COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Androgel 40,5 mg, transdermal gel in sachet (testosterone)

NL License RVG: 128946

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This module reflects the scientific discussion for the approval of Androgel 40,5 mg, transdermal gel in sachet. The procedure was finalised on 1 November 2022. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

AE	Adverse Event
ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FSH	Follicle Stimulating Hormone
ICH	International Conference of Harmonisation
LH	Luteinizing Hormone
MAH	Marketing Authorisation Holder
PD	Pharmacodynamics
PK	Pharmacokinetics
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
TEAE	Treatment-emergent Adverse Event
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the MEB has granted a marketing authorisation for Androgel 40,5 mg, transdermal gel in sachet, from Besins Healthcare Netherlands BV.

The product is indicated in adults as testosterone replacement therapy for male hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests (see SmPC section 4.4, Special warnings and precautions for use).

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

This national procedure concerns a line extension application (as defined under Regulation 1234/2009, Annex II) of the current marketing authorisation for Androgel 25 mg and 50 mg transdermal gel in sachet, which have been registered in the Netherlands via the mutual recognition procedure (FR/H/0203/001-002) since 12 June 2002 by Laboratoires Besins International. The current RMS for this procedure is the Netherlands NL/H/3240/002-003 (RVG 27740 and 27741) by Besins Healthcare Netherlands B.V. since 21 August 2002 (original products). The current product Androgel 40,5 mg, transdermal gel in sachet is an additional strength. Androgel 25 mg and 50 mg are gels containing 1% testosterone. Both products are referred to as Androgel 1%. The new strength 40,5 mg is a gel containing 16.2 mg/g testosterone which is equal to 1.62%. Therefore, it is also referred to as Androgel 1.62%.

The marketing authorisation has been granted pursuant to Article 8(3) (Full or full-mixed application (complete dossier)) of Directive 2001/83/EC. The dossier includes a complete quality module. Regarding the non-clinical and clinical modules, only data relevant for the line extension are included. For the non-clinical and clinical data of testosterone, reference is made to the existing marketing authorisations of Androgel 25 mg and 50 mg transdermal gel and Androgel 16,2 mg/g, gel (NL/H/3240/001/DC) which is the same product as Androgel 40,5 mg, transdermal gel in sachet (presented with an alternative name). The current procedure is a repetition of the procedure for Androgel 1.62% with the same studies and extension.

II. QUALITY ASPECTS

II.1 Introduction

Androgel 40,5 mg, transdermal gel in sachet is a transparent or slightly opalescent, colourless transdermal gel in sachet. One sachet of 2.5 g contains as active substance 40.5 mg of testosterone.

The excipients are: carbomer 980, isopropyl myristate, ethanol 96%, sodium hydroxide and water.

The transdermal gel is packed in a 2.5 g sachet of polyethylene terephthalate/Aluminium/ low density polyethylene (PET/Aluminium/LDPE). The sachets are packed in boxes.

II.2 Drug Substance

The active substance is testosterone, an established active substance described in the European Pharmacopoeia (Ph. Eur.). Testosterone is a white crystalline powder, or colourless or yellowish-white crystals. It is practically insoluble in water, freely soluble in alcohol and in methylene chloride, practically insoluble in fatty oils. Polymorphism is not relevant for this medicinal product since the pharmaceutical form is a gel in which the active substance is dissolved. A CEP has been provided.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph. Eur. The CEP does not cover information concerning the container closure system and stability.

Manufacturing process

A CEP has been submitted. Therefore, no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is in line with the Ph. Eur. and the additional requirements stated on the CEP. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been submitted for six production scale batches.

Stability of drug substance

Stability data on the active substance have been submitted for three production scale batches from site I, that were stored at 25°C/60% RH (60 months), 30°C/35% RH (60 months) and 30°C/70% RH (60 months) and for two production scale batches from site II stored at 40°C/75% RH (6 months). Two full scale batches of drug substance were stored at 40°C/75% RH (6 months) showing no trends or changes in any of the tested parameters. According to the Ph. Eur. monograph for testosterone, the drug substance should be stored protected from light. Based on the data submitted, the proposed re-test period of 5 years is considered acceptable, when stored in the original packaging in order to protect it from light.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The development of the product has been described, the choice of excipients is justified and their functions explained. The same excipients are used as in the already registered testosterone gel 25 and 50 mg, sachets. The main development studies performed aimed to improve the viscosity (viscosity

measurements of placebo gels containing different levels of excipients were performed) and the permeation (with *in vitro* tests). The level of ethanol in the formulation was demonstrated to provide sufficient antimicrobial activity and justify the absence of another preservative. The MAH has confirmed that the manufacturing process for the proposed product was developed by modifying the process parameters already established for the testosterone gel 25 and 50 mg product. Studies on the reproducibility of the delivered dose were performed on three batches of the 40.5 mg gel packaged in sachets. Sachets were emptied as instructed in the package leaflet. All three batches met the requirements for delivered dose according to the Ph. Eur. 2.9.40. The choice of the manufacturing process is justified. The proposed manufacturing process was also used for the batches used in the clinical studies.

Manufacturing process

The manufacturing process consist of the mixing of the active substance and excipients in several steps and the formation of the gel, using conventional manufacturing techniques. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three production scale batches from site I and two batches on pilot scale from site II. Process validation at full scale from site II will be performed post approval.

