ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ANDROGEL 16.2 mg/g, gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One gram of gel contains 16.2 mg testosterone. Each pump actuation delivers 1.25 g gel containing 20.25 mg testosterone.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gel

Transparent or slightly opalescent, colourless gel

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 (see 4.4 Special warnings and precautions for use).

4.2 Posology and method of administration

Transdermal use

Posology

Adults and elderly patients

The recommended dosage is two pump actuations (i.e. 40.5 mg testosterone) applied once daily at about the same time, preferably in the morning. The daily dose should be adjusted by the physician depending on the clinical or biological response of each patient, without exceeding four pump actuations, i.e. 81 mg testosterone per day. The dosage should be adjusted by one pump actuation each time.

The dose must be determined on the basis of morning blood testosterone concentrations prior to administration. Steady-state blood concentrations of testosterone are reached approximately from day 2 of treatment with ANDROGEL 16.2 mg/g, gel. The dosage is adjusted in relation to blood testosterone levels, measured on the morning prior to application of the product, once steady state has been reached. Blood testosterone concentrations must be periodically evaluated. The dosage can be reduced if blood testosterone exceeds the desired level. If the concentration is low, the dosage may be increased in steps without exceeding 81 mg testosterone (four pump actuations).

Treatment must be discontinued if blood testosterone levels constantly 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 obtained with the highest dose of 81 mg (5 g gel, i.e. four pump actuations).

Patients suffering from severe renal or hepatic insufficiency

Please consult section 4.4 Special warnings and precautions for use.

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.

Method of administration

The application should be performed by the patient himself, on clean, dry, healthy skin, on the shoulders and arms.

The gel must be spread simply as a thin layer over the skin. It is not necessary to rub the skin. Allow to dry for at least 3 to 5 minutes before getting dressed. Wash hands with soap and water after application and cover the The application should be performed by the patient himself, on clean, dry, healthy skin, on the shoulders and arms.

The gel must be spread simply as a thin layer over the skin. It is not necessary to rub the skin. Allow to dry for at least 3 to 5 minutes before getting dressed. Wash hands with soap and water after application and cover the application site(s) with an item of clothing after the gel has dried. Carefully wash the application site with soap and water before any situation where contact between the application site and another person's skin is envisaged. For more information on washing after administration, see section 4.4 (subsection Possible transfer of testosterone).

Do not apply the gel to the genital organs, as the large amount of alcohol in the gel may cause local irritation.

Before obtaining the first full dose, the canister pump must be primed. To do so, with the canister in the upright position, slowly and fully depress the plunger three times. Safely discard the gel from the first three actuations. It is only necessary to prime the pump before the first dose.

After priming, fully depress the plunger to deliver 1.25 g ANDROGEL 16.2 mg/g, gel into the palm of the hand and apply the gel to the shoulders and arms… application site(s) with an item of clothing after the gel has dried. Carefully wash the application site with soap and water before any situation where contact between the application site and another person's skin of is anticipated. For more information on washing after administration, see section 4.4 (subsection Possible transfer of testosterone).

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4.3 Contraindications

ANDROGEL 16.2 mg/g, gel is contraindicated:

- in cases of prostate cancer or breast carcinoma, suspected or confirmed,
- in cases of hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

ANDROGEL 16.2 mg/g, gel may only be used if hypogonadism (hypo- or hypergonadotropic) has been demonstrated and if other aetiologies that may be responsible for the symptoms have been excluded before starting treatment. Testosterone insufficiency must be clearly demonstrated by clinical signs (regression of secondary sexual characteristics, change in body composition, asthenia, reduced libido, erectile dysfunction, etc.) and confirmed by two separate measurements of blood testosterone. Currently, there is no consensus regarding normal blood testosterone values in relation to age. However, it should be taken into account that physiological blood testosterone values decrease with age.

Due to the variability of results between different laboratories, all measurements must be carried out by the same laboratory for any given patient.

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

Prior to initiating testosterone treatment, patients must imperatively undergo a thorough examination to exclude any risk of pre-existing prostate cancer. Careful and regular monitoring of the prostate and breasts must be performed in accordance with the recommended methods (digital rectal examination and measurement of PSA – prostate-specific antigen) at least once yearly in all patients on testosterone therapy and twice yearly in elderly patients and patients at risk (clinical or familial factors).

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

ANDROGEL 16.2 mg/g, gel must be used with caution in patients with cancer at risk of hypercalcaemia (and associated hypercalciuria), due to bone metastases. It is recommended that blood calcium levels be regularly monitored in these patients.

In patients suffering from severe cardiac, hepatic or renal insufficiency or ischaemic heart disease, treatment with testosterone could lead to severe complications characterised by oedema, with or without congestive heart failure. In this case, treatment must be stopped immediately. Furthermore, diuretic treatment may prove necessary.

