CBG MEB

Public Assessment Report

Scientific discussion

Testavan 20 mg/g transdermal gel

(testosterone)

NL/H/3958/001/DC

Date: 24 May 2019

This module reflects the scientific discussion for the approval of Testavan 20 mg/g transdermal gel. The procedure was finalised on 15 February 2018. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
BCF	Bio-Concentration Factor
BfArM	German Federal Institute for Drugs and Medical Devices
BMI	Body Mass Index
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
CMR	Carcinogenic, Mutagenic and Reprotoxic
CMS	Concerned Member State
CNS	Central Nervous System
DHT	5α-dihydrotestosterone
DT50	Degradation Time for 50% of a substance to be degraded under laboratory conditions
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
FAS	Full Analysis Set
FDA	United States Food and Drug Administration
GGA	Gamma-Glutamyl Transferase
Hct	Haematocrit
IIEF	International Index of Erectile Function
ICH	International Council for Harmonisation
ITT	Intention to Treat
K_{ow}	Octanol-Water partition coefficient
LFT	Liver Function Tests
LOCF	Last Observation Carried Forward
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board
NOEC	No Observed Effect Concentration
OECD	Organisation for Economic Co-operation and Development
PBT	Persistent, Bioaccumulative and Toxic
PEC	Predicted Environmental Concentration
Ph.Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PL	Package Leaflet
PP	Per-Protocol
PSA	Prostate Specific Antigen
RH	Relative Humidity
RMP	Risk Management Plan
SAE	Serious Adverse Event
SHBG	Sex-Hormone Binding Globulin
SmPC	Summary of Product Characteristics
TBD	To Be Determined
TEAE	Treatment Emergent Adverse Events
TSE	Transmissible Spongiform Encephalopathy
TRT	Testosterone Replacement Therapy
vPvB	very Persistent and very Bioaccumulative

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Testavan 20 mg/g transdermal gel from Ferring BV.

The product is indicated for testosterone replacement therapy (TRT) for adult male hypogonadism, when testosterone deficiency has been confirmed by clinical features and biochemical tests.

A comprehensive description of the indications and posology is given in the SmPC.

The goal of TRT in hypogonadal men (morning serum total testosterone <300 ng/dl or laboratory lower limit of normal on at least two occasions) is to restore testosterone levels to approximately the level of healthy men, thus alleviating the symptoms associated with testosterone deficiency such as reduced libido and vitality, decreased muscle mass, increased fat mass, depression, and others (EAU Guidelines, 2015; Stanworth and Jones 2008; Bashin et al., 2010).

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Germany, Denmark, Estonia, Greece, Spain, Finland, France, Croatia, Hungary, Ireland, Iceland, Italy, Liechtenstein, Lithuania, Latvia, Luxembourg, Malta, Norway, Poland, Portugal, Romania, Sweden, Slovenia, Slovakia and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC (a full-mixed dossier with administrative, quality, pre-clinical and clinical data).

For substantiation of the indication the MAH submitted clinical documentation which includes three phase I studies, two phase II studies and three phase III studies.
The phase I and II clinical trials provided data to support the dose titration scheme to be used in phase III clinical trials. The clinical documentation also included the proposed product labelling and a phase I bioavailability study to bridge the clinical data with the data from scientific literature.

Development program and regulatory advice
The development program was discussed with various regulatory authorities (FDA, BfArM and MEB). The pivotal phase III trial 000127 was performed in accordance with the FDA Special Protocol Assessment Agreement. It was agreed that the legal basis for the application is according to article 8(3) of Directive 2001/83/EC as a 'full-mixed' dossier. Hence, this application relies on the generated clinical data as well as literature references, in particular the scientific literature documenting TRT. Among others in the scientific meeting it was stressed that given the legal basis, the bridging to other testosterone containing gels was of importance and bridging should be scientific well justified.

II. QUALITY ASPECTS

II.1 Introduction

Testavan is a transdermal homogenous, translucent to slightly opalescent gel.

One gram of gel contains 20 mg testosterone.

The gel is packed in a multidose container. The container includes a metering pump with a laminate foil pouch in a bottle, and is provided with a cap applicator with a hygienic lid. The pump is composed of polypropylene, ethylene propylene diene monomer and stainless steel and the pouch is a polyethylene/polyethylene terephthalate/aluminium/polyethylene laminate encased in a rigid polypropylene bottle.

Each pump contains 85.5 g gel and is capable of dispensing 56 metered doses. One pump actuation delivers 1.15 g (1.25 ml) of gel equivalent to 23 mg of testosterone.

The excipients are ethanol (96%), purified water, propylene glycol (E1520), diethylene glycol monoethyl ether, carbomer 980, trolamine and disodium edetate.

II.2 Drug Substance

The active substance is testosterone, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The drug substance is a crystalline powder and practically insoluble in water and fatty oils, freely soluble in alcohol and in methylene chloride. Polymorphism is not relevant for the product at issue, since it concerns a gel in which the drug substance is dissolved.

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.

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 considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. The specification includes an additional requirement which is specified on the CEP. Batch analytical data demonstrating compliance with this specification have been provided for three production scale batches.

Stability of drug substance
Stability data has been provided for three batches stored for 60 months at 25°C/60% RH. Four additional batches have been stored between 12 to 48 months at 25°C/60% RH. Also three batches have been stored for six months at 40°C/75% RH. No specific up or downward trends have been observed. The drug substance remains stable. Based on the data submitted a retest period could be granted of 60 months, when stored in its original, unopened and undamaged container at temperatures not exceeding 25°C.

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 choice of excipients is justified and their functions explained. The main development studies aimed to optimise the viscosity and permeation of the gel. Several clinical trials were performed with the drug product. In addition to the clinical and the *in vitro* permeation studies, several extractable and leachable studies, related to the container closure system were performed. The proposed manufacturing process is representative for the process used to manufacture the batches that were used in the clinical studies.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
Testosterone gel is manufactured by mixing a testosterone solution and a non-aqueous solution. Subsequently, other excipients are added. After the final mixing, the bulk gel is discharged and filled out in the dispensers. 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 in accordance with the relevant European guidelines.

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, pH, viscosity, identity, assay, impurities, uniformity of dosage units, delivered dose per dispenser and microbiology. The release and shelf-life acceptance criteria are identical, except for the parameters assay of testosterone and the impurities (for both wider shelf-life limits are included). Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from twelve production scale and three laboratory scale from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product has been provided for six production-scale batches (three manufactured according to the new process, three according to the old process and from the former production site). The batches were stored at 25°C/60% RH for 36 months and at 40°C/75% RH for six months, and in different orientations (upright, horizontal and inverted). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the packaging proposed for marketing. Photostability studies were performed and showed that the product is photostable in the primary packaging. All parameters remain relatively stable and stay within the proposed specification limits. Therefore, the proposed shelf-life of 36 months, without additional storage conditions, is justified.

Stability data has been provided demonstrating that the product remains stable for 60 days following the first opening of the container when stored at 25°C/60% RH.

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 Testavan has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The MAH appropriately reviewed the relevant non-clinical literature for testosterone and summarised this in a non-clinical overview and non-clinical summaries. The MAH provided new studies, i.e. pharmacokinetic studies on the transdermal absorption and toxicology studies related to local tolerance and leachables in the product.

III.2 Pharmacology

The active substance in Testavan gel is testosterone. Testosterone is a very well established endogenous hormone. It is produced mainly by Leydig cells in testis or by theca cells in ovary. Testosterone is responsible for the growth and development of the male sex organs as well as for the development and maintenance of secondary sex characteristics and produces a multitude of physiological effects other than those related to sexual development. The primary and secondary pharmacological effects of testosterone as well as the safety pharmacology have been clinically well-established. Therefore, additional non-clinical or safety pharmacology testing is not needed.

III.3 Pharmacokinetics

The pharmacokinetics of testosterone is well understood and described in literature. In the circulation, only 2% of testosterone is free with the remainder being bound to either sex-hormone binding globulin (SHBG) or albumin. Once in the circulation, testosterone distributes to a variety of tissues. Distribution is determined by tissues containing the androgen receptor (e.g., bone marrow, mammary gland, muscle, prostate, stem cells, testes, preputial gland, scrotal skin and vagina). Testosterone is converted enzymatically to 5α-dihydrotestosterone (DHT) in target tissues and in the liver and to oestradiol in fat. The primary route of elimination is urine and small amount is excreted in the faeces.

The results of four *in vitro* pharmacokinetic studies assessing the percutaneous absorption of testosterone from the MAH's testosterone gel (1% and 2% strengths) using pig or human skin showed a higher transdermal drug delivery than with a comparator product.

III.4 Toxicology

The safety profile of testosterone has been well documented and well established. The toxicological investigations confirmed the generally known testosterone effects on reproductive, cardiovascular and central nervous system (CNS) organ systems as well as carcinogenicity in experimental animals. These effects related to parenteral dose ranges which are not achieved by topical administration of testosterone gel and are therefore considered to have very low relevance for human clinical safety in the applied treatment paradigm of TRT.

In addition to the available published information on testosterone, the MAH showed that testosterone did not pose a risk of inducing phototoxicity and conducted a local tolerance study using testosterone gel. No signs of irritancy or delayed contact hypersensitivity were registered in the guinea-pig sensitisation test.

The container closure system of testosterone gel consists of a metered-dose dispenser and a cap applicator. A safety evaluation based on data from the 24 month storage study concluded that all leachables from the metered-dose dispenser are within acceptable limits for the intended treatment. The cap applicator leachables study was performed over a period of 53 days (30°C/75% RH) to cover the worst-case climate zones. As no leachables were found above the detection limits, it is considered justified to use the applicator for 56 days.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Summary of main study results

Substance (INN/Invented Name):					
CAS-number (if available):					
PBT screening	**Test protocol**	Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	3.32			Not a potential PBT
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	3.32			
	BCF				
Persistence	DT50 or ready biodegradability				
Toxicity	NOEC or CMR				not T
PBT-statement :	TBD				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{\text{surface water}}$, default or refined (e.g. prevalence, literature)	0.345	µg/l			>0.01 threshold (Yes)
Other concerns (e.g. chemical class)	The substance is a hormone that influences both development and reproduction of fish				
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106 or …	TBD			List all values
Ready Biodegradability Test	OECD 301	TBD			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	TBD			Not required if readily biodegradable
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	TBD	µg/l	species
Daphnia sp. Reproduction	OECD 211	NOEC	TBD	µg/l	

Test					
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	TBD	µg/l	species
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	TBD	µg/l	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF	TBD	l/kg	%lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$	TBD		for all 4 soils
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect	TBD	mg/kg	
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC	TBD	mg/kg	
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	TBD	mg/kg	
Collembola, Reproduction Test	ISO 11267	NOEC	TBD	mg/kg	
Sediment dwelling organism		NOEC	TBD	mg/kg	species

Conclusions on studies for testosterone:
Testosterone is considered not to be PBT, nor vPvB.
Using the default F_{pen}, a PEC_{sw} of 0.345 µg/l was obtained, which exceeds the action limit of 0.01 µg/l. Furthermore, the active substance testosterone is a hormone that may affect the development and reproduction of animals. Consequently, a Phase II assessment is needed and a tailored risk assessment strategy should be followed that addresses its specific mechanism of action.

The MAH committed to follow a tailored risk assessment strategy and perform the requested Phase II assessment, including the fish full life cycle study that replaces the fish early life stage toxicity test, and update the ERA accordingly.

The MAH committed to provide the following studies (including reports):
- Adsorption-desorption using a batch equilibrium method (OECD 106) using 3 soil types and 2 types of sewage sludge;
- Ready biodegradability test (OECD 301)
- Aerobic and anaerobic transformation in aquatic sediment systems (OECD 308);
- Algal growth inhibition test (OECD 201);
- Daphnia sp. reproduction test (OECD 211, use version 2012);
- Fish full life cycle test to addresses the specific mechanism of action and to derive a valid NOEC/EC10 value (replacing the Fish, early life stage (E.L.S.) toxicity test (OECD 210));
- Activated sludge, respiration inhibition test (OECD 209, use version 2010). (NL)
- Bioaccumulation in Fish: Aqueous and Dietary Exposure (OECD 305; use version 2012)

The MAH committed to update the ERA and provide the following studies (including reports) if triggered:
- If the outcome of the adsorption study (OECD 106) is that K_{oc} >10,000 l/kg, a risk assessment for the terrestrial compartment is triggered, unless the compound is found readily biodegradable (OECD 301). In case a terrestrial risk assessment is triggered, the following tests are required:
  - Aerobic and anaerobic transformation in soil (OECD 307),
  - Soil Micro organisms: Nitrogen Transformation Test (OECD 216),
  - Terrestrial plants, growth test (OECD 208, use version 2006),
  - Earthworm, acute toxicity tests (OECD 207),
  - Collembola, reproduction test (OECD 232).
- If significant shifting to the sediment is observed (more than 10% at any time-point at or after 14 days is present in the sediment) in the OECD 308 water: sediment simulation study (unless the compound is found readily biodegradable), effects on a sediment dwelling organism should be investigated and compared to the $PEC_{sediment}$. Applicable tests are those with Hyalella sp; Lumbriculus sp. (OECD 225) or Chironomus sp. (OECD 218 or 219).

III.6 Discussion on the non-clinical aspects

Testosterone is an endogenous male sex hormone that is important for the development of male reproductive organs and for the development and maintenance of secondary male sexual characteristics. The safety and efficacy of exogenous testosterone in the treatment of male hypogonadism have been clearly demonstrated in humans over several decades and the effects on vital organ systems (cardiovascular, respiratory and CNS) are well known. The non-clinical overview has been found appropriate. The MAH provided new studies, i.e. pharmacokinetic studies on the transdermal absorption and toxicology studies related to local tolerance and leachables in the product:

- The *in vitro* pharmacokinetic studies assessing the percutaneous absorption of testosterone from the MAH's testosterone gel (1% and 2% strengths) using pig or human skin showed a higher transdermal drug delivery than with a comparator product.
- There was no evidence of skin sensitisation in the guinea-pig test using the MAH's testosterone gel formulation and testosterone did not pose a risk of inducing phototoxicity.
- All leachables from the metered-dose dispenser were considered to be of no safety concern for the intended treatment.

The MAH committed to update the ERA and provide several related studies.

IV. CLINICAL ASPECTS

IV.1 Introduction

Overview of studies

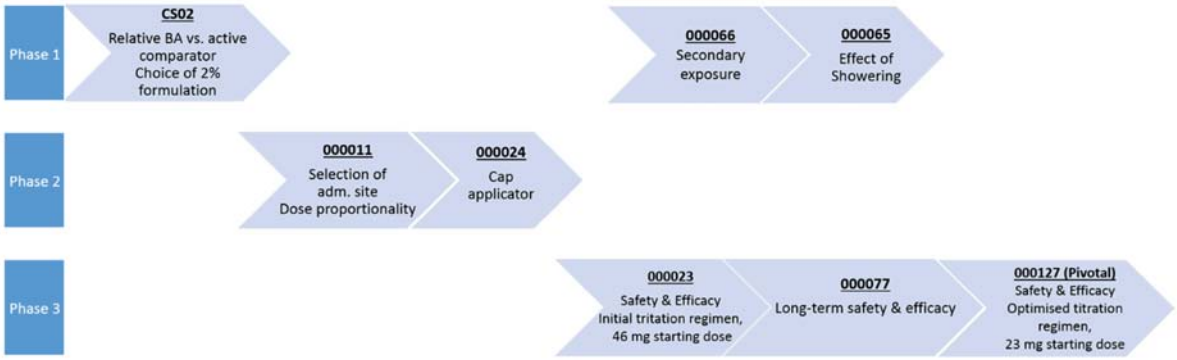
In support of the application, the MAH submitted the results of three phase I studies, two phase II studies and three phase III studies (Table 1)(Figure 1).

Table 1: Clinical development program for Testavan gel 2%.

Phase	Trial ID *Objective*	Design	Treatment(s) Dose	Subjects	Population
I	FE 999303 CS02 *Relative bioavailability (FE 999303 vs. active comparator)*	Open-label, randomised crossover	Testosterone gel (FE 999303) 1%, 50 mg Testosterone gel (FE 999303) 2%, 50 mg TESTOGEL 1% (Also registered as ANDROGEL 1%), 50 mg	Total: 11	Testosterone down-regulated healthy adult males
I	000065 *Single dose PK after showering*	Open-label, Randomised crossover	Testosterone gel (FE 999303) 2%, 69 mg	Total: 16	Adult hypogonadal males
I	000066 *Secondary exposure in non-treated females*	Open-label, Fixed sequence	Testosterone gel(FE 999303) 2%, 69 mg	Total: 30	Healthy males and their healthy female partners
II	000011 *Single dose and steady state PK; testosterone in normal physiologic range*	Open-label, sequential dose escalation	Testosterone gel (FE 999303) 2%, 23, 46, 69 mg	Total: 20	Adult hypogonadal males
II	000024 *Steady state PK; applicator feasibility*	Open-label, sequential dose escalation	Testosterone gel (FE 999303) 2% 46 mg (by hand) 23, 46, 69 mg (with applicator)	Total: 20	Adult hypogonadal males
III	000023 *Efficacy (PK); safety*	Open-label, nonrandomised	Testosterone gel (FE 999303) 2%, 23, 46 or 69	Total: 180	Adult hypogonadal

			mg based on titration criteria		males
III	000077 (extension of 000023) *Efficacy (PK); long term safety*	Open-label, nonrandomised	Testosterone gel (FE 999303) 2% Fixed dose established in 000023 (down-titrated if required)	Total: 145	Adult hypogonadal males
III	000127 (pivotal trial) *Efficacy (PK); safety*	Open-label, nonrandomised	Testosterone gel (FE 999303) 2% 23, 46 or 69 mg based on titration criteria	Total: 160	Adult hypogonadal males

Figure 1: Chronological presentation of clinical development program for Testavan gel 2%.



IV.2 Pharmacokinetics

IV.2.1 **Bioavailability study (phase I study CS02)**

Study design

To demonstrate that Testavan gel 1% and 2% had similar bioavailability and a similar kinetic profile, the MAH performed a phase I study (CS02) in ten chemical castrated males. This study is also used for dose finding, as no formal dose finding studies have been submitted.

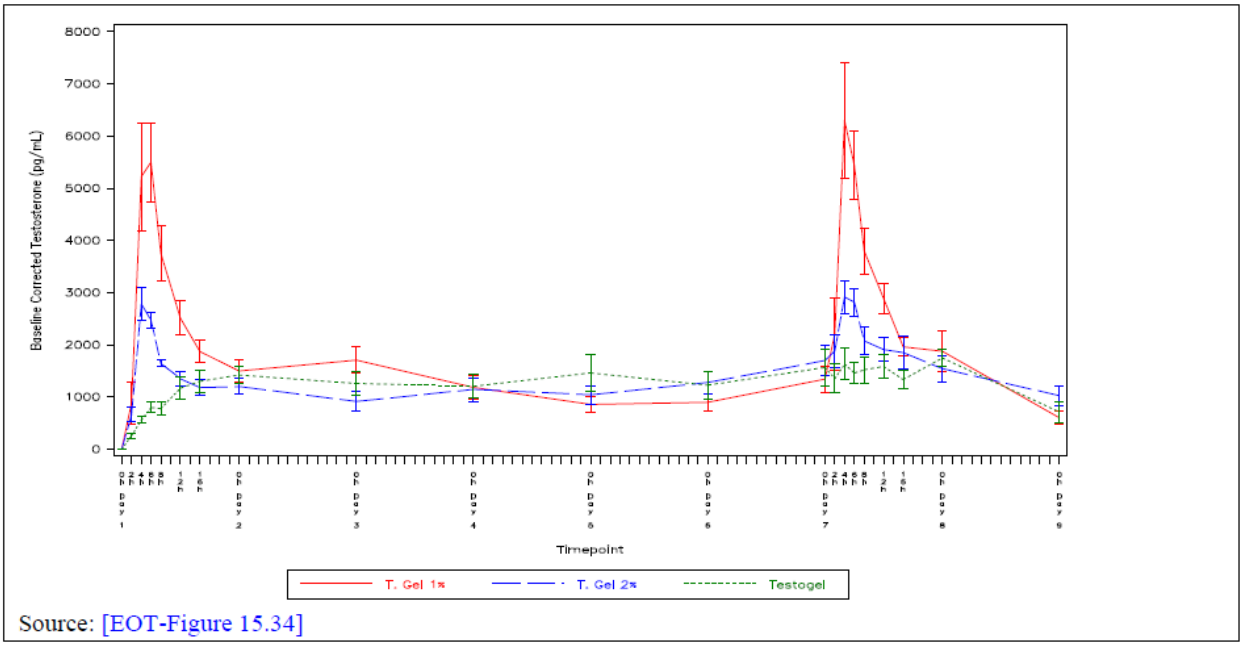
A total of 31 patients that received at least one Decapeptyl administration were screened, ten of whom completed all three study periods. Each subject received a daily administration for seven consecutive days of either 5 g Testavan gel 1%, 2.5 g Testavan gel 2%, or 5 g TESTOGEL 1%. This was administered to the same area (abdomen) during each of the three treatment periods.

The treatment periods were separated by washout-periods of 6-9 days, including the two days with no dosing at the end of each treatment period. The total treatment period for individual patients thus lasted for not more than 41 days, and the total duration of the study for an individual subject did not exceed 13 weeks.

Pharmacokinetic parameters were measured at day 1 and day 7 and involved analysis over 24 hrs (pre dose and at 2, 4, 6, 8, 12, and 16 hours after the first dose (day 1), pre-dose only on days 2-6, and pre-dose and at 2, 4, 6, 8, 12, 16, 24, 48 hours after the last administration (day 7)).

Study results

Figure 2: Time-course of baseline-corrected testosterone concentrations (days 1-9, mean (SE)).



Source: [EOT-Figure 15.34]

Table 2: Summary of baseline corrected primary pharmacokinetic parameters.

Pharmacokinetic Parameter	Day	Testavan gel 1% N=11	Testavan gel 2% N=10	Testogel 1% N=11
AUC_T (ng/ml•h)				
Mean (SD)	1	61.5 (24.2)	34.0 (5.8)	23.1 (8.7)
Geometric mean (%CV)		57.3 (39)	33.6 (17)	21.6 (38)
Range		32.0 - 105.6	24.5 - 44.1	10.3 - 41.8
AUC_T (ng/ml•h)				
Mean (SD)	7	71.5 (27.6)	47.6 (17.7)	35.8 (13.6)
Geometric mean (%CV)		66.9 (39)	44.9 (37)	33.4 (38)
Range		37.0 - 121.9	26.0 - 84.4	17.0 - 62.9
F_{rel} (% of Testogel)				
Mean (SD)	1	274 (70)	178 (70)	100
Range		157 - 377	86 - 306	
F_{rel} (% of Testogel)				
Mean (SD)	7	212 (112)	152 (80)	100
Range		93 - 455	52 - 315	

The bioavailability data shows that Testavan gel 2% shows less bioavailability (AUC_T) compared to the Testavan gel 1%. *In vitro* skin permeation tests suggested that the observed difference in bioavailability between Testavan 1% and Testavan 2% may be related to the difference in the relative amounts of excipients in the formulations and/or due to differences in the amount of gel applied.

The MAH did only apply for the 2% formulation, the 1% formulation was only used in study CS02, and all safety and efficacy data for Testavan were generated with the 2% formulation. Hence the finding of a higher bioavailability with the 1% formulation does not affect the overall assessment of benefit/risk.
With regard to other pharmacokinetics characteristics of testosterone the dossier was mainly based on literature references.

IV.2.2 Effect of showering on the absorption (phase I study 000065)

One phase I trial was conducted to provide information on the effect of showering on the absorption of Testavan gel 2% (trial 000065). Showering 1 h and 2 h after application of Testavan gel 2% decreased the 24 h average total testosterone concentration (C_{ave}) by 19.2% and 14.3%, respectively, compared to not showering after Testavan gel 2% administration. Showering 6 h following Testavan gel 2% administration did not result in a decrease in C_{ave}.

IV.2.3 Potential transfer of testosterone after administration (phase I study 000066)

One phase I trial was conducted to provide information on the transfer of testosterone from treated male patients to their female partners following application of Testavan gel 2% (trial 000066).
The potential for testosterone transfer of Testavan gel 2% applied to the intact skin of the shoulder and upper arm was evaluated. No statistically significant differences in secondary exposure to testosterone were noted in female patients when the male partner was clothed at the time of contact or had showered before contact.

IV.2.4 Evaluation of site of administration, dose response, and application technique (phase II studies 000011 and 000024)

Two phase II trials of Testavan gel 2% were conducted in adult hypogonadal male patients to evaluate the site of administration, evaluate dose response, and to compare application of Testavan gel 2% directly by hand vs. by cap applicator avoiding direct hand contact.

The shoulder and upper arm were selected as the site of administration of Testavan gel 2% based on the results of trial 000011, which was conducted in 20 patients. Application of Testavan gel 2% to the shoulder and upper arm resulted in greater absorption than application to the thigh or abdomen, based on difference in C_{ave} ($p < 0.05$).
The hands-free cap applicator was first introduced into clinical trials in trial 000024, which was conducted in hypogonadal males to compare Testavan gel 2% applied by hand vs. cap applicator. There was no apparent difference in the pharmacokinetics of testosterone absorption following the administration of 46 mg of testosterone to the shoulder and upper arm once daily for 7 days by hand or by cap applicator. This trial also showed a nearly linear increase in exposure to testosterone following administration of Testavan gel 2% 23, 46 or 69 mg once daily for 7 days using the cap applicator.

The results of trial 000024 demonstrated that 46 mg of Testavan gel 2% applied to the shoulder/upper arm using the cap applicator consistently led to serum testosterone levels within the therapeutic range (between 300 and 1050 ng/dl). In addition, for evaluation of restoration of testosterone levels to the normal range (after dosing with 46 mg or 69 mg testosterone), the following pharmacokinetic limits based on C_{max} were assessed: at least 85% of patients with C_{max} below 1500 ng/dl, at most 5% of patients with C_{max} between 1800 and 2499 ng/dl and no patients with C_{max} of 2500 ng/dl or more. The 46 mg dose did not result in any patients with C_{max} >1500 ng/dl, whereas this was the case in three (16.7%) patients treated with the 69 mg dose. The 46 mg testosterone dose was therefore selected as the starting dose for the first phase III trial 000023.

IV.2.5 Other pharmacokinetic characteristics

With regard to other pharmacokinetics characteristics of testosterone the dossier was mainly based on literature references.

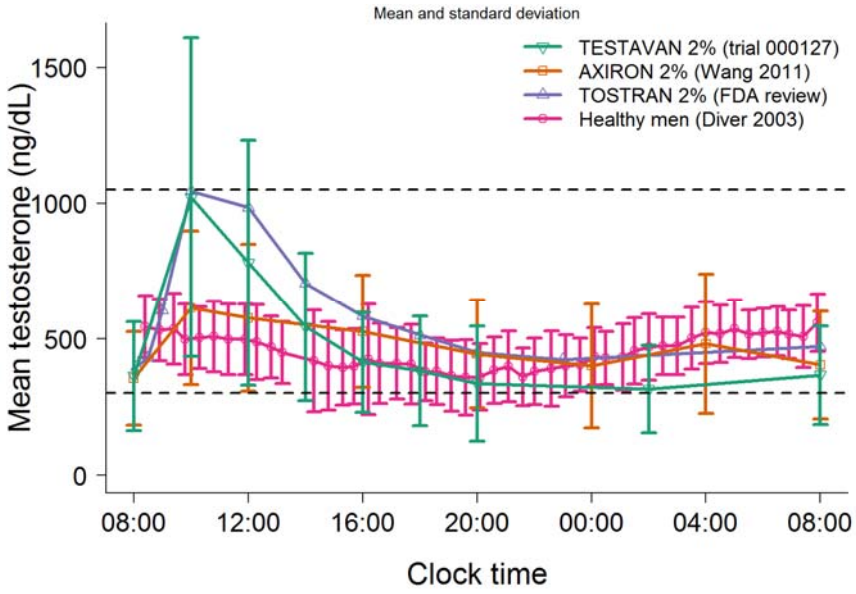
No absolute bioavailability was determined, however absorption of the 2% gel was compared with Androgel. Based on the calculations used to estimate the absolute bioavailability of Androgel, the MAH made an estimation of the absolute bioavailability 8-22% for Testavan 2% in hypogonadal males. This is roughly in line with the absolute bioavailability's 9-14% reported/estimated of other TRT products (Androgel, Testim and Tostrex). The absence of an absolute bioavailability study can be accepted as the dose and dose titration of Testavan 2% is based on clinical studies support the C_{ave} levels within the eugonadal range.

An across-study comparison of mean testosterone pharmacokinetic profiles for Testavan 2% with published data of other testosterone formulations Tostran 2%, Axiron 2%, Testim 1% and Androgel 1% was presented. At steady-state when the same dose (~50mg) was applied (Table 3), the 2% transdermal TRT products (Testavan 2%, Tostran 2% and Axiron 2%) showed a testosterone peak at

2 hours after application, thereafter maintaining a rather constant concentration throughout the day. Absorption of testosterone from Testim 1% and Androgel 1% was slower with a late peak. A similar fluctuation C_{max}/C_{min} ratio of~3 was observed for all products except Testim 1%, which showed a somewhat lower fluctuation of 2. Mean C_{min} levels were comparable for all products (Table 3).

In the clinical studies with dose titration applied, C_{max} values of Testavan 2% gel were similar to or slightly lower than those of Tostran 2% (Figure 3), and a similar fluctuation C_{max}/C_{min} was observed for Testavan 2% and Tostran 2%. A somewhat lower fluctuation of testosterone was observed for Axiron 2% ratio ~3. The pharmacokinetic profile of Testavan 2% is similar to that of Tostran 2% and Axiron 2%. Hence, bridging to literature is considered acceptable.

Figure 3 Mean testosterone profiles after dose titration with 2% transdermal testosterone products in hypogonadal men and endogenous levels in healthy middle-aged men.



Horizontal dashed lines indicate eugonadal range (300-1050 ng/dL). Standard deviation not reported for Tostran 2%. Testavan 2%: trial 000127 Day 90, titration to 23, 46 or 69 mg/day. Tostran 2%: Trial T 00-02-01 Day 182, titration to 40, 60 or 80 mg/day (FDA review 2010). Axiron 2%: Day 120, titration to 30, 60, 90 or 120 mg (Wang 2011).

Table 3 Testosterone pharmacokinetic parameters for approved transdermal products and Testavan 2% after repeated dosing of ~50 mg/day testosterone at a fixed dose in hypogonadal men

	Testavan 2%	Testavan 2%	Tostran 2%[#]	Axiron 2%	Androgen 1%	Testim 1%
Reference	study 000024	study 000011	FDA review 2010 (study T 00-02-03)	Wang 2011	Dobs 2004	Steidle 2003
Subjects	18	20	7	135	12	~100
Dose / duration	46 mg for 7 days	46 mg for 10 days	60 mg for 7 days	60 mg for 15 days	50 mg for 14 days	50 mg for 30 days
Amount of drug product	2.3 g	2.3 g	3 g (1.5 g on each thigh)	3 ml (1.5 ml on each axilla)	5 g	5 g
Site of application	Upper arms/shoulders	Upper arms/shoulders	Thigh	Axillae	Shoulders, arms, abdomen	Shoulders
C_{ave} (ng/dl)*	320 ± 110	506 ± 263	383 ± 134	507 ± 175	440 ± 140	398 ± 234
C_{max} (ng/dl)*	641 ± 319	907 ± 783	791 ± 459	840 ± 436	750 ± 350	562 ± 352
C_{min} (ng/dl)*	213 ± 69	289 ± 111	246 ± 65	288 ± 115	250 ± 90	251 ± 113
Median T_{max} (h)	3.77	4.0	4.0	-	13.6 ± 7.9*	-
Comments			Results published in Gould 2007, but without PK profiles	Data from an efficacy trial where dose was titrated beyond Day 15	Similar results from other trials presented in Mazer 2005, Wiehle 2013, Wittert 2016	Data from an efficacy trial where dose was titrated beyond Day 30

*-: value not reported; *Mean ± SD; [#]Values shown for subjects not showering after application of Tostran 2%*

IV.3 Pharmacodynamics

No formal pharmacodynamic studies were submitted.

IV.4 Clinical efficacy

The MAH submitted one open label single arm study (000023), a follow-up extension, single arm, open label study (000077) and one single arm, open label, pivotal study (000127), to support the proposed indication "TRT for adult male hypogonadism, when testosterone deficiency has been confirmed by clinical features and biochemical tests."

No formal dose finding studies were performed by the MAH. The MAH used the data available of the phase II and phase III studies (study 000023 and 000077) to determine the starting dose (23 mg testosterone) and sampling time for titration purposes (4 h post-dose) to be used in the pivotal study 000127.

IV.4.1 Phase III Study 000023

Study design
A phase III, open-label, non-randomised, clinical trial to evaluate the efficacy and safety of FE 999303 (testosterone gel) in adult hypogonadal males.

A total of 172 hypogonadal male patients completed this study. Of the 656 screened patients, 180 were considered eligible and were enrolled. Eight patients discontinued. Mean age of the patients was 56.8 ± 9.4 and mean BMI was 30.0 ± 3.4. 145/180 patients were aged ≤65 years. The starting dose was 46 mg daily with the titration decision made using a pre-dose testosterone level at day 14 and 49.

Study results
Data from the responder analysis (responder being a patient with serum testosterone C_{ave} values within the normal range of 300 to 1050 ng/dl), in the supportive study 000023 (Table 4), at day 90 showed that 147/172 patients (85.5%) had testosterone C_{ave} levels in the eugonadal zone. Twenty-four (24) patients had C_{ave} testosterone levels <300 ng/dl and one patient had levels above 1050 g/dl 2 h post dose (1274 ± 981 ng/dl).

Table 4: Responder Rate study 000023 - Day 90.

	Testosterone C_{ave}		
	Between 300 and 1050 ng/dl	<300 ng/dl	>1050 ng/dl
Overall (n=172)	147 (85.5%)	24 (14.0%)	1 (0.6%)
23 mg (n=5)	5 (2.9%)	--	--
46 mg (n=12)	8 (4.7%)	4 (2.3%)	--
69 mg (n=155)	134 (77.9)	20 (11.6%)	1 (0.6%)

In total 52/172 patients (30%) had C_{max} levels >1500 ng/dl and 14/172 patients had total testosterone C_{max} ≥2500 ng/dl at day 90 (Table 5), nine patients' DHT/T C_{max} ratio was outside of the normal range (0.05-0.33).

Table 5: Rate of Patients with Total Testosterone C_{max} outside the Normal Range and within Pre-Determined Safety Limits (study 000023).

	C_{max} (ng/dl)			
	≥1500 and ≤1799	≥1800 and ≤2499	>2500	Total >1500
Overall (n=172)	20 (11.6%)	18 (10.5%)	14 (8.1%).	52 (30.2)
23 mg (n=5)	0	0	0	0
46 mg (n=12)	1 (8.3%)	1 (8.3%)	0	2 (16.6%)
69 mg (n=155)	19 (12.3%)	17 (11.9%)	14 (9.0%)	50 (32.3%)

For the 52 patients with total testosterone C_{max} values above 1500 ng/dl (on day 90), the mean C_{ave} was 668 ± 177 ng/dl. There were 14 patients with C_{max} ≥2500 ng/dl at day 90. For one patient the DHT/total testosterone C_{ave} ratio was also outside of the normal range (0.0465).

The pharmacokinetic parameters (C_{max}, T_{max}, C_{min}, T_{min}, AUC_{0-24}, and C_{ave}) of total testosterone on day 1 and day 90 are presented in Table 6. For total testosterone, the mean values for C_{max}, C_{min}, AUC_{0-t}, and C_{ave} were higher on day 90 than day 1. For all three dose levels at day 90, the values for C_{ave} were comparable. The median T_{max} values for testosterone were between 2 h and 4 h, and most of the individual subject values were between 1 h and 6 h, indicating rapid absorption.

Table 6: PK Parameters for Total T– Day 1 and Day 90.

	C_{max} (ng/dl)	**T_{max} (hr)**	**C_{min} (ng/dl)**	**T_{min} (hr)**	**AUC_{0-24} (ng•hr/dl)**	**C_{ave} (ng/dl)**
	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Mean ± SD
Testosterone						
Day 1; 46 mg	490 ± 234	4.00	201 ± 65	0	7,616 ± 2,242	316 ± 92
Day 90; 23 mg	944 ± 253	4.00	317 ± 112	8.00	12,433 ± 3,100	515 ± 132
Day 90; 46 mg	916 ± 514	2.01	219 ± 76	12.1	9,835 ± 3,831	407 ± 160
Day 90; 69 mg	1,432 ± 1,050	2.03	222 ± 89	12.0	11,967 ± 4,439	495 ± 184
Day 90; all doses	1,382 ± 1,017	2.03	225 ± 90	12.0	11,825 ± 4,382	489 ± 182

Further, the MAH showed that on day 90, the DHT/testosterone ratios for C_{max} were within the reference range of 0.05 to 0.33 (Diver *et al*., 2003) for 148/172 (86.1%) of patients.

IV.4.2 Phase III Study 000077

Study design

A multicentre extension trial to evaluate the safety of FE 999303 (testosterone gel) in adult hypogonadal males.

This considers an extension study of study 000023. Of the 172 patients who completed study 000023, 145 patients were enrolled. One hundred twenty-seven (127) of the 145 patients finished the study. Treatment was similar to study 000023 and the pivotal study. Mean age of the population was 57.1 ± 9.4 years and 29/145 (20%) patients were >65 years of age. The primary endpoint of this study was safety. Start dose was the fixed dose at day 56 of study 000023.

Study results

Data from the responder analysis, in the supportive study 000077, at day 90 showed that 87/106 patients (82.1%) had C_{ave} testosterone levels in the eugonadal zone (300 to 1050 ng/dl) (Table 7). Eighteen patients had testosterone levels <300 ng/dl and one patient had levels above 1050 g/dl 2 h post dose (1182 ng/dl).

Table 7: Responder Rate study 000077 – PP Population.

	Testosterone C_{ave}		
	Between 300 and 1050 ng/dl	<300 ng/dl	>1050 ng/dl
Overall (n=106)	87 (82.1%)	18 (17.0%)	1 (0.9%)
23 mg (n=10)	6 (60%)	4 (40 %)-	-
46 mg (n=40)	34 (85%)	46(15.0%)	-
69 mg (n=56)	47 (83.9%)	20 (11.6%)	1 (1.8%)

Of the 106 patients, 12 patients (11.3%) had C_{max} values ≥1500 ng/dl, 6 (5.7%) of these with values between 1500 and 1799 ng/dl, 3 (2.8%) between 1800 and 2499 ng/dl and 3 (2.8%) ≥2500 ng/dl (Table 8).

Table 8: Patients with Total Testosterone C_{max} within Pre-Determined Safety Limits – 24- hour PK Assessment (PP Population, study 000077).

	C_{max} (ng/dl)				
	< 1500	≥ 1500	≥1500 and ≤1799	≥1800 and ≤2499	≥2500
Overall (n=106)	94 (88.7%)	12 (11.3%)	6 (5.7%)	3 (2.8%)	3 (2.8%)
23 mg (n=10)	10 (100%)	0	0	0	0
46 mg (n=40)	34 (85.0%)	6 (15.0%)	2 (5.0%)	2 (5.0%)	2 (5.0%)
69 mg (n=56)	50 (89.3%)	6 (10.7%)	4 (7.1%)	1 (1.8%)	1 (1.8%)

There were two patients with testosterone levels above 1500 ng/ml: one considered possible related to contamination with study treatment and one patient who had administered the gel twice.

IV.4.3 Phase III Study 000127

Study design

The MAH submitted the results of a phase III, open-label, clinical trial to evaluate the efficacy and safety of FE 999303 (testosterone gel) in adult hypogonadal males.

Out of 940 screened patients only 160 (17%) were eligible to be enrolled into the study. This raises the question if there is potential selection bias.
Safety and ITT population both included 159 male patients. Mean age of 54.1 ± 9.3 years. Twenty one 21/159 patients were ≥65 years. Majority of patients 123/159 were white. Mean BMI was 30.7 ± 3.2. According to the protocol ”The full analysis set (FAS) will include all subjects who completed day 90 visit with sufficient PK data to determine $C_{ave(0-24)}$ or discontinued the study early due to safety reasons”. The FAS population included 155 patients.

Patients were to wait at least 6 h after application of the gel to shower or bath. Patients were instructed to administer the study product as follows:

Table 9 Product administration

23 mg dose (one actuation)	46 mg dose (two actuations)	69 mg dose (three actuations)
• 1 actuation shoulder and upper arm A	• 1 actuation shoulder and upper arm A • 1 actuation shoulder and upper arm B	• 1 actuation shoulder and upper arm A • 1 actuation shoulder and upper arm B • 1 actuation shoulder and upper arm A

Patients applied Testavan gel 2%, using the cap applicator, throughout the entire study.

All patients received an initial dose of 23 mg. The maximum dose is 69 mg. The dose of testosterone gel was titrated based on 4 h post-dose serum testosterone measurements, with a range of 500-1050 ng/dl to be used for dose adjustment. Blood samples for titration determination were collected on days 14, 35 and 56. The dose of Testavan gel 2% remained unchanged or was titrated up or down on days 21, 42 and 63, respectively. The dose was fixed by day 63 and the subject remained on that dose until completion of the study.

Study results

At the end of the study (day 90), of the 155 patients (FAS) who had provided sufficient pharmacokinetic data or discontinued early due to safety reasons, primary efficacy results showed that 118 patients (76.1%) had serum testosterone C_{ave} values within the normal range of 300 to 1050 ng/dl (95% CI; 69.4%-82.8%). This FAS analysis (with LOCF method) met the by the MAH pre-defined efficacy criteria.

Further analysis showed that the responder rate is estimated at 78.2% (95% CI, 71.5%-84.8%) in the ITT analysis population with missing C_{ave} imputed using multiple imputation. The ITT, PP and PP completer populations showed that 74.2% (95% CI 67.4%-81.0%), 78.6% (95% CI 71.9%-85.3%) and 82.8% (95% CI 76.5%-89.2%) of the patients had serum testosterone C_{ave} values within the range of 300 to 1050 ng/dl, respectively. It should be noted that the MAH considers the study have met its efficacy criteria if the percentage of patients whose $C_{ave(0-24)}$ serum total testosterone levels were between 300 and 1050 ng/dl on day 90 was ≥75% and the lower bound of the belonging 95% confidence interval was ≥65%.

Table 10 Responder Rate - Day 90 (Sensitivity Analyses - ITT, PP, PP Completers).

	Population	Responder Rate (testosterone C_{ave} between 300 and 1050 ng/dl)	95% CI
Sensitivity Analyses of primary analysis	ITT (n=159)	118 (74.2%)	67.4%, 81.0%
	ITT MI (n=159)	- (78.2%)	71.5%, 84.8%
Sensitivity analysis for the hypothetical treatment effect	PP (n=145)	114 (78.6%)	71.9%, 85.3%
	PP Completers (n=134)	111 (82.8%)	76.5%, 89.2%

The pharmacokinetic parameters (C_{ave}, AUC_{0-tau}, T_{max}, C_{max} and C_{min}) of total T and DHT on Day 90 are presented in Table 11. Testosterone data at day 90 shows that for 139 patients the C_{ave} could be calculated. Five patients were treated with the 23 mg (1 actuation), 45 patients received 46 mg, and 89 patients received the 69 mg dose.

Table 11: PK Parameters for Total T and DHT – Day 90.

Dose on	C_{max} (ng/dl)	T_{max} (hr)	C_{min} (ng/dl)	AUC_{0-tau} (ng•hr/dl)	C_{ave} (ng/dl)	N
Day 90	Mean ±SD	Median	Mean ±SD	Mean ±SD	Mean ±SD	
Testosterone Parameters						
23 mg	721 ± 254	4.02	191 ± 49	8,831± 2,829	368 ± 121	5
46 mg	1,228 ± 640	2.02	277 ± 140	12,245 ± 5,010	506 ± 207	45
69 mg	1,099 ± 595	2.08	229 ± 82	10,590 ± 3,979	438 ± 164	89
DHT Parameters						
23 mg	91.4 ± 34.8	4.12	45.1 ± 21.0	1,579 ± 560	65.9 ± 24.1	5
46 mg	138 ± 66	3.75	62.5 ± 26.4	2,210 ± 956	91.2 ± 38.9	45
69 mg	118 ± 55	3.95	53.1 ± 29.7	1,876 ± 956	77.7 ± 39.7	89

Subgroup analysis considering supra-physiological testosterone concentrations was submitted. Patients were divided in patient with normal testosterone level (<1500 ng/dl), patients with mild testosterone increase (>=1500 ng/dl - <=1800 ng/dl), patients with moderate increase in maximal testosterone concentration (>1800 ng/dl - <=2500 ng/dl) and patients with serious increase in testosterone C_{max}. On day 14, prior to titration, all patients had C_{max} values <1500 ng/dl (**Fout! Verwijzingsbron niet gevonden.**12). On Day 35 after titration on day 14, four (2.6%) patients C_{max} values ≥1500 ng/dl and ≤1800 ng/dl and one (0.6%) had value >2500 ng/dl. On day 56, two (1.3%) patients had values ≥1500 ng/dl and ≤1800 ng/dl, ten (6.5%) had values >1800 and ≤2500 ng/dl, and three (1.9%) had values >2500 ng/dl. At the end of study (day 90), 14 (9.1%) patients had values

≥1500 ng/dl and ≤1800 ng/dl, 12 (7.8%) had values >1800 and ≤2500 ng/dl, and five (3.2%) had values >2500 ng/dl.

Similar results were observed in the FAS population without using LOCF method.

Table 12: Rate of Patients with Total Testosterone C_{max} within Pre-Determined Safety Limits (LOCF).

	C_{max} of total testosterone (ng/dl)			
	<1500 ng/dl	>=1500 ng/dl - <=1800 ng/dl	>1800 ng/dl - <=2500 ng/dl	>2500 ng/dl
N at Day 14	154 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
N at Day 35	149 (96.8%)	4 (2.6%)	0 (0.0%)	1 (0.6%)
N at Day 56	139 (90.3%)	2 (1.3%)	10 (6.5%)	3 (1.9%)
N at Day 90	123 (79.9%)	14 (9.1%)	12 (7.8%)	5 (3.2%)

In all three studies (000127, 000023, 000077) the International Index of Erectile Function (IIEF) Scores showed clinically relevant difference in sexual function from start of treatment to end of the study. A clinically relevant improvement was demonstrated in fatigue from baseline to the end of the study. Similar results were shown for the Short Form-12 (SF-12) Quality of Life Survey and Treatment Satisfaction Questionnaire.

IV.4.4 Responder rates from the clinical studies compared to published results

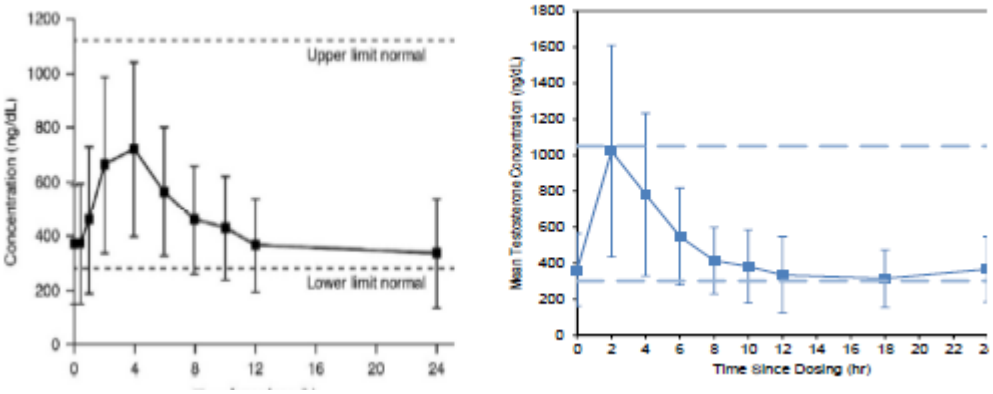
Responder analysis showed that at day 90 (end of study 000023) 85.5% and at the end of the study (study 000077) 82.1% had C_{ave} testosterone levels in the eugonadal zone. These responder data for C_{ave} are in line with the responder rates for other approved testosterone gels (e.g. Androgel 1.62%, responder rate at day 112 in PP 81.6%; EPAR Androgel 1.62%).

Table 13: Comparison of Percentages of Eugonadal C_{ave} Values for Androgel 1.62% and Testavan gel 2%.

Study Day	Percentage of C_{ave} Values Between 300-1000 ng/dl or 300-1050 ng/dl (Trial 00077 and Trial 000127)		
	Androgel 1.62% study		Testavan gel 2%
	Androgel 1.62%	Placebo	
14	65.7%[a]	29.7%	29.1%
35	--	-	60.7%
56	82.5%[a]	34.4%	75.0%
90	--	--	82.0%
112	81.6%[a]	37.0%	--
182	82.2%[a]	28.6%	82.1%[d]
266	78.4%	69.2%[b]	--
364	77.9%	87.0%[b]	--

a Statistically significant difference (p <0.0001) between Androgel 1.62% and Placebo.
b Switched from Placebo to Androgel 1.62% at Day 182.
c FAS population without LOCF.
d The C_{ave} value from Trial 00077 [000077] for 24-hour PK assessment after the Month 3 follow-up visit (after end of Trial 000023 [000023]) but before the end of the study, after they had been on a stabilised dose of Testavan gel 2% for at least 1 month.

Figure 4: Serum Profiles for Total Testosterone on Day 90.



Note: Dotted line indicate normal testosterone range, line represents mean total testosterone, and error bars represents standard deviation.

Tostrex 2%, from Dobs et al. Testosterone gel, from study 000127

IV.4.5 Special populations

Based on scientific data supported by pharmacokinetic data in males with mild and moderate renal impairment in studies 000127 and 000023, it is unlikely that dose adjustments of Testavan 2% is needed in men with mild to moderate renal or hepatic impairment. There are no data on pharmacokinetics of testosterone in males with severe renal or hepatic impairment,. Scientific data, confirmed by pharmacokinetic data from phase III trials 000127 and 000023, indicated that age, race and BMI have no relevant influence on the pharmacokinetics of Testavan 2%.
In clinical practice, serum testosterone levels will be monitored for all patients and the dose adjusted accordingly, this mechanism should take care of any modest effects of renal and hepatic impairment, age, BMI and race on the absorption, metabolism and elimination of testosterone.

Testosterone 2% gel is applied topically. No *in vitro* or *in vivo* interaction studies were performed. Systemic interactions with testosterone are well known.

Literature data with Androgel 1.62% suggest a limited effect of body lotion or sunscreen on the pharmacokinetics of testosterone when they are applied an hour after application of the TRT. Other conditions appear not to have been studied. The following warning is included in section 4.4 of the SmPC “Patients must be cautioned to minimise use of body lotion and sunscreen products at the area of application, at and just after, application of Testavan gel”.

IV.5 Clinical safety

Three hundred ninety five (395) patients treated with Testavan gel 2% were included in the safety analysis. The mean age of patients was 54.8 (range: 25-75) years and 62 (15.7%) patients were of age ≥65 years. The majority of patients were Caucasian (79.7%) and the mean BMI was 30.2 (range: 20-35) kg/m^2. The demographics and clinical characteristics for the phase III trial population (n =339) were similar as for the overall population.

Across the phase II and phase III trials of Testavan gel 2%, 141 (35.7%) patients experienced 269 treatment emergent adverse events (TEAEs). The majority (258/269) of the AEs were mild or moderate in intensity. The most commonly occurring AEs (≥1%) were upper respiratory tract infection reported in 11 (2.8%) patients, bronchitis, blood triglycerides increased, PSA increased, hypertension and cough each in seven (1.8%) patients, nasopharyngitis in six (1.5%) patients, and application site erythema, back pain, epididymitis, rash, gamma-glutamyl transferase (GGT) increase and Hct increased each in four (1%) patients. These side effects are well-known and also included in the labelling of other approved testosterone products.

In the pivotal study (000127) and the extension studies (000023, 000077) 54/339 patients reported an adverse drug reaction. Application site reactions (including rash and erythema), blood triglycerides increased/hypertriglyceridemia and PSA increased were most reported. This is well known for testosterone.

One 69-year-old subject with an ongoing medical history of hypertension, myopia, coronary artery disease, benign prostatic hyperplasia (BPH) and erectile dysfunction at the screening visit and on concomitant cardiovascular (CV) disease medications (hydrochlorothiazide, losartan, epinephrine), experienced a SAE 26 days after starting trial treatment, myocardial infarction, and this event led to the patient's death. The event was not considered to be related to the treatment.

In the pooled safety analysis 62/395 (15.7%) patients were ≥65 years of age. The frequency of AEs and ADRs were higher in patients ≥65 years compared to patient <65 years of age; AEs, 54.8% and 32.1%, respectively; ADRs, 16.1% and 13.5%, respectively. There was no clear difference in the frequency of SAEs between the age groups (3.2% and 2.1%, respectively).

The overall safety profile of Testavan gel 2% based on AEs, SAEs, skin tolerability profile, and laboratory parameters such as Hct, PSA, LFT was similar to that of other approved TRTs testosterone gels included in the safety analysis. Only 10 patients discontinued due to an AE in the clinical program.

Testosterone products have established class labelling for a number of potential safety issues. The MAH has sufficiently addressed the following class labelling: Worsening of Benign Prostatic Hyperplasia (BPH) and Potential Risk of Prostate Cancer; Polycythaemia; Clotting Disorders; Cardiovascular Risk; Potential for Adverse Effects on Spermatogenesis; Females and Males of Reproductive Potential – Effect on Fertility; Use in Pregnancy and Lactation; Hepatic Adverse Effects; Oedema; Gynecomastia; Sleep Apnoea; Lipids; Hypercalcemia; Decreased Thyroxine-binding Globulin.

Cardiovascular risk was subject of the recent article 31 referral (EMEA/H/A-31/1396; October 2014) which resulted in the recommendation to include additional warnings in the SmPC of testosterone containing medicinal products. These recommendations have been incorporated in the proposed SmPC.

In order to demonstrate that Testavan gel 2% had a similar safety profile Table 14 provides the comparison of baseline characteristics of patients included in the clinical development program of Testavan gel 2% compared to the demographics of patients included in studies published for Androgel 1.62% and Tostrex 2%.

Table 14: Demographics and Other Baseline Characteristics of patients included in Trials of Testosterone gel 2% and Published Studies on Approved TRT Gels

Trial/Study	Age (Years) (mean ±SD) Age range (years) Age group <65 Years (%)	BMI (kg/m^2) (Mean ±SD) BMI range (kg/m^2)	Total testosterone (ng/dl) (mean ±SD)	PSA (ng/ml)	IPSS	Hct (%) / haemoglobin (g/dl)
Testavan gel 2%						
Overall Population (n =395)[#]	54.8 ± 9.5 25 - 75 84.3	30.2 ± 3.3 20 - 35	≤300	<3*	≤19@	≤51 / --
Androgel 1.62%						
Kaufman et al. Placebo (n =37) (Phase III primary trial)	55.5 ± 10.3 -- 30	30.6 ± 4.1 --	294	≤2.5	≤15	<48 / <16
Kaufman et al. Androgel 1.62% (n =214) (Phase III extension trial)	53.6 ± 9.5 -- 184	31.3 ± 4.1 --	282	≤2.5	≤15	<48 / <16
Kaufman et al. Androgel 1.62% (n =170) (Phase III extension trial)	52.9 ± 9.6 -- 87.7	31.2 ± 4.2 --	--	≤2.5	≤15	<48 / <16
Tostrex 2%						

Dobs et al. Tostrex 2% (n =149) (Phase III primary trial)	54.5 ± 10.1 29 - 77 -	30.6 ± 3.5 22.1 - 41.0	195.4 ±65.7	--	--	-- / --

*# Overall Population: All adult hypogonadal male subjects enrolled in the six trials (000011, 000023, 000024, 000065, 000077 and 000127). * PSA ≤4 for Trial 000011, @ Not reported for Trial 000011.*

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 Testavan.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Secondary exposure
Important potential risks	• Prostate cancer • Cardiovascular risks • Oedema with or without congestive cardiac failure in patients suffering from severe cardiac, hepatic or renal insufficiency
Missing information	• Safety in elderly males ≥65 years of age

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

IV.7.1 Benefits

Responder analysis showed that at day 90 76.1% (study 00127) and 85.5% (study 000023) of the patients had C_{ave} testosterone levels in the eugonadal zone. At the end of the study 000077 82.1% of the patients had C_{ave} testosterone levels in the eugonadal zone.

At day 90 in the pivotal study 00127 the mean C_{max} after 23 mg, 46 mg, and 69 mg daily was 721 ± 254 ng/dl, 1,228 ± 640 ng/dl, and 1,099 ± 595 ng/dl respectively. The corresponding mean C_{min} values were 191 ± 49 ng/dl, 277 ± 140 ng/dl and 229 ± 82 ng/dl respectively. For study 000023 the mean C_{max} levels at day 90 were 944 ± 253 ng/dl, 916 ± 514 ng/dl and 1,432 ± 1,050 ng/dl, respectively. For mean C_{min} the following results were reported; 317 ± 112 ng/dl, 219 ± 76 ng/dl and 222 ± 89 ng/dl, respectively.

The International Index of Erectile Function (IIEF) Scores showed a consistent clinically relevant improvement in sexual function from start of treatment to end of the study. A consistent clinically relevant improvement was demonstrated in fatigue from baseline to the end of the study. Similar results were shown for the Short Form-12 (SF-12) Quality of Life Survey and Treatment Satisfaction Questionnaire.

IV.7.2 Uncertainties with regard to benefits

The observed mean C_{max} and mean C_{min} for studies 000127, 000023 and 000077 indicated that a considerable proportion of the patients experience testosterone levels outside the eugonadal range. The MAH substantiated that there is a natural variability in total serum testosterone through the day. Excursions to sub-physiological testosterone levels (<300 ng/dl) both in mean testosterone levels (C_{ave}) and trough levels (C_{min}) are more common than excursions to supra-physiological levels with the transdermal TRT products. Based on the available data from literature the MAH showed that excursions of C_{ave} above the eugonadal range are sporadic after an initial dose adjustment period with transdermal TRTs. With Testavan 2% the excursions (C_{ave}>1050 ng/dl = 2.2%) appear to less frequent than with Androgel 1% (C_{ave}>1050 ng/dl= 4.5%) and are comparable to the excursions of Tostran 2% (C_{ave}>1050 ng/dl = 0.7%). With respect to the excursions for C_{max} >1500 ng/dl, the percentage for

Testavan 2% was 22.3%, Tostran 2% was 28.6% and Androgel 1% 25.8%, respectively. Although the excursions for C_{max} appear somewhat higher.

Pivotal study 0000127 was an open-label, non randomised, single arm study. The choice for the non-controlled, open label study has been justified. It should be noted that as known from other placebo controlled studies a placebo response is to be expected. For the primary outcome, given the objective measurement, the placebo effect is probably explained by regression to the mean due to varying testosterone levels. Therefore, a placebo or an active control arm demonstrating at least non-inferiority to an existing product would have been advised. It was agreed during the meetings that provided bridging to scientific literature based on comparable pharmacokinetic profiles could be acceptable. Based on the submitted pharmacokinetic data bridging to scientific literature is considered acceptable.

In recent EU registrations for transdermal TRT products, the stated upper limits of the eugonadal range for testosterone varies from a C_{ave} of 1000 ng/dl up to 1140 ng/dl which underlines the current lack of consensus. The MAH has chosen the upper limit of 1050 ng/dl to use an accepted, conservative criteria for the therapeutical range of transdermal TRT.

The improvement in symptoms related to hypogonadism, fatigue and decreased libido cannot be interpreted clearly due to the lack of a placebo or comparator arm. Therefore, these effects must be interpreted with caution.

IV.7.3 Unfavourable effects

Testosterone is a well-known drug substance which has been approved worldwide for male hypogonadism in multiple strengths and formulations including transdermal gel, intramuscular (IM) preparations, scrotal and transdermal patches, and orally administered agents. The safety of the different testosterone preparations has been demonstrated in clinical practice over the past decades.

Across the phase II and phase III trials of Testavan gel, 141 (35.7%) patients experienced 269 treatment emergent adverse events (TEAEs). The majority (258/269) of the AEs were mild or moderate in intensity. The most commonly occurring AEs were upper respiratory tract infection, bronchitis, blood triglycerides increased, PSA increased, hypertension, cough, nasopharyngitis, application site erythema, back pain, epididymitis, rash, GGT increase and haematocrit increased. Only 19 patients in total experienced testosterone values >2500 ng/dl on day 90, eight of these 19 patients experienced 13 non-serious, mild to moderate AEs. From literature it is known that supra-physiological excursions during daily administrations with transdermal TRTs are generally reported as short, transient, isolated, and sporadic, infrequently affecting the testosterone/DHT ratios and without clear correlation to AEs.

In the pooled safety analysis 62/395 (15.7%) patients were ≥65 years of age. The frequency of AEs and ADRs were higher in patients ≥65 years compared to patient <65 years of age; AEs, 54.8% and 32.1%, respectively; ADRs, 16.1% and 13.5%, respectively. There was no clear difference in the frequency of SAEs between the age groups (3.2% and 2.1%, respectively).

In the clinical studies 7/395 patients (1.8%) had PSA increase TEAEs. Of these, three patients had events that were assessed by the investigator as possibly related to trial treatment. Overall, in the phase III trials, the mean PSA increase from baseline to the last measurement was 0.2 ng/ml, which is in line with similar studies with testosterone containing products (e.g. Androgel 1.62%, Tostrex 2%).

IV.7.4 Uncertainties and limitations about unfavourable effects

The studies were of open label design, hence the observed adverse events cannot be judged against placebo or comparator. The MAH has compared the data obtained in the clinical studies with the safety data from placebo controlled studies available in scientific literature. No major difference in adverse events were noticed, however caution in interpretation is advised.

IV.7.5 Benefit risk balance

Importance of favourable and unfavourable effects

For this application the testosterone pharmacokinetic profile is considered the most important measure. For the currently accepted gel formulations testosterone profile is currently considered a

surrogate parameter. Testosterone concentration can only be used as a surrogate parameter in case the pharmacokinetic profile indicates a stable testosterone steady state. Therefore the pharmacokinetic profile can be used to bridge the efficacy and safety data obtained in the pivotal study with the (literature) data of other registered testosterone gels.

The weakness of this application is that the MAH did not choose to either include a placebo nor a comparator arm in the pivotal study. This approach could be considered acceptable, provided that the gel under assessment is comparable with the gels already marketed, thereby allowing for bridging to literature. The observed testosterone pharmacokinetic profile of Testavan gel was not comparable with that of Androgel 1% (study SC02), but it was similar to that of Tostran 2% and Axiron 2%, other approved testosterone gels. Therefore, the data obtained in the clinical studies can be bridged to the data in literature.

The MAH has sufficiently demonstrated that with the proposed starting dose of 23 mg and titration schedule (2-4 h post dose approximately 14 days and 35 days after starting treatment) the excursions at the supra-physiological level (C_{ave}>1050 ng/dl) appears in line with the observed supra-physiological levels as reported for other testosterone gels. Further, it was demonstrated that the frequency of AEs (37.1%) in the pivotal study (0000127) were comparable or even somewhat less to those observed for other testosterone gels. Notably the frequency of AEs, in study 000023 was only (34.4%). As the pivotal study was an open label study the results should be interpreted with some caution. The data however is reassuring to agree with the proposed posology and titration scheme.

Data on other secondary efficacy parameters showed that patients improved in symptoms related to hypogonadism, fatigue and decreased libido. However, due to the lack of a placebo or comparator arm, it is uncertain how the observed improvement relates to the effects reported after the use of other testosterone containing gels.

The safety of Testavan gel 2% is in line with the known safety profile of testosterone. No new safety findings were observed. The MAH has taken the recent article 31 referral into account and sufficiently taken into account the known class effects of testosterone.

Balance of benefits and risks

The pharmacokinetic profile over 24 h and bioavailability reported after administration of Testavan 2% is comparable with those of other approved testosterone gels. Hence, the data obtained in the clinical studies can be bridged to the data reported in scientific literature.
The reported responder rates for Testavan 2% (which is based on average testosterone concentrations over 24 h) are comparable with the responder rates described in literature.
The safety of Testavan gel 2% is in line with the known safety profile of testosterone. No new safety findings were observed. The MAH has taken the recent article 31 referral into account and sufficiently taken into account the known class effects of testosterone.

In conclusion the benefit/risk ration of Testavan is positive.

V. USER CONSULTATION

The package leaflet has (PL) 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 test consisted of: a pilot test with two participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The member states, on the basis of the data submitted, considered that Testavan 20 mg/g transdermal gel demonstrated a satisfactory risk/benefit profile in the indication *TRT for adult male*

hypogonadism, when testosterone deficiency has been confirmed by clinical features and biochemical tests.
The product has a proven chemical-pharmaceutical quality. The non-clinical data in support of the application are sufficient

From a clinical point of view, the submitted studies demonstrate that the pharmacokinetic profile over 24 h, and bioavailability reported after administration of Testavan 2%, is comparable with those of other approved testosterone gels.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure.

The member states, on the basis of the data submitted, considered that adequate evidence of efficacy and safety has been demonstrated for the approved indication and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 15 February 2018.

Post-approval commitments have been made during the procedure:

- Commitments relating to the ERA of Testavan are listed on page 7 of this report.

VII. REFERENCES

Diver MJ, Imtiaz KE, Ahmad AM, Vora JP, Fraser WD. Diurnal rhythms of serum total, free and bioavailable testosterone and of SHBG in middle-aged men compared with those in young men. Clin Endocrinol (Oxf). 2003 Jun 58(6): 710-7.

Dobs AS, Matsumoto AM, Wang C, Kipnes MS. Short-term pharmacokinetic comparison of a novel testosterone buccal system and a testosterone gel in testosterone deficient men. Curr Med Res Opin. 2004 May;20(5):729-38.

Dobs AS, McGettigan J, Norwood P, Howell J, Waldie E, Chen Y. A novel testosterone 2% gel for the treatment of hypogonadal males. J Androl. 2012 Jul-Aug;33(4):601-7.

Bhasin S, Cunningham GR, Hayes FJ et al; Task Force, Endocrine Society. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2010 Jun;95(6):2536-59.

EAU Guidelines on Male Hypogonadism 2015. http://uroweb.org/wp-content/uploads/18-Male-Hypogonadism_LR1.pdf . Acessed on 16 December 2016.

Gould DC, A novel metered-dose 2% testosterone gel treatment for male hypogonadism, The Journal of Men's Health & Gender 2007; 4:419-427.

Kaufman JM, Miller MG, Garwin JL, Fitzpatrick S, McWhirter C, Brennan JJ. Efficacy and safety study of 1.62% testosterone gel for the treatment of hypogonadal men. J Sex Med. 2011 Jul;8(7):2079-89.

Kaufman JM, Miller MG, Fitzpatrick S, McWhirter C, and Brennan JJ. One-year efficacy and safety study of a 1.62% testosterone gel in hypogonadal men: Results of a 182-day open-label extension of a 6-month double-blind study. J Sex Med 2012;9:1149–1161.

Mazer N, Bell D, Wu J et al., Comparison of the steady-state pharmacokinetics, metabolism, and variability of a transdermal testosterone patch versus a transdermal testosterone gel in hypogonadal men. J Sex Med. 2005 Mar;2(2):213-26.

Stanworth RD, Jones TH. Testosterone for the aging male; current evidence and recommended practice. Clinical Interventions in Aging. 2008;3(1):25-44.

Steidle C, Schwartz S, Jacoby K et al. AA2500 testosterone gel normalizes androgen levels in aging males with improvements in body composition and sexual function. J Clin Endocrinol Metab. 88:2673-2681, 2003.

Wiehle R, Cunningham GR, Pitteloud N et al. Testosterone Restoration by Enclomiphene Citrate in Men with Secondary Hypogonadism: Pharmacodynamics and Pharmacokinetics. BJU Int. 2013 Jul 12.

Wittert GA, Harrison RW, Buckley MJ, Wlodarczyk J. An open-label, phase 2, single centre, randomized, crossover design bioequivalence study of AndroForte 5 testosterone cream and Testogel 1% testosterone gel in hypogonadal men: study LP101. Andrology. 2016 Jan;4(1):41-5.

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
NL/H/3958/001/IA/001/G	The Marketing Authorization Holder (MAH) in Italy (CMS), has changed the address.	--	5-11-2018	Approved	--
NL/H/3958/001/IB/002/G	MAH is submitting this grouped variation to apply for the approval of two consequential variations: • addition of secondary packaging site (Type IAIN B.II.b.I.a) • addition of pack size for the finished product (Type IB B.II.e.5.a.2)	--	27-2-2019	Approved	--