efficacy of ANDROGEL 16.2 mg/g gel in boys under 18 years of age have not been established. No data are available.

Mode of Administration

The application should be done by the patient himself, on clean, dry and healthy skin, on the right and left shoulders and upper arms.

The gel should be spread simply in a thin layer on the skin. It is not necessary to rub the skin. Allow to dry at least 3 to 5 minutes before getting dressed. Wash hands with soap and water after application and cover the application site(s) with clothing after the gel has dried. Wash the application site thoroughly with soap and water before any situation where contact is expected between the application site and another person's skin.
For further information on post- dose washing see section on Warning and Precautions: Risk of inadvertent testosterone transfer.

Do not apply the gel to the genitals, as the high alcohol content in the gel may cause local irritation. To obtain a full first dose, it is necessary to prime the canister pump. To do this, with the

canister in the upright position, slowly and fully depress the actuator three times. Safely discard the gel from the first three actuations. Pump priming is only necessary before the first dose.

After priming, fully depress the actuator to deliver 1.25 g of ANDROGEL 16.2 mg/g, gel into palm of hand and apply gel to shoulders and arms.

Contraindications

ANDROGEL 16.2 mg/g, gel is contraindicated:

- in case of confirmed or suspected prostate cancer or breast carcinoma
- in case of hypersensitivity to the active ingredient or to any of the excipients.

Warnings and Precautions

ANDROGEL 16.2 mg/g, gel should only be used if hypogonadism (hypo-or hypergonadotrophic) has been demonstrated and if other aetiologies, which may be the cause of the symptoms, have been ruled out before starting the treatment. Testosterone insufficiency should be clearly demonstrated by clinical signs (regression of secondary sexual characteristics, change in body composition, asthenia, reduced libido, erectile dysfunction, etc.) and confirmed by 2 separate blood testosterone assays. Currently, there is no consensus on age-based normal testosterone ranges. However, it should be taken into account that physiological blood testosterone values decrease with age.

Due to the variability of the outcomes between different laboratories, all assays must be performed by the same laboratory for a given subject.

ANDROGEL 16.2 mg/g gel is not indicated for the treatment of male sterility or impotence.

Before initiating a testosterone-based treatment, patients must undergo a thorough examination to rule out any risk of pre-existing prostate cancer. Careful and regular surveillance of the prostate and breasts should be carried out using the recommended methods (rectal examination and PSA-prostate-specific antigen assay) at least once a year in any patient receiving a testosterone treatment and twice a year in elderly subjects and patients at risk (clinical or family factors).

Androgens may accelerate the progression of subclinical prostate cancer or benign prostate hyperplasia.

ANDROGEL 16.2 mg/g, gel should be used with caution in patients with cancer with a risk of hypercalcaemia (and associated hypercalciuria), related to bone metastases. It is recommended to ensure regular monitoring of blood calcium levels in these patients.

In patients with severe heart, liver, or kidney failure or ischemic heart disease, treatment with testosterone could lead to severe complications characterised by oedema, with or without congestive heart failure. In this case, the treatment should be discontinued immediately. In

addition, diuretic treatment may be necessary.

ANDROGEL 16.2 mg/g gel should be used with caution in patients with ischemic heart disease.

Testosterone may cause blood pressure to increase. Therefore, ANDROGEL 16.2 mg/g should be used with caution in men with hypertension.

Blood clotting disorders

Testosterone should be used with caution in patients with thrombophilia or with risk factors for venous thromboembolism (VTE), as thromboembolic events have been reported in these patients while taking testosterone treatment, in studies and post-marketing follow-ups (e.g. deep vein thrombosis, pulmonary embolism, ocular thrombosis). In patients with thrombophilia, cases of VTE have been reported even while taking an anticoagulant treatment. Therefore, the continuation of the testosterone treatment after a first thrombotic event should be carefully evaluated. If the treatment is continued, further action should be taken to minimise the risk of VTE.

Testosterone levels should be monitored before starting treatment and at regular intervals during the treatment. Clinicians should adjust the dosage for each patient to ensure that the testosterone levels are maintained at a eugonadal level.

In patients on long-term androgen treatment, in addition to the biological assays of blood testosterone levels, the following laboratory parameters should be monitored regularly: haemoglobin levels, haematocrit (to detect polycythaemia), liver function, and lipid panel.

There is limited experience on the safety and efficacy of ANDROGEL 16.2 mg/g gel used in patients over 65 years of age. Currently, there is no consensus on baseline testosterone values based on age. However, the decrease in the physiological values of testosterone with age should be considered.

ANDROGEN 16.2 mg/g, gel should be used with caution in patients with epilepsy and migraine, as their condition may be aggravated.

Literature has reported risks of increased sleep apnoea during treatment with testosterone esters in subjects treated for hypogonadism, particularly in at-risk subjects with obesity or a chronic respiratory disease.

Improvement in insulin sensitivity may be observed in patients treated with androgens and may require a reduction in the dose of antidiabetic drugs.

Some clinical signs such as irritability, nervousness, weight gain, prolonged or frequent erections may indicate excessive androgen exposure requiring a dosage adjustment.

In case of severe reaction at the application site, treatment should be reconsidered and stopped if necessary.

With high doses of exogenous androgens, spermatogenesis may be suppressed through feedback of the pituitary follicle-stimulating hormone (FSH), potentially leading to adverse effects on semen parameters including sperm count.

Gynaecomastia may sometimes develop and persist in patients treated with androgens for hypogonadism. ANDROGEL 16.2 mg/g, should not be used in women due to possible virilising effects.
The attention of athletes should be drawn to the fact that this medicine contains an active ingredient (testosterone) that can induce a positive reaction to tests performed during anti- doping controls.

Risk of inadvertent testosterone transfer

If no precautions are taken, testosterone can be transferred to another person at any time after dosing by close skin contact with the area where the gel is applied, leading to an increase in testosterone levels and, in the event of repeated contact (inadvertent androgenisation), possible adverse effects (for example, growth of facial and/or body hair, deepening of the voice, irregularities in the menstrual cycle in women, and premature puberty and organ development in children). If virilisation occurs, testosterone treatment should be promptly discontinued until the cause of the virilisation has been identified.

The doctor should inform the patient about this risk of testosterone transfer and about the precautions for use (see below). ANDROGEL 16.2 mg/g, gel should not be prescribed in patients at major risk of non-compliance with the precautions for use (e.g. severe alcoholism, drug use, severe psychiatric disorders).

The possible risk of transfer is substantially reduced (but not eliminated) by wearing clothes (such as a sleeved shirt) covering the application area. Most residual testosterone is removed from the skin surface by washing with soap and water before contact.

Therefore, the following precautions are recommended:

For the patient:

- wash hands with soap and water after applying the gel,
- cover the application area with clothing (such as a sleeved shirt) after the gel has dried,

- have a shower and wash the application site(s) thoroughly with soap and water to remove any testosterone residue before any situation in which such contact is anticipated.

For people not treated with ANDROGEL 16.2 mg/g:

- in the event of contact with an application area that has not been washed or is not covered with clothing, wash the skin surface on which testosterone transfer may have occurred with soap and water as soon as possible
- report the appearance of signs of androgenisation such as acne or changes to hair

Wait at least 2 hours before swimming, washing or showering following application of ANDROGEL 1.62%. This will ensure that the greatest amount of ANDROGEL 1.62% is absorbed into the system.

To improve partner safety, the patient should be informed, for example, to wash the application area with soap and water before sexual intercourse or, if this is not possible, wear clothing, such as a T-shirt, covering the application site during the period of contact.

In addition, it is recommended to wear clothing covering the application site (such as a sleeved shirt) during contact periods with children to reduce the risk of contacting the children's skin.

Pregnant women must avoid contact with the application sites of ANDROGEL 16.2 mg/g, gel. In the case of pregnancy of a partner, the patient must be especially vigilant regarding the precautions for use.

This medicine contains 0.9 g of alcohol (ethanol) per 1.25 g measure of gel. This may cause a burning sensation on damaged skin.

This medicinal product may be flammable until the product dries.

Interactions with other medicines and other forms of interactions
Due to changes in the anticoagulant effect (increased effect of oral anticoagulant by modification of the hepatic synthesis of coagulation factors and competitive inhibition of plasma protein binding): more frequent monitoring of prothrombin and international normalised ration (INR) levels are recommended. Patients taking oral anticoagulants require close monitoring, especially at the start or discontinuation of androgen treatment.

The concomitant administration of testosterone and ACTH or corticosteroids may increase the risk of oedemas. Therefore, these medicines should be administered with caution, especially in patients with heart, kidney or liver disease.

Interaction with laboratory tests: androgens may decrease thyroxin-fixing globulin (TBG) levels, resulting in reduced T4 serum concentrations and increased T3 and T4 resin uptake. However, free thyroid hormone levels remain unchanged and there is no clinical evidence of thyroid insufficiency.

Changes in insulin sensitivity, glucose tolerance, glycaemic control, blood glucose, and glycosylated haemoglobin levels have been reported with androgens. In diabetic patients, a reduction in antidiabetic medicines may need to be considered.

The application of moisturizing lotion increased mean testosterone Cav and Cmax by 14 % and 7% respectively, compared to Androgel 1.62% administered alone. Application of sunscreen increased mean testosterone CaV and Cmax by 8% and 13 % respectively, compared to ANDROGEL 1.62 % applied alone.

Washing 2 or 6 hours after application resulted in 14% and 10% decreases in mean testosterone Cav, respectively, compared to no washing. Washing 10 hours after application had no effect on bioavailability.

Use during Pregnancy/Lactation
ANDROGEL 16.2 mg/g, gel is intended for use by men only.

Pregnancy and Breast-feeding

ANDROGEL 16.2 mg/g gel is not indicated in pregnant or breast-feeding women due to the potentially virilising effects on the foetus.

Pregnant women must avoid any contact with the application sites of ANDROGEL 16.2 mg/g, gel. In the case of contact, wash with soap and water as soon as possible.

Fertility

Spermatogenesis may be reversibly suppressed by ANDROGEL 16.2 mg/g, gel.

Adverse Effects/ Undesirable Effects
At the recommended dosage, the most common adverse reactions observed with ANDROGEL 16.2 mg/g gel were psychiatric disorders and skin reactions at the application site.

The table below shows the adverse reactions reported during the 182-day double-blind period of a Phase III clinical trial of ANDROGEL 16.2 mg/g gel and more frequently in the ANDROGEL
16.2 mg/g gel treated group (n=234) than in the placebo treated group (n=40).

Table 1 Frequency of Adverse Reactions from the Phase III Study of ANDROGEL 16.2 mg/g, gel

MedDRA system organ class	**Preferred Terms**	
	Common ≥ 1/100 to< 1/10	**Rare ≥ 1/1,000 to< 1/100**
Psychiatric disorders	Emotional symptoms* (mood swings, affective disorders, anger, aggression, impatience, insomnia, abnormal dreams, increased libido)	
Vascular disorders		Malignant hypertension, flushing, phlebitis
Gastrointestinal conditions		Diarrhoea, abdominal distension, oral pain
Skin and subcutaneous tissue disorders	Skin reactions* (acne, alopecia, dry skin, skin lesions, contact dermatitis, hair color changes, rash, application site hypersensitivity, application site pruritus)	
Reproductive system and breast disorders		Gynaecomastia, nipple disorders, testicular pain, increased erections
General disorders and administration site conditions		Pitting oedema
Investigations	Increased PSA, increase in haematocrit or haemoglobin	

* Events grouped

Due to the presence of alcohol in this medicine, frequent application to the skin may cause skin irritation and dryness.

The following adverse reactions have been identified during the post-approval period of ANDROGEL 16.2 mg/g gel. Because these adverse reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a clear causal relationship with drug exposure.

Table 2 Adverse reactions spontaneously reported with ANDROGEL 16.2 mg/g, gel

MedDRA system organ class	***Adverse Reactions - Preferred Terms***
Blood and lymphatic system disorders	Polycythaemia, anaemia
Psychiatric disorders	Insomnia, depression, anxiety, aggression
Nervous system disorders	Headache, dizziness, paraesthesia
Vascular disorders	Vasodilation (hot flushes), deep vein thrombosis
Respiratory, thoracic, and mediastinal disorders	Dyspnoea
Gastrointestinal conditions	Nausea
Skin and subcutaneous tissue disorders	Application site reaction, acne, alopecia, sweating hypertrichosis
Musculoskeletal and connective tissue	Musculoskeletal pain
Kidney and urinary diseases	Impaired urination
Reproductive system and breast disorders	Gynaecomastia, testicular disorders, prostate enlargement, oligospermia, benign prostate hyperplasia
General disorders and administration site conditions	Asthenia, oedema, malaise
Investigations	Weight gain, elevated PSA, haematocrit, or haemoglobin

The following adverse reactions were identified during the post- approval period for products containing testosterone.

Table 3 Adverse reactions with products containing testosterone

MedDRA system organ class	***Adverse Reactions - Preferred Terms***
	Common ≥1/100 to <1/10
Blood and lymphatic system disorders	Increased haematocrit, increased red blood cell count, increased haemoglobin

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 the national reporting system. (HSA_productsafety@hsa.gov.sg)

Overdose and Treatment
Only one case of acute testosterone overdose following an injection has been reported in the literature. This was a case of stroke in a patient with elevated plasma testosterone concentration of 114 ng/mL (395 nmol/L). It is very unlikely that such plasma testosterone concentrations would be achieved using transdermal treatment.
Treatment of overdose consists of discontinuation of ANDROGEL 16.2 mg/g, gel combined with appropriate supportive care.

Incompatibilities
Not applicable

Storage Conditions
Store below 30ºC.
Shelf-life

3 years
Discard the product after 60 days of first opening.
Presentations
Multi-dose container (comprised of a polypropylene canister with an LDPE lined pouch) with a dosing pump that contains 88 g of gel and delivers a minimum of 60 doses.
Pack sizes: 1, 2, 3 or 6 containers per carton. Not all sizes may be marketed.

Name of Manufacturer
Laboratoires Besins International
13, rue Perier, 92120 Montrouge- France

Versions 01

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