ANDROGEL 16.2 mg/g, gel must be used with caution in patients with ischaemic heart disease.

Testosterone may cause a rise in blood pressure. As a result, ANDROGEL 16.2 mg/g, gel must be used with caution in men with hypertension.

Testosterone levels must be monitored prior to the start of treatment and then at regular intervals during treatment. Clinicians must adjust the dosage for each patient, in order to ensure that testosterone levels are maintained at a eugonadal level.

In patients on long-term androgen therapy, in addition to biological tests to measure blood testosterone levels, the following biological parameters must be monitored regularly: levels of haemoglobin, haematocrit (to detect polyglobulia), liver function and lipid profile.

Available experience is limited regarding the safety and efficacy of ANDROGEL 16.2 mg/g, gel used in patients over 65 years of age. Currently, there is no consensus regarding reference values for blood testosterone in relation to age. However, the reduction in physiological blood testosterone values with age must be taken into account.

ANDROGEL 16.2 mg/g, gel must be used with caution in patients suffering from epilepsy and migraine, as their condition might be aggravated.

In the literature, there have been reports of a risk of increased sleep apnoea during treatment with testosterone esters in subjects treated for hypogonadism, particularly in at-risk patients with obesity or chronic respiratory disease.

An improvement in insulin sensitivity may be observed in patients treated with androgens and may necessitate a reduction in the antidiabetic dosage.

Certain clinical signs, such as irritability, nervousness, weight gain, prolonged or frequent erections, may indicate excessive androgenisation and necessitate an adjustment in dosage.

In the event of a severe reaction at the application site, treatment must be reviewed and discontinued if necessary.

With high doses of exogenous androgens, spermatogenesis may be suppressed due to feedback inhibition of the pituitary follicle-stimulating hormone (FSH), which may potentially lead to undesirable effects on semen parameters, including sperm count.

Gynaecomastia can sometimes develop and persist in patients treated with androgens for hypogonadism.

ANDROGEL 16.2 mg/g, gel must not be used in women due to possible virilising effects.

Athletes must be alerted to the fact that this medicinal product contains an active substance (testosterone) that may induce a positive reaction in tests conducted during anti-doping controls.

Risk of accidental transfer of testosterone

If no precautions are taken, testosterone may be transferred to others at any time after administration during close skin contact with the gel application site, inducing an increase in testosterone levels and, in the case of repeated contact (accidental androgenisation), possible undesirable effects (for example, increased facial and/or body hair, deepening of the voice, menstrual cycle irregularities in women, premature puberty and development of genital organs in children). If virilisation occurs, treatment with testosterone must be rapidly discontinued until the cause has been identified.

The physician must inform the patient about this risk of testosterone transfer and about the precautions for use (see below). ANDROGEL 16.2 mg/g, gel must not be prescribed in patients at major risk of non-adherence to the precautions for use (for example, in cases of severe alcoholism, drug abuse, severe psychiatric disorders).

The possible risk of transfer is considerably reduced (but not eliminated) by wearing an item of clothing (such as a sleeved shirt) covering the application site. Most of the residual testosterone is eliminated from the skin surface by washing with water and soap prior to contact.

Consequently, the following precautions are recommended:

For the patient:

- wash hands with soap and water after applying the gel,
- cover the application site with an item of clothing (such as a sleeved shirt) after the gel has dried,
- take a shower and carefully wash the application site(s) with soap and water, in order to eliminate all residues of testosterone prior to any circumstances where such contact is envisaged.

For people not treated with ANDROGEL 16.2 mg/g:

- in the event of contact with an application site not washed or covered by an item of clothing, wash the skin surface where testosterone transfer may have occurred as soon as possible, using soap and water,
- report the onset of signs of androgenisation, such as acne or changes in hair distribution.

According to *in vivo* absorption studies on testosterone conducted with ANDROGEL 16.2 mg/g, it seems preferable that patients should observe a period of at least 2 hours between application of the gel and taking a bath or shower. However, occasional baths or showers taken between 2 and 6 hours after application of the gel should not significantly influence the effect of treatment.

To improve their partner's safety, patients must be informed, for instance, to wash the application site with soap and water before engaging in any sexual activity, or, if this is not possible, to wear an item of clothing, such as a T-shirt, covering the application site during the period of contact.

Furthermore, it is recommended that clothes covering the application site (such as a sleeved shirt) be worn during periods of contact with children, in order to reduce the risk of contaminating the children's skin.

Pregnant women must avoid all contact with application sites of ANDROGEL 16.2 mg/g, gel. In the event of pregnancy in their partner, patients must be particularly vigilant regarding the precautions for use outlined above (see also section 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

Due to changes in the anticoagulant effect (increase in the oral anticoagulant effect due to impaired hepatic synthesis of clotting factors and competitive inhibition of plasma protein binding), more frequent monitoring of prothrombin levels and the international normalised ratio (INR) is recommended. Patients on oral anticoagulants require close surveillance, particularly at the start or discontinuation of androgen treatment.

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

Interaction with laboratory tests: androgens can decrease levels of thyroxine-binding globulin (TBG), leading to a reduction in serum T_4 concentrations and an increase in resin uptake of T_3 and T_4. Nevertheless, free thyroid hormone levels remain unchanged and without any clinical manifestation of thyroid insufficiency.

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

Application of a sunscreen or lotion does not reduce the efficacy of this medicinal product.

Washing 2 hours after application has no significant effect on the blood concentrations of testosterone.

4.6 Fertility, pregnancy and lactation

ANDROGEL 16.2 mg/g, gel is intended for men only.

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

Pregnant women must avoid all contact with application sites of ANDROGEL 16.2 mg/g, gel (see section 4.4). In case of contact, wash with soap and water as soon as possible.

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

4.7 Effects on ability to drive and use machines

ANDROGEL 16.2 mg/g, gel has no or negligible effect on the ability to drive and use machines.

4.8 Undesirable effects

At the recommended dosage, the most common undesirable effects observed with ANDROGEL 16.2 mg/g, gel have been psychiatric disorders and skin reactions at the application site.

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

Table 1 Frequency of adverse reactions in the phase III study conducted with 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, aggressiveness, impatience, insomnia, abnormal dreams, increased libido)	
Vascular disorders		Malignant hypertension, vasomotor flushes, phlebitis
Gastrointestinal disorders		Diarrhoea, abdominal distension, oral pain
Skin and subcutaneous tissue disorders	Skin reactions* (acne, alopecia, dry skin, skin lesions, contact dermatitis, changes in hair colour, rash, hypersensitivity, pruritus at the application site)	

Reproductive system and breast disorders		Gynaecomastia, nipple disorders, testicular pain, increased erections
General disorders and administration site conditions		Pitting oedema
Investigations	PSA increased, increase in haematocrit or haemoglobin	

*Pooled events

Due to the presence of alcohol in this medicinal product, frequent applications to the skin may cause irritation and dry skin.

The following undesirable effects have been identified during the post-marketing phase of ANDROGEL 16.2 mg/g, gel. As these undesirable effects are reported on a voluntary basis among a population of uncertain size, it is not possible to reliably estimate their frequency or establish any clear causal relationship with exposure to the medicine.

Table 2 Undesirable effects reported spontaneously with ANDROGEL 16.2 mg/g, gel

MedDRA system organ class	***Undesirable effects – preferred terms***
Blood and lymphatic system disorders	Polyglobulia, anaemia
Psychiatric disorders	Insomnia, depression, anxiety, aggressiveness
Nervous system disorders	Headache, dizziness, paraesthesia
Vascular disorders	Vasodilation (hot flushes), deep vein thrombosis
Respiratory, thoracic and mediastinal disorders	Dyspnoea
Gastrointestinal disorders	Nausea
Skin and subcutaneous tissue disorders	Reaction at the application site, acne, alopecia, sweating, hypertrichosis
Musculoskeletal and connective tissue disorders	Musculoskeletal pain
Renal and urinary disorders	Difficulty in micturition
Reproductive system and breast disorders	Gynaecomastia, testicular disorders, prostate enlargement, oligospermia, benign prostatic hyperplasia
General disorders and administration site conditions	Asthenia, oedema, malaise
Investigations	Weight gain, PSA increased, increased haematocrit or haemoglobin

The following undesirable effects have been identified during the post-marketing phase for products containing testosterone.

Table 3 Undesirable effects with products containing testosterone

MedDRA system organ class	***Undesirable effects – Preferred terms***
	Common ≥1/100 to <1/10
Blood and lymphatic system disorders	Haematocrit increased, red blood cell count increased, haemoglobin increased

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: *Agence nationale de sécurité du médicament et des produits de santé (ANSM) et réseau des Centres Régionaux de Pharmacovigilance* (National Agency for the Safety of Medicines and Health Products and Network of Regional Pharmacovigilance Centres) - Website: www.ansm.sante.fr.

4.9 Overdose

One single case of acute testosterone overdose, subsequent to an injection, has been reported in the literature. This involved a case of stroke in a patient with a raised plasma testosterone concentration of 114 ng/mL (395 nmol/L). It is highly unlikely that transdermal treatment might lead to such plasma concentrations of testosterone.

Treatment of an overdose consists of discontinuing ANDROGEL 16.2 mg/g, gel, combined with appropriate symptomatic care.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Androgens, ATC code: G03B A03.

Endogenous androgens, mainly 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 secondary sexual characteristics (development of hair growth, deepening of the voice, onset of libido). Androgens also have an effect on protein anabolism, the development of skeletal muscle and body fat distribution and the reduction of urinary excretion of nitrogen, sodium, potassium, chloride, phosphate and water.

