ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ANDROGEL 50 mg, gel in sachet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One sachet of 5 g contains 50 mg of testosterone.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gel in sachet.

Transparent or slightly opalescent, colourless gel in sachet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Testosterone replacement therapy for male hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests (see 4.4 Special warnings and precautions for use).

4.2 Posology and method of administration

Cutaneous use.

Adult and Elderly men
The recommended dose is 5 g of gel (i.e. 50 mg of testosterone) applied once daily at about the same time, preferably in the morning. The daily dose should be adjusted by the doctor depending on the clinical or laboratory response in individual patients, not exceeding 10 g of gel per day. The adjustment of posology should be achieved by 2.5 g of gel steps.
The application should be administered by the patient himself, onto clean, dry, healthy skin over both shoulders, or both arms or abdomen.
After opening the sachets, the total contents must be extracted from the sachet and applied immediately onto the skin. The gel has just to be simply spread on the skin gently as a thin layer. It is not necessary to rub it on the skin. Allow drying for at least 3-5 minutes before dressing. Wash hands with soap and water after applications.

Do not apply to the genital areas as the high alcohol content may cause local irritation.

Steady state plasma testosterone concentrations are reached approximately on the 2nd day of treatment by Androgel. In order to adjust the testosterone dose, serum testosterone concentrations must be measured in the morning before application from the 3rd day on after starting treatment (one week seems reasonable). The dose may be reduced if the plasma testosterone concentrations are raised above the desired level. If the concentrations are low, the dosage may be increased, not exceeding 10 g of gel per day.

Children
Androgel is not indicated for use in children and has not been evaluated clinically in males under 18 years of age.

4.3 Contraindications

Androgel is contraindicated:
- in cases of known or suspected prostatic cancer or breast carcinoma,
- in cases of known hypersensitivity to testosterone or to any other constituent of the gel.

4.4 Special warnings and precautions for use

Androgel should be used only if hypogonadism (hyper- and hypogonadotrophic) has been demonstrated and if other etiology, 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. 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.

Due to variability in laboratory values, all measures of testosterone should be carried out in the same laboratory.

Androgel is not a treatment for male sterility or impotence.

Prior to testosterone initiation, all patients must undergo a detailed examination in order to exclude a risk of pre-existing prostatic cancer. Careful and regular monitoring of the prostate gland and breast must be performed in accordance with recommended methods (digital rectal examination and estimation of serum PSA) in patients receiving testosterone therapy at least once yearly and twice yearly in elderly patients and at risk patients (those with clinical or familial factors).

Androgens may accelerate the progression of sub-clinical prostatic cancer and benign prostatic hyperplasia.

Androgel should be used with caution in cancer patients at risk of hypercalcaemia (and associated hypercalciuria), due to bone metastases. Regular monitoring of serum calcium concentrations is recommended in these patients.

In patients suffering from severe cardiac, hepatic or renal insufficiency, treatment with Androgel may cause severe complications characterised by oedema with or without

congestive cardiac failure. In this case, treatment must be stopped immediately. In addition, diuretic therapy may be required.
Androgel should be used with caution in patients with ischemic heart disease.

Testosterone may cause a rise in blood pressure and Androgel should be used with caution in patients with hypertension.

Beside laboratory tests of the testosterone concentrations in patients on long-term androgen therapy the following laboratory parameters should be checked periodically: hemoglobin, hematocrit (to detect polycythaemia), liver function tests, and determination of lipids profile.

Androgel should be used with caution in patients with epilepsy and migraine as these conditions may be aggravated.

There are published reports of increased risk of sleep apnoea in hypogonadal subjects treated with testosterone esters, especially in those with risk factors such as obesity and chronic respiratory disease.

Improved insulin sensitivity may occur in patients treated with androgens who achieve normal testosterone plasma concentrations following replacement therapy.

Certain clinical signs: irritability, nervousness, weight gain, prolonged or frequent erections may indicate excessive androgen exposure requiring dosage adjustment.

If the patient develops a severe application site reaction, treatment should be reviewed and discontinued if necessary.