Control of excipients

The excipients comply with the Ph. Eur. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identity (of testosterone and ethanol), pH, viscosity, uniformity of mass of delivered doses, assays (testosterone, ethanol and isopropyl myristate), related substances, number of delivered doses, extractable content and microbiological quality. The release and shelf-life limits are identical except for the assay of one excipient and for related substances, for which a wider limit is set at shelf life. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production sites have been submitted for five batches, three from site I and two batches from site II, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been submitted for three pilot scale batches. The batches were stored at 25°C/60% RH (36 months) and at 40°C/75% RH (6 months). All three batches were manufactured with active drug substance from a former manufacturing site. However, as all drug substance manufacturers produce testosterone that complies with the Ph. Eur., this is acceptable. The conditions used in the stability studies are according to the ICH stability guidelines. The batches were stored in the packaging proposed for marketing. The parameters remain relatively stable and stay within the proposed specification limits. No photostability

study has been reported for the current product (Androgel 40,5 mg, in sachet). However, from procedure NL/H/3735/003/DC it is known that the product is sensitive to direct light exposure, but the packaging materials are expected to provide sufficient protection from light. This is acceptable. Based on the submitted stability data, a shelf life of 3 years was granted without any special storage requirements.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Androgel 40,5 mg, transdermal gel has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The active substance in Androgel 40,5 mg (1.62%) transdermal gel is testosterone. Testosterone is a very well-established endogenous hormone. The pharmacology, pharmacokinetics and toxicology of testosterone at normal concentrations and the pharmacology of hypogonadism are both well understood. The MAH refers to existing nonclinical studies originally conducted, when the testosterone formulation was first established more than 20 years ago, and recent literature data that support the pharmacology and toxicology of transdermal testosterone.

III.2 Pharmacology

The primary pharmacology of testosterone at normal concentrations and the pharmacology of hypogonadism (condition in which little or no hormone is produced by the testes or ovaries) are well understood. Testosterone has different effects on the reproductive system at different stages of life and is essential for the development of the male phenotype. Male hypogonadism results from insufficient secretion of testosterone and is characterised by low serum testosterone concentrations. The testosterone drug substance in Androgel 1.62% gel is chemically identical to the naturally occurring steroid hormone. Treatment with exogenous testosterone alleviates testosterone deficiency by elevating plasma concentrations of testosterone, dihydrotestosterone and androstenedione, resulting in a normalisation of gonadotropin levels. The primary pharmacological effects of testosterone include the reproductive system, bone and skeletal tissue, adipose tissue, glucose metabolism and insulin resistance, erythropoiesis and hair growth and sebaceous glands. The secondary pharmacological effects of testosterone include anti-inflammatory activity in the prostate

(Vignozzi et al., 2012), effects on cardiac tissue and blood vessels (Carnes & Dech 2002; Mukherjee et al., 2002; Razmara et al., 2005), effects on the kidneys (Carrero & Stenvinkel 2012; Diamond-Stanic et al., 2012), activities in auto-immune disease (Fairweather et al., 2008; Spence & Voskuhl, 2012), and enhancement of athletic performance (Shahidi 2001, Gooren & Behre 2008; Goodman & Gilman, 2011). These secondary pharmacological effects as well as the safety pharmacology and the pharmacodynamics drug interactions of testosterone have been clinically well-established.

III.3 Pharmacokinetics

The pharmacokinetic profile of testosterone in men following transdermal administration from hydroalcoholic gel formulations is extensively documented and well understood. According to literature, approximately 10% of a testosterone dose applied on the skin is absorbed into the systemic circulation. The key parameter which influences the consistency of the pharmacokinetic profile for transdermal use is the composition of the formulation. The use of an hydroalcoholic base for the formulation and the management of skin cleansing routines to optimise absorption, and subsequent sustained release into the systemic circulation, assures an effective pharmacokinetic profile following application of the drug product. *In vitro* percutaneous absorption studies were performed to investigate the permeation process of testosterone through the skin to identify factors that influence transdermal transfer. These studies demonstrated that the majority of applied testosterone is associated with the skin surface, and that a solvent is required in the formulation to enhance mobilisation of the hormone across the skin. The transdermal formulations therefore comprise a hydroalcoholic gel containing the drug substance testosterone Ph. Eur. with the solvent ethanol 96% (ethanol Ph. Eur.). The *in vivo* pharmacokinetic profile of transdermal testosterone from gel formulations has been investigated clinically using both the 1% and the 1.62% formulations. Testosterone is converted to dihydrotestosterone by 5 alpha-reductase presents in skin and is converted to estradiol through aromatisation (Weng et al., 2010). Inactivation of testosterone mainly occurs in the liver where it is metabolised to various 17-ketosteroids (Goodman & Gilman 2011; HSDB, 2013; Martindale, 2014). The main elimination pathway is via the urine (90%) (Molina, 2011), with some (6%) excretion in the faeces (Marbury 2003 in Martindale, 2014). Blood concentration of testosterone after administration of Androgel 1.62% at the proposed maximal dose do not exceed normal values of 300-1000 ng/dL (dihydrotestosterone 31 - 193 ng/dL) (Swerdloff et al., 2000; Wang et al., 2000). The geometric mean dihydrotestosterone/testosterone ratio across all doses and study days for subjects on testosterone gel 1.62% treatment was 0.156 and the 95% prediction interval was 0.074-0.330 which is within the normal range of approximately 0.05-0.33 reported in the literature. The pharmacokinetic drug interaction profile of testosterone has been established by its extensive clinical use.