Testosterone reduces the pituitary secretion of gonadotropins.

The effects of testosterone on certain target organs manifest only after peripheral conversion of testosterone to oestradiol, which then binds to nuclear oestrogen receptors in target cells, e.g. in the pituitary, adipose tissue, brain, bone and testicular Leydig cells.

5.2 Pharmacokinetic properties

Percutaneous absorption of testosterone after administration of ANDROGEL 16.2 mg/g, gel varies between 1% and 8.5%.

After percutaneous absorption, testosterone diffuses into the systemic circulation at relatively constant rates during the 24-hour cycle.

Blood testosterone concentrations increase from the first hour after application to reach steady state from day 2. Daily variations in the testosterone level are thus of a similar magnitude as those observed during the circadian rhythm of endogenous testosterone. Thus, the percutaneous route avoids the peaks in blood distribution induced by injections. It does not lead to any supra-physiological hepatic concentrations of the steroid, unlike androgen therapy via the oral route.

Administration of 5 g ANDROGEL 16.2 mg/g, gel produces a mean increase in the plasma testosterone level of about 2.3 ng/mL (8.0 nmol/L).

Upon discontinuation of treatment, the decrease in testosterone levels starts about 2 hours after the final administration. The return to baseline levels occurs within 72 to 96 hours after the final administration.

The main active metabolites of testosterone are dihydrotestosterone and oestradiol.

Testosterone is eliminated mainly in the urine as conjugated metabolites, with a small amount eliminated unchanged in the faeces.

During the phase III, double-blind study, at the end of a 112-day treatment period, during which it was possible to determine the dose of ANDROGEL 16.2 mg/g, gel based on total testosterone concentrations, 81.6% (CI 75.1-87.0%) of men had a total testosterone concentration within the normal range for eugonadal young men (300 – 1,000 ng/dL). In patients taking a daily dose of ANDROGEL 16.2 mg/g, gel, the average (±SD) daily testosterone concentration on day 112 (C_{av}) was 561 (±259) ng/dL, mean C_{max} was 845 (±480) ng/dL and mean C_{min} was 334 (±155) ng/dL. The corresponding concentrations on day 182 (double-blind period) were C_{av} 536 (±236) ng/dL, mean C_{max} 810 (±497) ng/dL and mean C_{min} 330 (±147) ng/dL.

During the phase III open-label study, at the end of a 264-day treatment period, during which it was possible to determine the dose of ANDROGEL 16.2 mg/g, gel based on total testosterone concentrations, 77% (CI 69.8-83.2%) of men had a total testosterone concentration within the normal range for eugonadal young men (300 – 1,000 ng/dL).

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

5.3 Preclinical safety data

Testosterone was found to be non-mutagenic *in vitro* using the reverse mutation model (Ames test) or the hamster ovary cell model. A link between treatment with androgens and certain cancers was seen in studies on laboratory animals. Experimental data in rats have shown an increase in the incidence of prostate cancer after treatment with testosterone.

Sex hormones are known to facilitate the development of certain tumours induced by known carcinogenic agents. The importance of these results and the actual risk for human beings have not been elucidated.

Administration of exogenous testosterone has been reported to suppress spermatogenesis in rats, dogs and non-human primates; this suppression was reversible upon discontinuation of treatment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carbomer 980
Isopropyl myristate
96% ethanol
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

Multidose container (comprised of a polypropylene canister with an LDPE-lined pouch) and a metered-dose pump containing 88 g gel and delivering a minimum of 60 doses.

Pack sizes:

- 1 container per cardboard box
- Boxes of 1, 2, 3 or 6 containers.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7. MARKETING AUTHORISATION HOLDER

BESINS HEALTHCARE
AVENUE LOUISE 287
1050 BRUSSELS
BELGIUM

8. MARKETING AUTHORISATION NUMBER(S)

- 34009 300 537 0 6: Multidose container (comprised of a polypropylene canister with an LDPE-lined pouch). Box of 1 container.
- 34009 300 537 1 3: Multidose container (comprised of a polypropylene canister with an LDPE-lined pouch). Box of 2 containers.
- 34009 550 190 1 5: Multidose container (comprised of a polypropylene canister with an LDPE-lined pouch). Box of 3 containers.
- 34009 550 190 2 2: Multidose container (comprised of a polypropylene canister with an LDPE-lined pouch). Box of 6 containers.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[to be subsequently completed by the holder]

10. DATE OF REVISION OF THE TEXT

[to be subsequently completed by the holder]

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.

GENERAL CLASSIFICATION FOR SUPPLY

List I

Medicinal product subject to medical prescription only by specialists in endocrinology, urology or gynaecology.

No restrictions on repeat prescriptions.