The attention of athletes is drawn to the fact that this proprietary medicinal product contains an active substance (testosterone) which may produce a positive reaction in anti-doping tests.

Androgel should not be used by women, due to possibly virilizing effects.

Potential testosterone transfer
If no precaution is taken, testosterone gel can be transferred to other persons by close skin to skin contact, resulting in increased testosterone serum levels and possibly adverse effects (e.g. growth of facial and/or body hair, deepening of the voice, irregularities of the menstrual cycle) in case of repeat contact (inadvertent androgenization).

The physician should inform the patient carefully about the risk of testosterone transfer and about safety instructions (see below). Androgel should not be prescribed in patients with a major risk of non-compliance with safety instructions (e.g. severe alcoholism, drug abuse, severe psychiatric disorders).

This transfer is avoided by wearing clothes covering the application area or showering prior to contact.

As a result, the following precautions are recommended:
*** for the patient:**
- wash hands with soap and water after applying the gel,

- cover the application area with clothing once the gel has dried,
- shower before any situation in which this type of contact is foreseen.

*** for people not being treated with Androgel:**
- in the event of contact with an application area which has not been washed or is not covered with clothing, wash the area of skin onto which testosterone may have been transferred as soon as possible, using soap and water,
- report the development of signs of excessive androgen exposure such as acne or hair modification.

According to in vitro absorption studies on testosterone conducted with Androgel, it seems preferable for patients to observe at least 6 hours between gel application and bathing or showering. Occasional baths or showers taken between 1 and 6 hours after application of the gel should not significantly influence the treatment outcome.

To guarantee partner safety the patient should be advised for example to observe a long interval between Androgel application and sexual intercourse, to wear a T-shirt covering the application site, during contact period or to shower before sexual intercourse.
Furthermore, it is recommended to wear a T-shirt, covering the application site, during contact period with children, in order to avoid a contamination risk of children skin.

Pregnant women must avoid any contact with Androgel application sites. In case of pregnancy of the partner, the patient must reinforce his attention to the precautions for use (see section 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

+ Oral anticoagulants
Changes in anticoagulant activity (the increased effect of the oral anticoagulant by modification of coagulation factor hepatic synthesis and competitive inhibition of plasma protein binding):
Increased monitoring of the prothrombin time, and INR determinations, are recommended. Patients receiving oral anticoagulants require close monitoring especially when androgens are started or stopped.

Concomitant administration of testosterone and ACTH or corticosteroids may increase the risk of developing oedema. As a result, these medicinal products should be administered cautiously, particularly in patients suffering from cardiac, renal or hepatic disease.

Interaction with laboratory tests: androgens may decrease levels of thyroxin binding globulin, resulting in decreased T_4 serum concentrations and in increased resin uptake of T_3 and T_4. Free thyroid hormone levels, however, remain unchanged and there is no clinical evidence of thyroid insufficiency.

4.6 Pregnancy and lactation

Androgel is intended for use by men only.
Androgel is not indicated in pregnant or breast feeding women. No clinical trials have been conducted with this treatment in women.

Pregnant women must avoid any contact with Androgel application sites (see section 4.4). This product may have adverse virilizing effects on the fœtus. In the event of contact, wash with soap and water as soon as possible.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

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4.8 Undesirable effects

The most frequently observed adverse drug reactions at the recommended dosage of 5 g of gel per day were skin reactions (10%): reaction at the application site, erythema, acne, dry skin.

Adverse drug reactions reported in 1 - <10% of patients treated with Androgel in the controlled clinical trials are listed in the following table:

Organ system class	**Common adverse reactions (>1/100,<1/10)**
Blood and lymphatic system disorders	Changes in laboratory tests (polycythaemia, lipids)
General disorders and administration site conditions	Headache
Renal and urinary disorders	Prostatic disorders
Reproductive system and breast disorders	Gynaecomastia, mastodynia
Nervous system-disorders	Dizziness, paraesthesia, amnesia, hyperaesthesia
Psychiatric disorders	Mood disorders
Vascular disorders	Hypertension
Gastro-intestinal disorders	Diarrhoea
Skin and subcutaneous disorders	Alopecia, urticaria

Gynaecomastia, which may be persistent, is a common finding in patients treated for hypogonadism.