III.4 Toxicology

The need for toxicity data for testosterone is overridden by the extensive clinical safety experience with testosterone. Therefore, the non-clinical overview focuses on published toxicology data. Since testosterone levels after administration of Androgel 1.62% do not exceed normal values and since this product is intended to restore normal levels of testosterone, no increased risk is expected. Overall, the available data indicate that

testosterone is of very low acute and repeated dose toxicity to animals. The available genotoxicity data point to a lack of genotoxic risk for testosterone. The potential exists for hyper-proliferative effects due to testosterone, as indicated in animal models, but at exposure levels well in excess of normal physiological levels. Testosterone exhibits reproductive and developmental toxicity when administered prenatally (Walker, 2010; RTECS, 2013), however this is of little consequence to the proposed drug product, which is indicated for the treatment of male hypogonadism. The local tolerance studies demonstrated a satisfactory Androgel local tolerance in rabbits and guinea pigs (study numbers 14039 and 14040). In the rabbit study, 0.5 mL of Androgel or placebo gel was applied to the skin of male New-Zealand rabbits. No erythema or oedema was observed in any rabbit at any observation time. In the guinea pig study, no clinical signs and no deaths related to treatment were reported and, during the challenge phase of the experiment, neither erythema nor oedema was observed in any animal at any observation time.

III.5 Ecotoxicity/environmental risk assessment (ERA)

For the Ecotoxicity/environmental risk assessment, the MAH has submitted the following study results.

Table 1. Main study results Ecotoxicity/environmental risk assessment of testosterone.

Substance (INN/Invented Name): testosterone					
CAS-number (if available): 58-22-0					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	3.38			not PBT or vPvB
PBT-statement :	Testosterone is not PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surface\ water}$, refined Fpen	1.42	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)	hormone				Phase II assessment is required
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106 or …	P.M.			
Ready Biodegradability Test	OECD 301	P.M.			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	P.M.			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	P.M.	µg/L	
Daphnia sp. Reproduction Test	OECD 211	NOEC	P.M.	µg/L	
Fish, Full Life Cycle Toxicity Test/*Species*	OECD 210	NOEC	P.M.	µg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	P.M.	µg/L	
Phase IIb Studies					
Bioaccumulation/*Species*	OECD 305	BCF	P.M.	L/kg	%lipids:
Sediment dwelling organism/*Species*		NOEC	NA	mg/kg	normalised to 10% o.c.
PBT persistent, bioaccumulative or toxic					

vPvB	very persistent, very bioaccumulative
$PEC_{surface\ water}$	predicted environmental concentrations in surface water
Fpen	penetration factor
P.M.	particulate matter
NOEC	no observed effect concentration
EC	effective concentration
BCF	bioconcentration factor
NA	not available.

Conclusions on studies:
The results show that testosterone is not a PBT (persistent, bioaccumulative or toxic), nor a vPvB (very persistent, very bioaccumulative). However, the dossier is incomplete and the Environmental Risk Assessment cannot be finalised. To support the ERA and finalised the dossier, the following post-approval commitment was advised:

The MAH will submit (post-approval) the following requested studies:

1. Adsorption-desorption using a batch equilibrium method (OECD 106) using three soil types and two types of sewage sludge
2. Ready biodegradability test (OECD 301)
3. Aerobic and anaerobic transformation in aquatic sediment systems (OECD 308)
4. Algal growth inhibition test (OECD 201)
5. Daphnia sp. reproduction test (OECD 211, use version 2012)
6. Fish full life cycle test
7. Activated sludge, respiration inhibition test (OECD 209, use version 2010)
8. Bioaccumulation in Fish: Aqueous and Dietary Exposure (OECD 305; version 2012).

The substance is a hormone that influences both development and reproduction of fish. Therefore, a fish full life cycle test is requested. This study should be used to addresses the specific mechanism of action and to derive a valid NOEC/EC10 value.

Please note that a timeline for submission of these studies needs to be submitted (specifying the quarter) and that the updated ERA uses the previously agreed upon refined $PEC_{surface\ water}$ of 1.42 µg/L. Moreover, in view of the 3R's principles, the MAH is discouraged to repeat studies with vertebrate animals where these are already available. Instead, the MAH is recommended to contact other stakeholders to investigate whether ERA studies are available for data sharing.

In response to this request, the MAH has submitted a signed commitment to provide the requested study results post approval, by the end of 2024 following the outcome of the scientific advice. This is acceptable.

III.6 Discussion on the non-clinical aspects

The submitted non-clinical overview to support the pharmacology, pharmacokinetics and toxicology of transdermal testosterone is adequate. There are four *in vitro* pharmacokinetic studies assessing a percutaneous absorption of testosterone from Androgel in human cadaver skin and two local tolerance studies assessing an acute dermal irritation in rabbits and a skin sensitisation in guinea pigs. Regarding the testosterone amount transferred across the human skin, the data are consistent with the clinical observations with a bioavailability estimated

between 6 to 13%. The local tolerance studies demonstrated a satisfactory Androgel local tolerance in rabbits and guinea pigs. The submitted Environmental risk assessment is acceptable however not complete. A post approval commitment was made by the MAH to submit the requested missing information.

IV. CLINICAL ASPECTS

IV.1 Introduction

The current proposed product, Androgel 40,5 mg, transdermal gel in sachet, is a 16.2 mg/g testosterone gel supplied in a sachet containing 2.5 mg testosterone 1.62% transdermal gel (which is equal to 40.5 mg testosterone). Androgel 40,5 mg, gel is intended for the treatment of hypogonadal (testosterone serum concentration <300 ng/dL) in adult males. The male eugonadal testosterone range is 300 to 1000 ng/dL. In clinical practice the hypogonadal patient is titrated based on serum testosterone levels. Depending on the testosterone shortage, a testosterone gel can be prescribed. The skin serves as a reservoir for the sustained release of testosterone into the systemic circulation. According to the SmPC, the product can be applied once daily on the upper arms/shoulders, this is agreed and in line with the already marketed 1% testosterone gel. Further specific interactions like post-dose washing, use of moisturisers and sunscreen lotion are stated in the SmPC.

For this line extension application, the MAH submitted one clinical trial Phase III for safety and efficacy (pivotal study), three bioavailability studies and eight pharmacokinetic studies. The studies were performed with the already approved Androgel 16.2 mg/g (same product as Androgel 40,5 mg, with an alternative name). An overview of the design and results of these studies is presented in the table below.

Table 2. Overview of studies performed with Androgel gel 40.5 mg (16.2 mg/g (1.62%)).

Number	Type of study	Study identifier	Objectives of the study	Study design and type of control; Diagnosis of Patients	Test Product; Dosage regimen; Route of Administration	Subjects Enrolled; Completed; Age Range (years)	Duration of treatment
1	Efficacy and Safety	S176.3.104 **(pivotal)**	The primary efficacy parameter was the percentage of patients with serum total testosterone C_{av} within the normal range of 300-1000 ng/dL. Success in the study was defined as >75% of patients on active treatment within the normal serum testosterone concentration range of 300-1000 ng/dL. In addition, the lower	Randomized, double-blind, placebo controlled with an open label extension; hypogonadal males	Testosterone gel 1.62%; 1.25 g, 2.50 g, 3.75, and 5.00 g, once daily, topical	274 patients (234 Testosterone-gel 1.62%; 40 placebo) 196 patients (168 Testosterone-gel 1.62%; 28 placebo) (Day 182); 26-79 191 patients (163	Double-blind phase: 182 days Open-label phase: additional 182 days

			bound of the 95% CI could not be less than 65% based on the Day 112 PK results for the pivotal phase of the trial.			previously on Testosterone-gel 1.62%; 28 previously on placebo) (Day 364)	
2	BA	S176.1.005	To determine the multiple dose PK of testosterone after administration of testosterone gel 1.62% in hypogonadal males with and without post-dose skin washing.	Randomized, open-label, three-way crossover; hypogonadal males	Testosterone gel 1.62%; 5.00 g, once daily in the AM to the upper arms/shoulders for seven days during each treatment period, topical.	24 17 34-77	21 days of exposure
3	BA	S176.1.006	To determine the multiple dose PK of testosterone after administration of testosterone gel 1.62% in hypogonadal males with and without moisturizer lotion or sunscreen.	Randomized, open-label, three-way crossover; hypogonadal males	Testosterone gel 1.62%; 2.50 g, once daily in the AM to the upper arms/shoulders for seven days during each treatment period, topical.	18 15 31-60	21 days of exposure
4	BA	S176.1.007	To determine the single and multiple dose relative bioavailability of testosterone after administration of testosterone gel 1.62% to the abdomen, upper arms/shoulders, and a combination of both application sites using a rotation schedule.	Randomized, open-label, three-way crossover; hypogonadal males	Testosterone gel 1.62%; 5.00 g, once daily in the AM to the abdomen, upper arms/shoulders, and a combination of both application sites using a rotation schedule, topical.	36 32 29-73	31 days of exposure (including a 5-day washout period between treatments).
5	PK	S176.1.003	To determine the PK of total testosterone concentrations in female patients after single and multiple episodes of contact with a male partner dosed with testosterone gel 1.62%.	Randomized, open-label, parallel; healthy male and female patients	Males: testosterone gel 1.62%; 5.00 g once daily in the AM to the abdomen for seven days, topical. Females: 15 minutes of contact time; no direct dose application.	96 patients (48 couples) 95 patients (47 males, 48 females) 18-65	7 days of exposure
6	PK	S176.1.008	To evaluate the effects of dose, Post dose washing, and application site on the transfer potential of testosterone gel 1.62% from dosed males to a non-dosed female partner.	Randomized, open-label, parallel group; healthy male and female patients	Males: testosterone gel 1.62%; 2.50 or 5.00 g, two single doses once daily in the AM to the abdomen or upper arms/shoulders, topical.	48 patients (24 couples) 48 patients (24 couples) 18-59	2 days of exposure, separated by a 1-week washout

					Females: 15 minutes of contact time; no direct dose application.		
7	PK	S176.1.009	To determine the PK of total testosterone concentrations in female patients after a single episode of contact with a male partner dosed with testosterone gel 1.62%.	Randomized, open-label, parallel; healthy male and female patients	Males: testosterone gel 1.62%; 5.00 g single dose to the upper arms, shoulders and abdomen, topical. Females: 15 minutes of contact time; no direct dose application.	24 patients (12 couples) 24 patients (12 males, 12 females) 23-52	Single dose
8	PK	S176.1.011	To determine the PK of total testosterone concentrations in female patients after a single episode of contact with a male partner dosed with testosterone gel 1.62%.	Randomized, open-label, parallel; healthy male and female patients	Males: testosterone gel 1.62%; 5.00 g single dose to the upper arms, shoulders only, topical. Females: 15 minutes of contact time; no direct dose application.	24 patients (12 couples) 24 patients (12 males, 12 females) 21-59	Single dose
9	PK	S176.1.004	To evaluate the sensitization and skin irritation potential of testosterone gel 1.62% on intact skin of healthy adult male patients.	Randomized, double-blind, placebo controlled; healthy patients	Testosterone gel 1.62%; 100 mg gel/3.14 cm2 patch, topical	235 214 18-79	6 weeks (three phases: 21-day induction; 12-17 day rest; 5 day challenge)
10	PK	S176.1.001 and amendment	To determine the multiple dose PK and comparative bioavailability of testosterone after administration of testosterone gel, 1.22%, 1.42%, and 1.62% at doses of 1.25, 2.50, and 3.75 g.	Randomized, open-label, parallel; hypogonadal males	Testosterone gel; once daily in the AM to the abdomen for 5 days at each dose level of 1.25, 2.50, and 3.75 g, topical	38 36 26-72	20 days of exposure (5 days at each dose of testosterone gel and 5 days of Androgel® 1%)
11	PK	S176.1.002	To determine the single and multiple dose PK of testosterone after administration of testosterone gel 1.62% at doses of 1.25 g, 2.50 g, 3.75, 5.00, and 6.25 g	Randomized, open-label, parallel; hypogonadal males	Testosterone gel 1.62%; 1.25 g, 2.50 g, 3.75, 5.00, or 6.25 g once daily in the AM to the abdomen or upper arms/shoulders (rotation schedule), Topical.	56 51 27-69	14 days of exposure

12	PK	S176.1.010	To determine the multiple dose PK and comparative bioavailability of testosterone after different sites of administration of testosterone gel 1.62% at a dose of 5.00 g.	Randomized, open-label, two period, cross-over; hypogonadal males	Testosterone gel 1.62%; 5.00 g once daily A: to the abdomen or upper arms/shoulders (rotation schedule), B: to a combination of upper arms/shoulders and abdomen, topical.	62 62 29-74	14 days of exposure

Abbreviations: BA = bioavailability; PK = Pharmacokinetics.

IV.2 Pharmacokinetics

Androgel 40,5 mg (1.62%) was selected based on skin permeation test and phase I pharmacokinetics (PK) data. The MAH has chosen the 1.62 % strength based on the observation that the PK profile - in patients using 1.62% gel - was similar to the profiles as seen with the currently marketed 1% testosterone gel. For all phase I to III trials, the MAH has measured testosterone, dihydrotestosterone and estradiol in serum. All analytical procedures were accurate, precise and sensitive. No concerns were noted.

Several PK studies were performed in hypogonadal men with testosterone levels below the normal (i.e. 300 ng/dL). After single dosing (one application to the upper arms-shoulders of 1.25, 2.50, 3.75, 5.00 or 6.25 g testosterone 1.62% gel) testosterone concentration showed a continuous increase up to 8 hours post-dose (C_{max}) at all dose levels, after which testosterone concentrations remained consistent and within the eugonadal range (300 to 1000 ng/dL) for the remainder of the 24 hour dosing interval. Eugonadal testosterone concentrations were reached 2-4 hours post-dose. Baseline concentrations of testosterone were obtained 48-72 hours after cessation of treatment. Upon multiple dosing - once daily (conform a rotational scheme) application of 1.25, 2.50, 3.75, 5.00 or 6.25 g testosterone 1.62% gel - C_{max} was reached at 8 hours post-dose. Eugonadal testosterone concentration were obtained 2 hours post-dose and eugonadal concentrations were maintained over the whole 14 days treatment period. No unexpected accumulation was observed. A trend towards dose proportionality for testosterone was observed at day 14 for 1.25-5.00 g, when baseline adjusted. In general, it is observed that all metabolites (dihydrotestosterone (DHT) and estradiol (E2)) follow the same trend in concentrations as testosterone. The calculated bioavailability of testosterone from this gel was 1.0-8.5%. This was lower than the bioavailability from the already marketed 1% gel. However, accurate evaluation of true bioavailability for drugs applied by transdermal route of administration is somewhat questionable, due to wide variance and taking into consideration the skin reservoir effect and the slow release of the drug during the full PK curve evaluation. Data on contact transfer with female partner of testosterone after application 2 hours post-dose, with or without t-shirt; with or with-out washing, demonstrated that the best method for avoiding transfer of testosterone to the female partner is to use a t-shirt when physical body contact is involved. This is stated in the proposed SmPC and is in line with already registered testosterone 1% gels.

No formal studies of testosterone gel 1.62% have been conducted in patients with renal or hepatic insufficiency. As Androgel 40,5 mg is administered topically, first-pass metabolism in

the liver is bypassed. The metabolites of testosterone are renally excreted as inactive glucuronides and sulphates. Therefore, renal or hepatic impairment is unlikely to have significant effects on testosterone levels and no specific dosage recommendations are necessary for these patients.

No *in vitro* interaction studies were performed. This is acceptable, as the interactions are well known and the SmPC is brought in line with the approved SmPC of Androgel 1%. The MAH has conducted *in vivo* interactions studies with moisturising lotion and sunscreen lotion. Applying sunscreen or moisturising lotion one hour after applying Androgel 40,5 mg slightly increased the bioavailability. These interactions e.g. the use of sunscreen or moisturising lotion and post-dose washing are stated in the proposed SmPC.

IV.3 Pharmacodynamics

Pharmacodynamics of testosterone are well known from the already approved testosterone 1% gels. Therefore, no pharmacologic studies were submitted. This is acceptable.

IV.4 Clinical efficacy

Efficacy of testosterone in the treatment of hypogonadal adult males has already been demonstrated for the 1% testosterone gels.

Main study

Design

The phase III pivotal study (S176.3.104) was a multi-centre, randomised, double-blind, placebo controlled study with an open-label extension of Androgel 16.2 mg/g, gel for the treatment of hypogonadism in adult males. The study was performed in 274 hypogonadal adult male patients (aged 18-80 years). The duration of the blinded period was 182 days total. After the blinded periods, patients were able to be enrolled in the open label part of the study which also lasted 182 days (total study duration 364 days). In the blinded part of the study, 234 patients were treated with Androgel 16.2 mg/g and 40 patients were included in the placebo group. After 182 days of treatment (blinded part), patients could agree to continue into an open-label, active treatment maintenance phase of the study. Placebo-treated patients from the pivotal 182-day phase of the study were started on 2.5 g of testosterone gel 1.62% and titrated to pre-specified serum total testosterone concentrations within the normal range over two clinic visits at days 196 and 210. These patients continued on a stable dose of testosterone gel 1.62% for the remainder of the 364 day study unless they did not remain within the pre-specified serum total testosterone concentration range. Patients who did not remain within the prespecified serum total testosterone concentration range could be titrated to a new dose on day 266.

No differentiation has been made for patients with primary and secondary hypogonadism in the in- and exclusion criteria. The baseline testosterone concentrations in the placebo group were near the lower limit of the eugonadal concentrations (300-1000 ng/dL) of testosterone. Before treatment, mean testosterone values in the placebo group were 294 ng/dL (SD 126 ng/dL) and in the treatment group these were 282 ng/dL (SD 291 ng/dL).

All patients were started at a mid-range dose level of testosterone gel 1.62% (2.50 g) and were then individually titrated up or down (if necessary) to an optimal dose level (1.25 g – 5.00 g). The optimal dose level was based on periodic measurement of serum testosterone level over the first 42 days, after which they were maintained at this dose level for approximately 140 days. The gel was applied conform a rotational scheme: 3 days stomach and 4 days upper arms/shoulder. The overall mean compliance for the full analysis (FA) sample was similar for the testosterone gel 1.62% groups and the placebo group (94.29% versus 97.70%).

Endpoints
The primary endpoint is the proportion of patients on active treatment with a day 112 (double-blind period) or day 364 (open-label period) C_{av} within the normal serum testosterone concentration range of 300-1000 ng/dL. Success was defined as ≥75% of patients on active treatment within the normal serum testosterone concentration range (300-1000 ng/dL) on these days. Additionally, the lower bound of the 95% CI was to be not less than 65%, based on the day 112 and 364 PK results.

For the double-blind period, the critical secondary efficacy endpoint was to evaluate total testosterone Cmax values during the first 182 days of the study. For the open-label period, the critical secondary efficacy endpoint was to evaluate total testosterone C_{max} values for each treatment group (Formerly Placebo and Continuing Active) for days 266 and 364. The individual total testosterone Cmax values were to be in the following ranges:
C_{max} ≤1500 ng/dL in ≥85% of the patients
C_{max} between 1800 – 2500 ng/dL in ≤5% of the patients
C_{max} >2500 ng/dL in none of the patients.

All other secondary efficacy variables were based on change from Baseline to day 182 (Visit 10) or day 364 (Visit 14). The primary endpoints as well as the secondary endpoints are acceptable.

Results
During the double blinded period (day 0-182), a total of 66 subjects were withdrawn from the study: 25 subjects due to adverse events, 19 subjects withdrew consent, 2 subjects experienced lack of efficacy, 3 subjects were lost at follow-up, 10 subjects had protocol violations and 5 patients were lost due to administrative reasons. In the double blind period, a total of 251/274 patients (91.6%) were included in the FA analysis (testosterone gel 1.62%: 214/234 patients, 91.5%; placebo: 37/40 patients, 92.5%). In the open-label phase, 191 patients (163 patients previously on active treatment and 28 patients previously on placebo) were allocated to treatment and analysed for safety and included in the FA analysis for efficacy.

The primary efficacy variable in the blinded part of the study was total testosterone Cav on day 112. On day 112, 81.6% of patients on testosterone treatment (95% CI of 75.1% - 87.0%) had Cav values within the target range, which met the criteria for primary efficacy.

Table 3. Number and percentage of patients achieving target range for testosterone C_{av} by day and treatment.

Population	Study Day	Testosterone gel 1.62%		Placebo		p-value
		n/N (%)	95% CI	n/N (%)	95% CI	
FA	14	138/210 (65.7)	(58.9, 72.1)	11/37 (29.7)	(15.9, 47.0)	<0.0001
	56	151/183 (82.5)	(76.2, 87.7)	11/32 (34.4)	(18.6, 53.2)	<0.0001
	112	**146/179 (81.6)**	**(75.1, 87.0)**	**10/27 (37.0)**	**(19.4, 57.6)**	**<0.0001**
	182	139/169 (82.2)	(75.6, 87.7)	8/28 (28.6)	(13.2, 48.7)	<0.0001
Efficacy	14	115/175 (65.7)	(58.2, 72.7)	7/27 (25.9)	(11.1, 46.3)	<0.0001
	56	138/165 (83.6)	(77.1, 88.9)	8/26 (30.8)	(14.3, 51.8)	<0.0001
	112	**146/179 (81.6)**	**(75.1, 87.0)**	**10/27 (37.0)**	**(19.4, 57.6)**	**<0.0001**
	182	135/165 (81.8)	(75.1, 87.4)	8/27 (29.6)	(13.8, 50.2)	<0.0001
PP	14	94/147 (63.9)	(55.6, 71.7)	5/27 (18.5)	(6.3, 38.1)	<0.0001
	56	112/131 (85.5)	(78.3, 91.0)	7/24 (29.2)	(12.6, 51.1)	<0.0001
	112	**102/124 (82.3)**	**(74.4, 88.5)**	**7/20 (35.0)**	**(15.4, 59.2)**	**<0.0001**
	182	101/118 (85.6)	(77.9, 91.4)	8/21 (38.1)	(18.1, 61.6)	<0.0001

n number of patients achieving target range
N number of patients with evaluable PK parameter for the given study day
CI Confidence interval
FA Full Analysis Sample
PP Per-Protocol Sample

Note 1: One patient included in the Efficacy Sample did not have sufficient data for C_{av} determination, but C_{max} was identified for this patient. At Day 112 the Efficacy Sample equals the FA Sample.
Note 2: 95% CI are based on exact binominal distribution. P-values are calculated from Cochran-Mantael-Haenszel tests for equality of the response percentages between testosterone gel 1.62% and placebo, across pooled study sites.

After day 182, patients could continue in an open label setting for another 182 days. A total of 191 patients continued (163 for the active treatment group and 28 from the former placebo group). The same primary endpoint was used as for the blinded period, however at day 364. On day 364, 77.9% of patients continuing on active testosterone treatment (95% CI of 70.0% - 84.6%) had C_{av} values within the target range, which meets the criteria for primary efficacy.

Table 4. Number and percentage of patients achieving C_{max} ranges by day and treatment for the open-label period (all samples).

Population	Study Day	Continuing active Testosterone gel 1.62% n/N (%)	95% CI	Formerly Placebo n/N (%)	95% CI	Combined (CA and FP) n/N (%)	95% CI
FA	266	109/139 (78.4)	(70.6-84.9)	18/26 (69.2)	(48.2-85.7)	127/165 (77.0)	(69.8 – 83.2)
	364	106/136 (77.9)	(70.0-84.6)	20/23 (87.0)	(66.4-97.2)	126/159 (79.2)	(72.1 – 85.3)
Efficacy	266	102/131 (77.9)	(69.8 – 84.6)	16/23 (69.6)	(47.1-86.8)	118/154 (76.6)	(69.1-83.1)
	364	106/136 (77.9)	(70.0 – 84.6)	20/23 (87.0)	(66.4-97.2)	126/159 (79.2)	(72.1-85.3)
PP	266	61/74 (82.4)	(71.8-90.3)	6/12 (50.0)	(21.1-78.9)	67/86 (77.9)	(67.7-86.1)
	364	54/71 (76.1)	(64.5-85.4)	8/9 (88.9)	(51.8-99.7)	62/80 (77.5)	(66.8-86.1)

For the overall results, n= number of observations and N= number of evaluable observations across all study days.

Pop	Population
CA	Continuing Active
FP	Formerly Placebo
FA	Full Analysis Sample
PP	Per-protocol Sample
n	number of patients achieving range
N	number of patients with evaluable PK parameter for the given study day.

The secondary endpoints in the blinded part (total testosterone C_{av} on day 14, 56 and 182) and open label part of the study (total testosterone C_{av} on day 266) were met. A decrease in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) concentrations is observed in the treatment groups at day 84 and day 182, whereas no change from baseline was observed in the placebo group for both hormones. This indicates that testosterone treatment with the gel product is effective in hypogonadal male patients.

IV.5 Clinical safety

A total of 483 adult hypogonadal male subjects were enrolled in the Phase III study (S176.3.104) and six Phase I studies (S176.1.001, S176.1.002, S176.1.005, S176.1.006, S176.1.007, S176.1.010) combined. Across the entire testosterone gel 1.62% clinical program (all studies), the highest proposed dose of 5.00 g had the longest duration of exposure. In addition, more subjects across the clinical programme were exposed to the 5.00 g dose than any other individual dose.

Adverse events

In the pivotal study (S176.3.104) treatment-emergent adverse events (TEAE) were reported for 5/234 (2.1%) of the patients in the testosterone gel group versus 1/40 (2.5%) for the placebo group. In the testosterone gel group, a higher proportion (25/234, 10.7%) of patients experienced TEAEs that led to permanent discontinuation of the study in comparison with the placebo group (0 patients). Severe TEAEs were reported in 11/234 (4.7%) patients of the testosterone gel group and in none of the patients in the placebo group. Severe TEAEs included: back pain, myocardial infarction, tachycardia, diarrhoea, dyspepsia, gastroenteritis, pneumonia, fall, diabetes mellitus, pituitary tumour, radicular pain, libido increased, sleep disorder and erection increased. The events concerning back pain and myalgia were

considered unlikely or not related to the study drug. The observed incidences are consistent with an older at-risk patient population. The most common TEAE leading to discontinuation was PSA (prostate-specific antigen) increased, which was pre-specified in the protocol as a discontinuation criterion. The percentage of patients who experienced at least one TEAE during the study was 58.1% (136/234) for the testosterone gel and 37.5% (15/40) for the placebo group. The incidence of TEAEs in the 11 phase I studies was as expected in this type of study with a low incidence of moderate or severe TEAEs and no clinically relevant signals emerging. In the contact transfer studies rash and application site pruritus were reported.

Serious adverse event and deaths

In the pivotal study (S176.3.104) there were no deaths. There were Serious Adverse Events (SAEs) reported for 9 patients during this study (myocardial infarction, tachycardia, pituitary tumour, malignant hypertension, back pain and radicular pain (the events of back pain and radicular pain occurred in the same subject), atrial fibrillation, gastrointestinal haemorrhage, non-cardiac chest pain, and prostate cancer). These incidents were only reported by patients who had received active treatment.

In the 11 phase I studies and contact transfer studies, no deaths were reported. In total, two patients experienced a serious adverse event after receiving the study drug. In a contact transfer study, two patients were discontinued from study participation due to rash AEs.

Discontinuation due to AEs

Increased PSA level was the TEAE that led to study discontinuation (conform study protocols). Testosterone has an effect on prostate tumour growth. Tumour growth is related to the higher PSA levels. In the SmPC it is advised to check the patient for (pre-existing) prostate cancer prior to testosterone treatment. PSA levels should be checked twice yearly.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Androgel 40,5 mg. At the time of approval, the most recent version of the RMP was version 6.0 dated 23 December 2020.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	• Cardiovascular events • Thromboembolic risk secondary to haematocrit increase
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.7 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies that were performed with Testosterone gel 1.62%. The application for Androgel 40,5 mg, transdermal gel in sachet (1.62%) gel is sustained by 11 phase I studies and one phase III pivotal study, this is considered to be adequate. Risk management is adequately addressed. This medicinal product can be used for the specified indications.

Androgel 40,5 mg, transdermal gel in sachet can be prescribed to hypogonadal patients (testosterone concentration <300 ng/dL) in order to raise testosterone concentrations into the eugonadal range (300-1000 ng/dL). Pharmacokinetic data from the PK studies and the pivotal study in hypogonadal males indicate that after first dosing, eugonadal concentrations are reached within 2-4 hours and levels remain within this range for 24 hours. C_{max} is obtained after 8 hours. Patients maintained eugonadal concentrations upon multiple once daily dosing in the phase I/II pivotal studies.

Based on the several bioavailability studies the following can be concluded:

- application of the gel only to upper arms/shoulder demonstrates the highest testosterone levels post dosing.
- application via a rotational scheme (3 days abdomen and 4 days upper arm/shoulders) showed similar PK profiles compared to upper arms/shoulders only.
- no unexpected accumulation of testosterone occurred when applying the gel once daily for a longer time period (multiple dosing).

Based on the submitted efficacy data, efficacy of the Androgel 40,5 mg, transdermal gel in sachet formulation in the treatment of hypogonadal adult males is proven. After applying testosterone 1.62% gel, patients' eugonadal testosterone levels were reached and maintained throughout the study. The primary endpoints were met:

- On day 112 of the blinded part, 81.6% of patients on testosterone treatment (95% CI of 75.1% - 87.0%) had C_{av} values within the target range.
- On day 364, 77.9% of patients continuing on active testosterone treatment (95% CI of 70.0% - 84.6%) had C_{av} values within the target range.

Secondary endpoints were met as well.

In the pivotal study, it was observed that patients enrolled in the placebo group had testosterone baseline values close to the lower limit of the eugonadal range. These patients reached eugonadal testosterone concentrations within the study. In- and exclusion criteria did not distinguish between patients with primary and secondary hypogonadism. In the FA set this is clearly notable from the large observed variation in both treatment groups. Although the best study population would have been patients with primary hypogonadism, the primary goal of the study was met as it was demonstrated that Androgel 40,5 mg, transdermal gel in sachet restored testosterone levels within eugonadal boundaries.

With respect to safety of the product, no notable difference was observed compared to the safety profile already known for the registered testosterone 1% gels. Risk management is adequately addressed.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The MAH submitted a bridging statement making reference to a previously assessed and approved patient consultation/bridging report for Androgel 16,2 mg/g gel in a pump pack. As Androgel 16,2 mg/g gel in pump pack was a line-extension of Androgel 25 mg/50 mg sachets and is an alternative name for the current Androgel 40,5 mg, this approach is acceptable and the patient consultation does not need to be repeated. The user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Androgel 16,2 mg/g, gel (NL/H/3240/001/DC). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Androgel 40,5 mg, transdermal gel in sachet (1.62%), has a proven chemical-pharmaceutical quality and is considered to be a line-extension of Androgel 25 mg or 50 mg (Androgel 1%) transdermal gel in sachets. Androgel 25 mg and 50 mg are well-known medicinal products with an established favourable efficacy and safety profile. The new formulation is considered to be an approvable addition to the original product. This product provides a better dosing capability compared to the already approved 1% testosterone gels in sachets.

Sufficient non-clinical and clinical data relevant to the extension have been submitted. The efficacy and safety results were satisfactory, and in line with the known efficacy and safety of the existing testosterone gel formulations.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Androgel 40,5 mg, transdermal gel in sachet with the reference product, and have therefore granted a marketing authorisation. The national procedure was finalised with a positive outcome on 1 November 2022.

With regard to the non-clinical data, several concerns regarding the Environmental Risk assessment remain uncertain. Therefore, additional studies were requested. The MAH has submitted an amended signed commitment to assure that these studies will be submitted post approval by the end of 2024 the latest, following the outcome of the scientific advice. This is acceptable.

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STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
992301	Change in the name and/or address of a manufacturer/importer of the finished product (including batch release or quality control testing sites): - Manufacturer responsible for batch release. Change in the name and/or address of the marketing authorisation holder.	Yes Yes	19-01-2023	Approved	N.A.
1003776	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: for an active substance, for a starting material/ reagent/ intermediate used in the manufacturing process of the active substance, for an excipient. - European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. Updated certificate from an already approved manufacturer.	No	07-03-2023	Approved	N.A.
1039515	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: for an active substance, for a starting material/ reagent/ intermediate used in the manufacturing process of the active substance, for an excipient. - European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. New certificate from a new manufacturer (replacement	No	05-10-2023	Approved	N.A.

	or addition).				
1040310	Change in control of the Finished Product. Change in the specification parameters and/or limits of the finished product: - Addition or replacement (excluding biological or immunological product) of a specification parameter with its corresponding test method as a result of a safety or quality issue.	No	27-12-2023	Approved	N.A.
1058331	Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the risk management plan. - Other variation. To update the Risk Management Plan (RMP) as per the current EU RMP template.	No	22-08-2024	Approved	N.A.
1063630	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products - Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data.	Yes	11-02-2025	Approved	N.A.
1096823	Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacturing process of the active substance: - Up to 10-fold increase compared to the originally approved batch size.	No	07-10-2024	Approved	N.A.