According to the literature, other known undesirable effects have been reported following testosterone oral or inject able treatment and are listed in the following table:

Organ system	**Adverse reactions**
Metabolism and nutrition disorders	Weight gain, electrolyte changes (retention of sodium, chloride, potassium, calcium, inorganic phosphate and water) during high dose and/or prolonged treatment
Musculoskeletal system	Muscle cramps
Nervous system	Nervousness, depression, hostility
Respiratory system	Sleep apnoea
Hepatobiliary disorders	In very rare cases jaundice and liver function test abnormalities
Skin and appendages	Various skin reactions may occur including acne, seborrhoea, and balding

Reproductive system and breast disorders	Libido changes, increased frequency of erections; therapy with high doses of testosterone preparations commonly reversibly interrupts or reduces spermatogenesis, thereby reducing the size of the testicles; testosterone replacement therapy of hypogonadism can in rare cases cause persistent, painful erections (priapism), prostate abnormalities, prostate cancer*, urinary obstruction
General disorders and administration site conditions	High dose or long-term administration of testosterone occasionally increases the occurrences of water retention and oedema; hypersensitivity reactions may occur.

* Data on prostate cancer risk in association with testosterone therapy are inconclusive.

Other rare known undesirable effects associated with excessive dosages of testosterone include hepatic neoplasms.

Because of the alcohol contained in the product, frequent applications to the skin may cause irritation and dry skin.

4.9 Overdose

Only one case of acute testosterone overdose following an injection has been reported in the literature. This was a case of a cerebrovascular accident in a patient with a high plasma testosterone concentration of 114 ng/ml (395 nmol/l). It would be most unlikely that such plasma testosterone concentrations be achieved using the transdermal route.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Androgens. ATC code: G03B A03.

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.
Testosterone does not produce testicular development: it reduces the pituitary secretion of gonadotropins.

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

5.2 Pharmacokinetic properties

The percutaneous absorption of testosterone ranges from approximately 9% to 14% of the applied dose.

Following percutaneous absorption, testosterone diffuses into the systemic circulation at relatively constant concentrations during the 24 hour cycle.

Serum testosterone concentrations increase from the first hour after an application, reaching steady state from day two. Daily changes in testosterone concentrations are then of similar amplitude to those observed during the circadian rhythm of endogenous testosterone. The percutaneous route therefore avoids the blood distribution peaks produced by injections. It does not produce supra-physiological hepatic concentrations of the steroid in contrast to oral androgen therapy.

Administration of 5 g of Androgel produces an average testosterone concentration increase of approximately 2.5 ng/ml (8,7 nmol/l) in plasma.

When treatment is stopped, testosterone concentrations start decreasing approximately 24 hours after the last dose. Concentrations return to baseline approximately 72 to 96 hours after the final dose.

The major active metabolites of testosterone are dihydrotestosterone and estradiol.

Testosterone is excreted, mostly in urine, and in faeces as conjugated testosterone metabolites.

5.3 Preclinical safety data

Testosterone has been found to be non-mutagenic in vitro using the reverse mutation model (Ames test) or hamster ovary cells. A relationship between androgen treatment and certain cancers has been found in studies on laboratory animals. Experimental data in rats have shown increased incidences of prostate cancer after treatment with testosterone.
Sex hormones are known to facilitate the development of certain tumours induced by known carcinogenic agents. No correlation between these findings and the actual risk in human beings has been established.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carbomer 980
Isopropyl myristate
Ethanol 96%
Sodium hydroxide
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

5 g in sachet(PET/Aluminium/LDPE)**.**
Boxes of 1, 2, 7, 10, 14, 28, 30, 50, 60, 90 or 100 sachets.
Not all pack sizes may be marketed.

6.6 Instructions for use, handling and disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Laboratoires BESINS INTERNATIONAL
3, rue du Bourg l'Abbé
75003 PARIS
France

8. MARKETING AUTHORISATION NUMBERS

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT