Decentralised Procedure

RMS Final Assessment report

OVERVIEW AND LIST OF QUESTIONS

Testavan 20mg/g gel voor transdermaal gebruik
(Testosterone)

NL/H/3958/001/DC

Applicant: Ferring BV

Reference Member State	The Netherlands
Start of the procedure:	6 March 2017
Date of this report:	15 February 2018

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ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product in the RMS	**Testavan 20mg/g** **gel voor transdermaal gebruik**
Name of the drug substance (INN name):	testosterone
Pharmaco-therapeutic group (ATC Code):	Androgens (ATC code: G03B A03)
Pharmaceutical form(s) and strength(s):	23 mg of testosterone per actuation
Reference Number(s) for the Decentralised Procedure	NL/H/3958/001/DC
Reference Member State:	NL
Concerned Member States:	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MT, NO, PT, RO, SE, SI, SK and UK
Legal basis of application:	Article 8(3), mixed dossier
Applicant (name and address)	Ferring BV Polarisavenue 144, 2132JX Hoofddorp, NL
Names and addresses of all proposed manufacturer(s) responsible for batch release in the EEA	Ferring Controlled Therapeutics Limited 1 Redwood Place, Peel Park Campus, East Kilbride Glasgow, G745PB, UK
Names and addresses of all proposed manufacturer(s) of the medicinal products	<u>Batch control testing:</u> Orion Pharma Turku 20360, Finland Orion Pharma Espoo 02200, Finland Lunaria spol s.r.o. Videnska 125 Brno CZ-61900, CZ <u>Packaging:</u> Ferring Controlled Therapeutics Limited 1 Redwood Place, Peel Park Campus, East Kilbride Glasgow, G745PB, UK Orion Pharma Turku 20360, Finland

Names and addresses of all proposed manufacturers of the active substance	Aspen Oss B.V. Kloosterstraat 6, 5349 AB, Oss, NL/ Veersemeer 4, 5347JN, Oss, NL
Names and addresses of all proposed ASMF holders (if different from manufacturer of active substance)	*N/A*
Names and addresses of all proposed CEP holders (if different from manufacturer of active substance)	*See above*
RMS contact person	**Name** [redacted] Tel: Email:
Names of the assessors:	**Quality**: [redacted] **Name(s)** **Non-clinical**: **Name(s)** **Clinical** : **Name(s**) **Pharmacovigilance / Risk Management Plan:** **Name** [redacted]

LIST OF ABBREVIATIONS

ACTH	Adrenocorticotropic hormone
ADR	Adverse Drug Reaction
AE	Adverse Event
AUC	Area Under Curve
BfArM	German Federal Institute for Drugs and Medical Devices
BMI	Body Mass Index
BPH	Benign Prostatic Hyperplasia
Cave	Average concentration
CI	Confidence Interval
CV	Cardiovascular
DHT	Dihydrotestosterone
DRE	Digital Rectal Examination
ECG	Electrocardiogram
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle-stimulating Hormone
GCP	Good Clinical Practice
GFI	Global Fatigue Index
GGT	Gamma-glutamyl Transferase
Hct	Haematocrit
HPLC	High Performance Liquid Chromatography
ICH	International Council for Harmonisation
IIEF	International Index of Erectile Function
INR	International normalised ratio
IM	Intramuscular
ISS	Integrated Summary of Safety
ITT	Intention-to-Treat
LFT	Liver Function Tests
LH	Luteinising Hormone
LHRH	Luteinising hormone-releasing hormone
LOCF	Last Observation Carried Forward
MACE	Major Adverse Cardiovascular Events
MAF	Multidimensional Assessment of Fatigue
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MEB	Medicines Evaluation Board
MI	Multiple Imputation
PCS	Physical Component Summary
PE	Pulmonary Embolism
PK	Pharmacokinetics
PP	Per Protocol
PSA	Prostate Specific Antigen
SAE	Serious Adverse Event
SF-12	Short Form 12 Health Survey
SHBG	Sex Hormone-binding Globulin
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SPA	Special Protocol Assessment
TEAE	Treatment-Emergent Adverse Event
TRT	Testosterone Replacement Therapy

I RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Testavan 20mg/g gel voor transdermaal gebruik as *Testosterone replacement therapy for adult male hypogonadism, when testosterone deficiency has been confirmed by clinical features and biochemical tests*, **is approvable.**

II EXECUTIVE SUMMARY

II.1 Problem statement

Male hypogonadism is a clinical condition characterised by a low serum testosterone level (morning serum total testosterone levels is less than 300 ng/dl [10 nmol/l]) in combination with a diversity of symptoms and signs such as reduced libido and vitality, decreased muscle mass, increased fat mass, depression, and others. Hypogonadism is caused by insufficient testosterone secretion by the testes, and two basic types of male hypogonadism are identified:

- Primary hypogonadism (congenital or acquired): testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (follicle stimulating hormone [FSH], luteinising hormone [LH]) above the normal range
- Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or luteinising hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumours, trauma, or radiation. These men have low testosterone serum concentrations, but have gonadotropins in the normal or low range.

In adult-onset hypogonadism Testosterone Replacement Therapy (TRT) may improve symptoms, but weight reduction, lifestyle modification and good treatment of comorbidities are important also.

The goal of testosterone replacement therapy (TRT) in hypogonadal men is to restore testosterone levels to approximately the level of healthy men and to alleviate the symptoms associated with testosterone deficiency (body composition, metabolic control, psychological and sexual well-being). Randomised trials show a correlation between restored physiological testosterone levels, muscle mass and strength measured as leg press strength and quadriceps muscle volume[1]. Similar positive results are shown in meta-analysis addressed to value the role of exogenous testosterone in bone mineral density[1]. Body composition is influenced by testosterone therapy in hypogonadal men, with a consequent decrease of fat mass and an increase in lean body mass[1]. TRT presents positive effects in glycaemic and lipid control, insulin resistance and visceral adiposity in hypogonadal men with impaired glucose tolerance and lipid profile with a consequent decrease of mortality[1]. A strong correlation between decreased testosterone levels and increased cardiovascular mortality has been reported in meta-analyses and retrospective studies showing that total-testosterone and free-testosterone in the normal range are related to reduced all-cause mortality[1].

The risks associated with testosterone substitution are controversial. Most widely discussed is the possible stimulation of prostate cancer by testosterone. Other possible risks include worsening symptoms of benign prostatic hypertrophy, liver toxicity, hyperviscosity, erythrocytosis, worsening untreated sleep apnoea or severe heart failure.

[1] Guidelines on Male Hypogonadism, European Association of Urology 2015.

Testosterone is a well-known endogenous substance which has been approved and used as replacement therapy worldwide for decades and is available as approved products in several strengths and formulations, including intramuscular (IM) preparations, scrotal and transdermal patches, transdermal gel, and orally administered agents.

The available TRT formulations differ in pharmacokinetics (PK) and safety profiles. Some TRT formulations (especially intramuscular injection of short-acting testosterone esters) result in supraphysiological peaks and hypogonadal troughs in testosterone levels. These fluctuations in testosterone levels may yield variations in libido, sexual function, energy, and mood[2]. A "roller coaster" effect can also occur, characterized by alternating periods of symptomatic benefit and a return to base-line symptoms, corresponding to the fluctuations in serum testosterone levels[3,4]. Oral formulations are achieving variable levels of testosterone within the eugonadal range with need of several daily doses. With the later developed scrotal and transdermal patches, products with steady-state testosterone levels became available to patients. The patches are associated with high frequency of application site reactions.

It has been recommended that the optimal serum testosterone level for efficacy and safety should be in the mid range to lower young-adult-male serum testosterone levels as the therapeutic goal[5].

Testosterone containing gels all advise a staring dose in the mid-rang of the product (50 – 60 mg daily) with a titration decision based on a pre-dose testosterone level.

In common for the topical formulations, is the risk of secondary exposure to others if appropriate precautions are not taken. Recent development efforts have therefore focused on increasing the bioavailability to minimise the amount of unabsorbed testosterone on the skin.

II.2 About the product

Testosterone (or FE 999303) belongs to the pharmacotherapeutic class of androgens (ATC code: G03B A03). Testavan gel is delivered as a transdermal gel to be applied to the upper arm and shoulder using a cap applicator.

Testosterone, the primary androgenic hormone, and the metabolite dihydrotestosterone (DHT) are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex and other male characteristics.

The goal of testosterone replacement therapy (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).

Therapeutic indications

Testosterone replacement therapy for adult male hypogonadism, when testosterone deficiency has been confirmed by clinical features and biochemical tests.

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[2] McClure RD, Oses R, Ernest ML: Hypogonadal impotence treated by transdermal testosterone. *Urology*. 1991;37(3):224.

[3] Bhasin S, Bremner WJ. Emerging issues in androgen replacement therapy. J Clin Endocrinol Metab. 1997;82:3–8.

[4] Comhaire FH. Andropause: hormone replacement therapy in the aging male. EurUrol. 2000;38:655–662.

[5] Zitzmann M, Nieschlag E. Androgen receptor gene CAG repeat length and body mass index modulate the safety of long-term intramuscular testosterone undecanoate therapy in hypogonadal men. J Clin Endocrinol Metab. 2007;92:3844–3853.

The recommended starting dose of Testavan gel is **23 mg testosterone** (one pump actuation) applied once daily. To ensure proper dosing, serum testosterone levels should be periodically measured and dose titrated to maintain serum testosterone levels.

The serum testosterone level should be measured **2-4 hours after dosing** approximately 14 days and 35 days after starting treatment or after a dose adjustment. If the serum testosterone concentration is **below 17.3 nmol/l (500 ng/dl)**, the daily Testavan dose may be increased by 1 pump actuation. If the serum testosterone concentration **exceeds 36.4 nmol/l (1050 ng/dl)**, the daily Testavan dose may be decreased by 1 pump actuation.

Dose titration should be based on both serum testosterone levels and the existence of clinical signs and symptoms related to testosterone deficiency.

Development program and regulatory advice

The development program was discussed with various regulatory authorities (FDA, BfArM and MEB). The pivotal phase 3 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 testosterone replacement therapy. 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.3 General comments on the submitted dossier

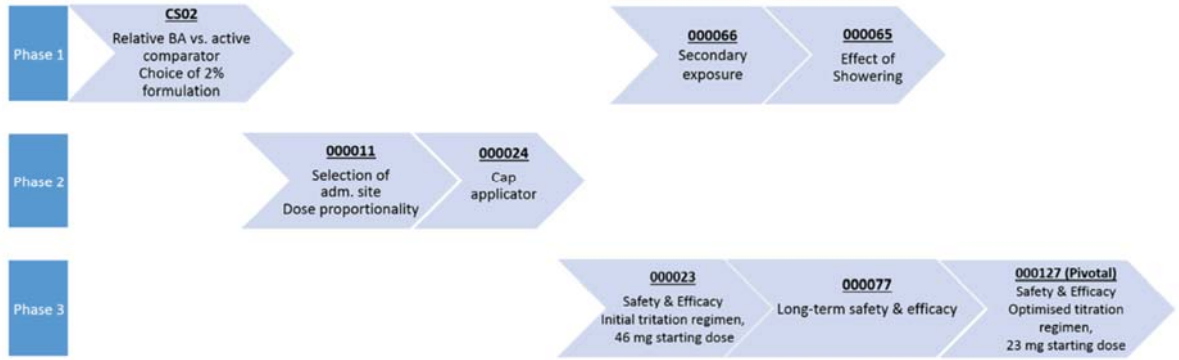
The legal basis for the application is according to article 8(3) of Directive 2001/83/EC as a 'full-mixed' dossier (see above). With the Netherlands acting as Reference member state the applicant applies for a registration in the following members states: **NL**, AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MT, NO, PT, RO, SE, SI, SK and UK.

For substantiation of the proposed indication (see above) the applicant submitted the following clinical program which includes phase 1 and 2 clinical trials that provided data to support the dose titration scheme to be used in phase 3 clinical trials and the proposed product labelling and a phase 1 bioavailability study to bridge the clinical data with the data from scientific literature (Table 1 and Figure 1).

Table 1: Clinical Development Program for Testavan gel 2%.

Phase	Trial ID ***Objective***	Design	Treatment(s) **Dose**	Subjects	Population
1	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
1	000065 *Single dose PK after showering*	Open-label, Randomised crossover	Testosterone gel (FE 999303) 2%, 69 mg	Total: 16	Adult hypogonadal males
1	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
2	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
2	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
3	000023 *Efficacy (PK); safety*	Open-label, nonrandomised	Testosterone gel (FE 999303) 2%, 23, 46 or 69 mg based on titration criteria	Total: 180	Adult hypogonadal males
3	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
3	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%.



II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug Substance
General information
The drug substance is testosterone, an established active substance described in the European Pharmacopoeia. 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.
A CEP has been provided. The CEP does not cover information concerning container closure system and stability. The CEP holder is Aspen Oss B.V. and the CEP number is: R1-CEP 2000-037-Rev 03.

Manufacturing process
The drug substance is manufactured by Aspen Oss B.V., The Netherlands. The manufacturing process is covered by the CEP.

Quality control of drug substance
The drug substance specification is in line with the Ph. Eur.. and the additional requirement as included on the CEP. The specification is acceptable. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three production scale batches.

Stability of drug substance
The CEP does not describe a re-test period of the drug substance. Therefore, the applicant has

included stability data for the drug substance, on the basis of the provided data a re-test period of 60 months, when stored below 25°C, can be granted.

Drug Product

Composition

The product at issue concerns a transdermal gel with 2% testosterone. The list of excipients: ethanol 96 %, propylene glycol, diethylene glycol monoethyl ether, carbomer homopolymer type C (Carbomer 980), trolamine, disodium edetate and purified water. The proposed product is filled into a metered dose-dispenser, and a cap-applicator. The cap applicator has been CE-marked as a class I medical device. The excipients and packaging are usual for this type of dosage form.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies aimed to optimise the viscosity (by varying the concentrations of carbomer, trolamine and sodium edetate) and permeation (by testing various testosterone gel formulations on pig and human skin) 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

[redacted]

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.

Excipients

The excipients comply with the Ph. Eur. These specifications are acceptable, and include a separate limit for the viscosity of carbomer.

Quality control of drug product

The product specification includes tests for appearance, pH, viscosity, identity (of the drug substance), assay (of the drug substance, ethanol, diethylene glycol monoethyl ether, propylene glycol), 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). The analytical methods have been adequately described and validated. The methods used for the assay and impurities have been shown to be stability indicating.
Batch analytical data from the proposed production sites have been provided for twelve production-scale and three laboratory-scale batches. Compliance with the release specification has been demonstrated.

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 6 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 (the accompanying dose-dispenser). 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.

Other information

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.

III.2 Non clinical aspects

Discussion on 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.

Non-clinical overview and summaries on the pre-clinical pharmacology, pharmacokinetics and toxicology have been provided. The applicant reviewed the relevant literature for testosterone from 1968 up to 2016 and summarises this in the non-clinical overview and non-clinical summaries, which are of acceptable quality and appropriate. The applicant provided a few new studies, i.e. pharmacokinetic studies on the transdermal absorption and toxicology studies related to local tolerance and leachables in the product.

Pharmacology

The active substance in Testavan gel is testosterone. Testosterone is a very well established endogenous hormone. The primary and secondary pharmacological effects of testosterone as well as the safety pharmacology have been clinically well-established. Therefore, additional nonclinical or safety pharmacology testing is not needed.

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 SHBG or albumin. Once in the circulation, testosterone distributes to a variety of tissues. 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 new in vitro pharmacokinetic studies assessing the percutaneous absorption of testosterone from Ferring's testosterone gel (FE 999303, 1 and 2% strengths) using pig or human skin showed a higher transdermal drug delivery than with a comparator product.

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 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 testosterone replacement therapy.

In addition to the available published information on testosterone, Ferring 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 sensitization 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 36 month storage study concluded that all leachables from the metered-dose dispenser were considered to be of no safety concern for the intended treatment. The cap applicator leachables study was performed over a period of 53 days

(30/75% 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.

Environmental Risk Assessment (ERA)

Summary of main study results for testosterone

Substance (INN/Invented Name): testosterone					
CAS-number (if available): 58-22-0					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or …	3.32			not P
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	3.32			
	BCF	-			
Persistence	ready biodegradability	-			
	DegT50 (compartment)	-			
Toxicity	NOEC algae NOEC crustacea NOEC fish	-			
	CMR	-			not P
PBT-statement :	TBD				Testosteron
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surface\ water}$, default	0.345	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)	The substance is a hormone that influences both development and reproduction of fish				(Y)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	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	
Daphnia sp. Reproduction Test	OECD 211	NOEC	TBD	µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	TBD	µg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	TBD	µg/L	respiration
Phase IIb Studies					
Bioaccumulation/*Species*	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/*Species*	OECD 207	NOEC	TBD	mg/kg	
Collembola, Reproduction Test/*Species*	ISO 11267	NOEC	TBD	mg/kg	
Sediment dwelling organism/*Species*	OECD 218	NOEC	TBD	mg/kg	

TBD = to be determined

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 dossier is incomplete. An ERA cannot be performed in absence of data. The applicant 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 applicant 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 applicant 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 Koc >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 PECsediment. Applicable tests are those with Hyalella sp; Lumbriculus sp. (OECD 225) or Chironomus sp. (OECD 218 or 219).

III.3 Clinical aspects

III.3.1 Pharmacology

III.3.1.1 Pharmacokinetics

To demonstrate that Testavan gel 1% and 2% had similar bioavailability and a similar kinetic profile the applicant performed a phase 1 study (CS02) in 10 chemical castrated males. Further this study was used for dose finding, as no formal dose finding studies were submitted.

III.3.1.1.1 study (CS02)

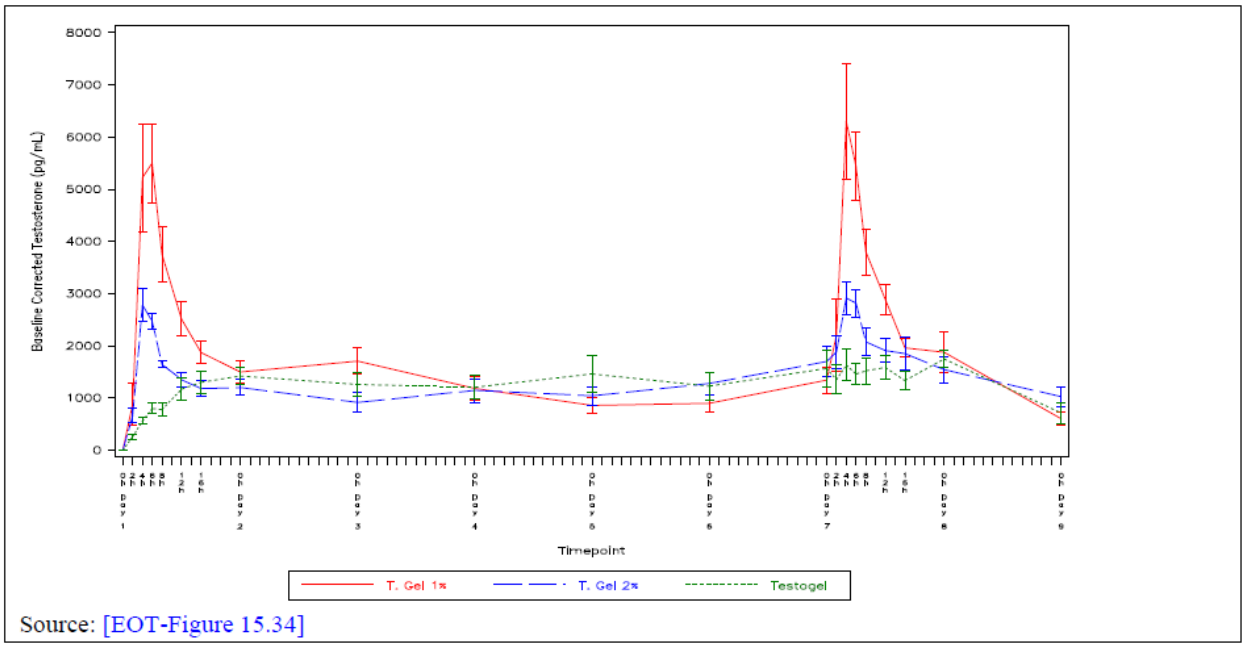
Title FE 999303 CS02: A Randomised, Open-label, Active Control, Multiple Dose 3-Way Cross-over Relative Bioavailability Study of two new Testosterone Gel (FE 999303) Formulations in Comparison to TESTOGEL in Down-regulated Healthy Men.

A total of 31 patients were screened, 15 of whom were enrolled into the run-in phase and received at least one DECAPEPTYL administrations. 11 patients were randomised into one of six possible treatment sequences, while 3 patients were not randomised due to not fulfilling the inclusion/exclusion criteria on Day -1 and 1 subject withdrew consent prior to randomisation. Two patients each were randomised to each of the treatment sequences except for the sequence TESTOGEL 1% (or Androgel 1%) – Testavan gel 1% - Testavan gel 2%, to which only one subject was randomised. All randomised subjects received the study medication in the first period as intended, while one subject withdrew consent during treatment period 2. Thus, 10 patients completed all three periods. Each subject received a daily administration for 7 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 treatment period.

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.

PK was 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)).

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 PK parameters.

Pharmacokinetic Parameter	Day	Testavan gel 1% N=11	Testavan gel 2% N=10	TESTOGEL 1% N=11
AUCT (ng/ml•h) Mean (SD) Geometric mean (%CV) Range	1	 61.5 (24.2) 57.3 (39) 32.0-105.6	 34.0 (5.8) 33.6 (17) 24.5-44.1	 23.1 (8.7) 21.6 (38) 10.3-41.8
AUCT (ng/ml•h)	7			

Mean (SD) Geometric mean (%CV) Range		71.5 (27.6) 66.9 (39) 37.0-121.9	47.6 (17.7) 44.9 (37) 26.0-84.4	35.8 (13.6) 33.4 (38) 17.0-62.9
F_{rel} (% of TESTOGEL) Mean (SD) Range	1	274 (70) 157-377	178 (70) 86-306	100
F_{rel} (% of TESTOGEL) Mean (SD) Range	7	212 (112) 93-455	152 (80) 52-315	100

The bioavailability data shows that Testavan gel 2% shows less bioavailability 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.

Based on this study the applicant decided to use the Testavan gel 2% for further development in the clinical program.

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

Two other phase 1 trials were conducted to provide information on the effect of showering on the absorption of Testavan gel 2% (Trial 000065) and the transfer of testosterone from treated male patients to their female partners following application of Testavan gel 2% (trial 000066).Showering 1 and 2 hours after application of Testavan gel 2% decreased the 24-hour average total testosterone concentration (C_{ave}) by 19.2% and 14.3%, respectively, compared to not showering after Testavan gel 2% administration. Showering 6 hours following Testavan gel 2% administration did not result in a decrease in C_{ave}.

The potential for testosterone transfer of Testavan gel 2% applied to the intact skin of the shoulder and upper arm was evaluated in Trial 000066 (trial 000066). 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. Two phase 2 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 was 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} ($p < 0.05$). This information should be added to the SmPC section 5.2.

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 PK 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.

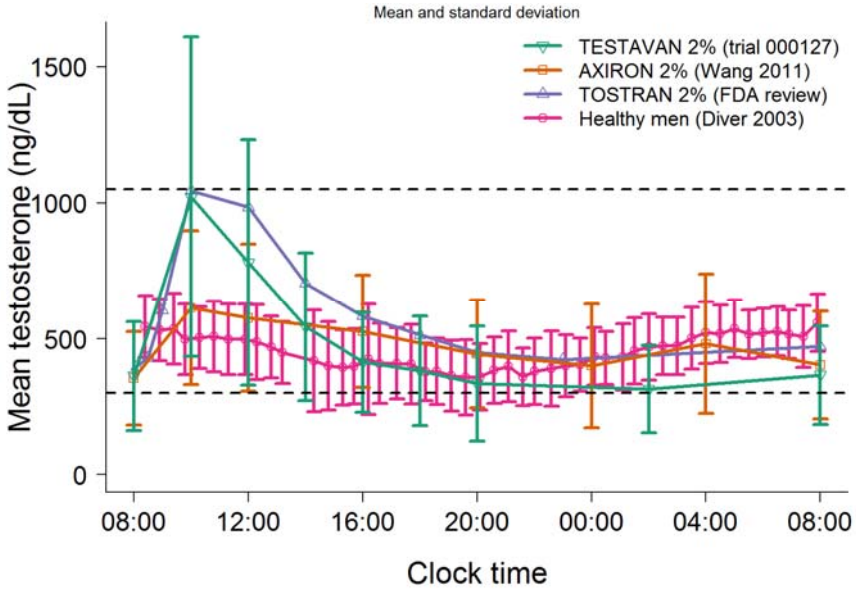
The results of Trial 000024 demonstrated that 46 mg of Testavan gel 2% applied to the shoulder/upper arm using the cap applicator consistently led to serum testosterone levels within the therapeutic range (between 300 and 1050 ng/dl). In addition, for evaluation of restoration of testosterone levels to the normal range, the following PK limits based on Cmax were assessed: at least 85% of patients with Cmax below 1500 ng/dl, at most 5% of patients with Cmax between 1800 and 2499 ng/dl and no patients with Cmax of 2500 ng/dl or more. The 46 mg dose did not result in any patients with Cmax >1500 ng/dl, whereas this was the case in 3 (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 3 Trial 000023.

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 applicant made a estimation of the absolute bioavailability 8-22% for Testavan 2% in hypogonadal males. This is roughly in line with the absolute bioavailabilities 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 PK 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 Cmax/Cmin ratio of~3 was observed for all products except TESTIM 1%, which showed a somewhat lower fluctuation of 2. Mean Cmin levels were comparable for all products (Table 3).

In the clinical studies with dose titration applied, Cmax values of TESTAVAN 2% gel were similar to or slightly lower than those of TOSTRAN 2% (Figure 3), and a similar fluctuation Cmax/Cmin was observed for TESTAVAN 2% and TOSTRAN 2%. A somewhat lower fluctuation of testosterone was observed for AXIRON 2% ratio ~3. The PK 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 PK 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%	ANDROGEL 1%	TESTIM 1%
Reference	[000024, 5.3.3.2]	[000011, 5.3.3.2]	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%*

Special populations.
Based on scientific data supported by PK 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, this has been acknowledged in the SmPC. Scientific data, confirmed by PK data from phase 3 trials 000127 and 000023, indicated that age, race and BMI have no relevant influence on the PK 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 applicant proposes the following warning 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".
The proposed warning for the SmPC is agreed with.

III.3.1.2 Pharmacodynamics
No formal pharmacodynamic studies were performed.

III.3.2 Clinical efficacy

No formal dose finding studies were performed by the applicant. The applicant used the data available of the phase 2 and phase 3 studies (e.g. study 000023 and 000077) to determine the starting dose (e.g. **23 mg testosterone**) and sampling time for titration purposes (**4 hrs post-dose**) to be used in the pivotal study 000127.

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

III.3.2.1 Study 000127
A Phase 3, 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 hours after application** of the gel to shower or bath. Patients were instructed to administer the study product as follows:

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-hour post-dose** serum T 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.

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

Table 4: Responder Rate (FAS population)

RESPONSE	YES	118/155 (76.1%)
	95% CI	(69.4%, 82.8%)

Response: Cave serum total Testosterone levels between 300 and 1050 ng/dl, inclusive. 95% CI of the proportion for responder is based on the normal approximation to the binomial distribution.
A subject will be considered treatment failure, if no sufficient PK data is available from any of the visits.
Patients withdrawn for safety reasons are considered treatment failures regardless of their PK results.

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% (67.4%, 81.0%), 78.6% (71.9%, 85.3%) and 82.8% (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 applicant 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 5 Responder Rate - Day 90 (Sensitivity Analyses - ITT, PP, PP Completers).

	Population	Responder Rate (Testosterone Cave 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}, $AUC_{0\text{-}tau}$, T_{max}, C_{max} and C_{min}) of total T and DHT on Day 90 are presented in Table 6. 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 6: PK Parameters for Total T and DHT – Day 90.

Dose on	**C_{max} (ng/dl)**	**T_{max} (hr)**	**C_{min} (ng/dl)**	**$AUC_{0\text{-}tau}$ (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 (Table 7). On Day 35 after titration on Day 14, 4 (2.6%) patients had C_{max} values ≥1500 ng/dl and ≤1800 ng/dl and one (0.6%) had value >2500 ng/dl. On Day 56, 2 (1.3%) patients had values ≥1500 ng/dl and ≤1800 ng/dl, 10 (6.5%) had values >1800 and ≤2500 ng/dl, and 3 (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 5 (3.2%) had values >2500 ng/dl.

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

Table 7: Rate of Patients with Total Testosterone C_{max} within Pre-Determined Safety Limits (LOCF).

C_{max} OF TOTAL TESTOSTERONE(ng/dl)	DAY 14	N	154
		<1500 ng/dl	154 (100.0%)
		>=1500 ng/dl - <=1800 ng/dl	0 (0.0%)
		>1800 ng/dl - <=2500 ng/dl	0 (0.0%)
		>2500 ng/dl	0 (0.0%)
	DAY 35	N	154
		<1500 ng/dl	149 (96.8%)
		>=1500 ng/dl - <=1800 ng/dl	4 (2.6%)
		>1800 ng/dl - <=2500 ng/dl	0 (0.0%)
		>2500 ng/dl	1 (0.6%)
	DAY 56	N	154
		<1500 ng/dl	139 (90.3%)
		>=1500 ng/dl - <=1800 ng/dl	2 (1.3%)
		>1800 ng/dl - <=2500 ng/dl	10 (6.5%)
		>2500 ng/dl	3 (1.9%)
	DAY 90	N	154

		<1500 ng/dl	123 (79.9%)
		>=1500 ng/dl - <=1800 ng/dl	14 (9.1%)
		>1800 ng/dl - <=2500 ng/dl	12 (7.8%)
		>2500 ng/dl	5 (3.2%)

III.3.2.2 Study 000023

A Phase 3, Open-Label, Non-Randomized, 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 ± 9.8 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 56.

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 8), 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 1 patient had levels above 1050 g/dl 2 hrs post dose (1274 ± 981 ng/dl).

Table 8: 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 14/52 patients had total T C_{max} ≥2500 ng/dl at Day 90 (Table 9), 9 patients' DHT/T C_{max} ratio was outside of the normal range (0.05-0.33).

Table 9: Rate of Patients with Total Testosterone C_{max} outside the Normal Range and within Pre-Determined Safety Limits (study 000023).

C_{max} (ng/dl)	23 mg (n=5)	46 mg (n=12)	69 mg (n=155)	Overall (n=172)
≥1500 and ≤1799	0	1 (8.3%)	19 (12.3%)	20 (11.6%)
≥1800 and ≤2499	0	1 (8.3%)	17 (11.9%)	18 (10.5%)
>2500	0	0	14 (9.0%)	14 (8.1%)
Total >1500	0	2 (16.6%)	50 (32,3%)	52 (30.2%).

For the 52 patients with total T 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 (14S017) the DHT/T Cave ratio was also outside of the normal range (0.0465).

PK Parameters for Total T

The pharmacokinetic parameters (C_{max}, T_{max}, C_{min}, T_{min}, AUC_{0-24}, and C_{ave}) of total T on Day 1 and Day 90 are presented in Table 10. For total T, 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 and 4 hours, and most of the individual subject values were between 1 and 6 hours, indicating rapid absorption.

Table 10: 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 applicant 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.

III.3.2.3 Study 000077

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 ± 9.5 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.

Data from the responder analysis (Table 11), 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 11). Eighteen patients had testosterone levels <300 ng/dl and 1 patient had levels above 1050 g/dl 2 hrs post dose (1182 ng/dl).

Table 11: 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 12).

Table 12: Patients with Total Testosterone C_{max} within Pre-Determined Safety Limits – 24- hour PK Assessment (PP Population, study 000077).

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

There were two patients with testosterone levels above 1500 ng/ml that was possible related to contamination and one patient who had administered the gels twice.

In all three studies (e.g. 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.

III.3.2.4 Responder rates from the clinical studies compared to published results

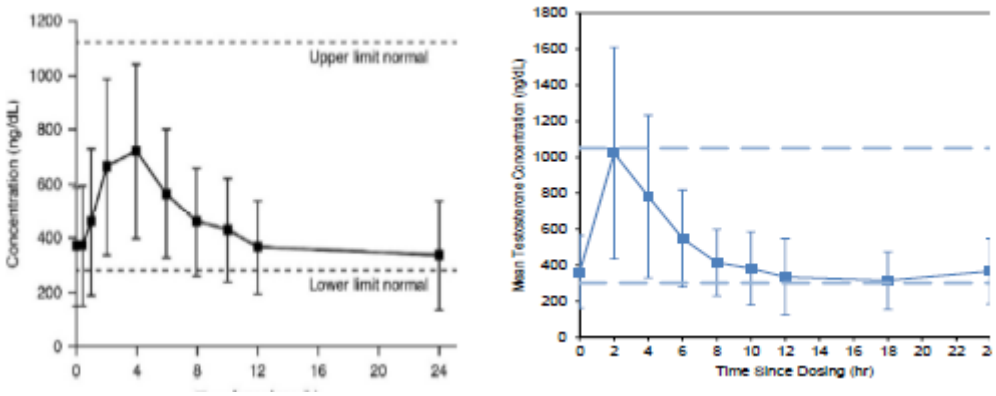
Responder analysis showed that at day 90 (end of study 000023) 85.5% and at the end of the study (study 000077) 82.1% had C_{ave} testosterone levels in the eugonadal zone. These responder data for C_{ave} are in line with the responder rates for other approved testosterone gels (e.g. Androgel 1.62%,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

Table 13: Comparison of Percentages of Eugonadal Cave Values for ANDROGEL 1.62% and Testavan gel 2%.

	Percentage of C_{ave} Values Between 300-1000 ng/dl or 300-1050 ng/dl (Trial 00077 and Trial 000127)		
Study Day	**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 Cave value from Trial 00077 [000077, 5.3.5.4] for 24-hour PK assessment after the Month 3 follow-up visit (after end of Trial 000023 [000023, 5.3.5.4]) 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

III.3.3 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 3 trial population (n =339) were similar as for the overall population.

Across the phase 2 and phase 3 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 7 (1.8%) patients, nasopharyngitis in 6 (1.5%) patients, and application site erythema, back pain, epididymitis, rash, GGT (Gamma-glutamyl Transferase) increase and Hct increased each in 4 (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 study (000023/000077) 24/339 patients (7.1%) 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. The applicant has addressed these ADRs in the SmPC.

One [redacted] subject with an ongoing medical history [redacted] experienced a SAE [redacted] 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 applicant 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 (see SmPC assessment).

The applicant has also addressed the other identified class labelling in the proposed SmPC (see SmPC assessment).

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/m²) (Mean ±SD) BMI range (kg/m²)	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. (4) Placebo (n =37) (Phase 3 primary trial)	55.5 ± 10.3 - 30	30.6 ±4.1 -	294	≤2.5	≤15	<48 / <16
Kaufman et al. (4) ANDROGEL 1.62% (n =214) (Phase 3 extension trial)	53.6 ± 9.5 - 184	31.3 ±4.1 -	282	≤2.5	≤15	<48 / <16
Kaufman et al. (5) ANDROGEL 1.62% (n =170) (Phase 3 extension trial)	52.9 ± 9.6 - 87.7	31.2 ±4.2 -	-	≤2.5	≤15	<48 / <16
TOSTREX 2%						
Dobs et al. (6,17) TOSTREX 2% (n =149) (Phase 3 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.*
BMI: Body Mass Index; Hct: Haematocrit; IPSS: International Prostate Symptom Score; PSA: Prostate-Specific Antigen; SD: Standard Deviation

Summary Pharmacovigilance system

The Applicant has submitted a signed Summary of the Applicant's and/or Proposed Future MAH's* Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

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 (*insert name of medicinal product*)."

Safety specification

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

Pharmacovigilance Plan

The applicant proposes only routine pharmacovigilance activities.

Risk minimisation measures

The applicant provided the summary table of risk minimisation measures, which could be found from page 84 -90 of the updated RMP, version 2.0, dated 20 September 2017.

No additional risk minimisation measures are proposed by the applicant, which is acceptable. The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

VI.2.1 Overview of disease epidemiology

Male hypogonadism is a condition in which the body does not produce enough testosterone. Testosterone is made naturally in your body in your testicles. It helps produce sperm and to develop and maintain the male sexual characteristics such as deep voice and body hair. It is also necessary for normal sexual function and sex drive. Testosterone also helps to maintain muscle size and strength.

There is a high prevalence of hypogonadism in the older adult male population. Hypogonadism increases with age and is significantly associated with obesity, type 2 diabetes, hypertension, osteoporosis and metabolic syndrome. Prevalence is low in men less than 70 years of age (3.1-7.0%) and increased to 18.4% in males above 70 years of age. No differences are seen between ethnic groups. **The main symptoms of hypogonadism are reduced libido, erectile dysfunction, reduced muscle mass and strength, increased adiposity, low bone mass, depressed mood and fatigue.**

Summary of treatment benefits

Based on the available data from clinical studies and clinical experience of several years it is shown that testosterone, such as Testavan, represents an effective drug in the treatment of male hypogonadism.
If administered as indicated in the Summary of Product Characteristics and taking into account the contraindications, the warnings and precautions, Testavan can be considered effective in the approved indications.

Summary of the RMP

The applicant has submitted an updated RMP, version 2.0, dated 20 September 2017, in which all of the above comments have been adequately addressed. The updated RMP, version 2.0, is therefore considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

Common renewal date
A common renewal date of 5 years after approval is proposed by the RMS.

IV BENEFIT RISK ASSESSMENT

1.1. Therapeutic Context

1.1.1. Disease or condition
The proposed indication by the applicant reads: "*Testosterone replacement therapy for adult male hypogonadism, when testosterone deficiency has been confirmed by clinical features and biochemical tests*".

Male hypogonadism is a clinical condition characterised by a low serum testosterone level (morning serum total testosterone levels is less than 300 ng/dl [10 nmol/l]) in combination with a diversity of symptoms and signs such as reduced libido and vitality, decreased muscle mass, increased fat mass, depression, and others.

The goal of testosterone replacement therapy (TRT) in hypogonadal men is to restore testosterone levels to approximately the level of healthy men and to alleviate the symptoms associated with testosterone deficiency (body composition, metabolic control, psychological and sexual well-being).

1.1.2. Available therapies and unmet medical need
The available TRT formulations (oral treatment, patches, gels, injectable formulations and depots) differ in pharmacokinetics (PK) and safety profiles. Some TRT formulations (especially intramuscular injection of short-acting testosterone esters) result in supra-physiological peaks and hypogonadal troughs in testosterone levels. These fluctuations in testosterone levels may yield variations in libido, sexual function, energy, and mood. A "roller coaster" effect can also occur, characterized by alternating periods of symptomatic benefit and a return to base-line symptoms, corresponding to the fluctuations in serum testosterone levels.

Oral formulations are achieving variable levels of testosterone within the eugonadal range with need of several daily doses.
Using scrotal and transdermal patches testosterone levels are at the desired stable level within the eugonadal range. The patches, however, are associated with high frequency of application site reactions.

The currently available testosterone gels provide a stable testosterone level within the eugonadal zone with limited fluctuations, without the locally site reactions seen with the various patches.

As the proposed formulation considers yet another testosterone containing gel it is not considered to meet an unmet medical need.

1.1.3. Main clinical studies
The clinical development program consisted of 3 phase 1 studies, 2 phase 2 studies and 3 phase 3 studies.

The phase 1 trial (CS02) was conducted to evaluate the relative bioavailability of two formulations of Testavan gel 1% and 2% versus the active comparator TESTOGEL 1% (also registered as Androgel 1%) to select a final formulation for the continued development program. Both Testavan gel formulations exhibited greater bioavailability than Androgel 1%, with the 1% formulation showing the highest absorption rate. Also, the PK profile of Testavan 2% was different from that observed for Androgel 1%. On the other hand, the applicant showed that the PK profile of TESTAVAN 2% is similar to that of TOSTRAN 2% and AXIRON 2%, other approved testosterone gels.

One single arm, open label, non controlled, pivotal study (000127), a **non controlled, open label single arm study** (000023) and a **follow-up extension, single arm, open label study** (000077) were submitted to support the proposed indication.

In all three protocols in- and exclusion criteria endpoints and statistical analysis plan were similar. The treatment and titration regimen in study 00127 was somewhat different compared to study 000023/000077. Currently, the treatment axiom used for the registered testosterone gels is as follows: a starting dose of 46 mg daily with a dose titration on day 14 and 56 with the titration decision based on a pre-dose testosterone level. In contrast, in **pivotal study (00127)** the **starting dose was 23 mg daily** with a dose titration based on **a 2 -4 hour post dose** testosterone level at **day 14 and 35**. The applicant has discussed and demonstrated that within the approved testosterone gels different starting dose and titration schemes are approved, hence the proposed starting dose and titration scheme, in line with the pivotal study, is considered acceptable.

Patients included in the studies had signs and symptoms of reduced libido, impotence, loss of secondary sexual characteristics or infertility. In pivotal study 000127, all but one patient [redacted] responded yes to at least one question in the ADAM questionnaire assessing clinical symptoms of low testosterone/hypogonadism. 82.4% of the patients answered that their erections were less strong, 82.4% decreased in libido (sex drive), 84.3% decreased in strength and/or endurance of erection, and 86.2% of patients felt lack of energy at the time of screening.

1.1.4. Favourable effects

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 23mg, 46mg, and 69mg 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.

1.1.5. Uncertainties and limitations about favourable effects

The observed mean C_{max} and mean C_{min} for both study 000127 and 000023/000077 indicated that a considerable proportion of the patients experience testosterone levels outside the eugonadal range. The applicant 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 applicant 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 = 0.6%) 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 30.2%, 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 applicant does not provide a clear rationale for the choice of a non-controlled open-label trial. 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 PK 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 applicant 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.

1.1.6. 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 2 and phase 3 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 (Gamma-glutamyl Transferase) increase and haematocrit increased. Only 19 patients in total experienced testosterone values >2500 ng/dL on Day 90, 8 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 T/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, 3 patients had events that were assessed by the investigator as possibly related to trial treatment. Overall, in the phase 3 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%).

1.1.7. 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 applicant 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.

1.1.8. Benefit-risk assessment and discussion

1.1.8.1. Importance of favourable and unfavourable effects

For this application the testosterone PK 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 PK profile indicates a stable testosterone steady state. Therefore the PK 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 applicant 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 PK 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 applicant has sufficiently demonstrated that with the proposed **starting dose of 23 mg** and titration schedule (**2-4 hrs 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 t**he 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 applicant has taken the recent article 31 referral into account and sufficiently taken into account the known class effects of testosterone.

1.1.8.2. Balance of benefits and risks

The PK profile over 24 hours 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 bridge to the data reported in scientific literature.

The reported responder rates for Testavan 2% (which is based on average testosterone concentrations over 24 hours) 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 applicant has taken the recent article 31 referral into account and sufficiently taken into account the known class effects of testosterone. Refer to the SmPC assessment further details.

1.1.9. Conclusions

In conclusion, the application for Testavan 20mg/g gel voor transdermaal gebruik as *Testosterone replacement therapy for adult male hypogonadism, when testosterone deficiency has been confirmed by clinical features and biochemical tests*, **is approvable**.

V LIST OF QUESTIONS as proposed by RMS

V.1 Quality aspects

Major objections
n/a.

Other concerns

n/a

V.2 Non clinical aspects

Major objections

n/a

Other concerns

V.3 Clinical aspects

Major objections

Pharmacokinetics

Pharmacodynamics
N/A

Efficacy/Pharmacokinetics

n/a

Safety
n/a

Pharmacovigilance system
n/a

Risk Management Plan
n/a

Other concerns

Pharmacokinetics
none

Pharmacodynamics

N/A

Efficacy
n/a

Safety
n/a

Risk Management Plan
n/a

VI RECOMMENDED CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

VI.1 Legal Status

The legal status of supply for this medicinal product is: a prescription only medicine.

VI.2 Proposed list of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

The applicant committed to provide the specified Phase IIa studies (incl. study reports), and if triggered, the specified Phase IIb studies (incl. study reports). Furthermore, the applicant also confirmed to update the ERA accordingly. The accepted log K_{ow} of 3.32, which corresponding to a K_{ow} of ~2089 (Yalkowsky *et al.*, 1983) exceeds K_{ow} >1000, thus a fish bioconcentration study (OECD 305) is triggered. The applicant already committed to perform Phase IIb studies that are triggered, and thus a new commitment is not deemed necessary, and the BCF study will be added to the list of studies (incl. study report) that need to be submitted post approval.

The applicant 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).
- Bioaccumulation in Fish: Aqueous and Dietary Exposure (OECD 305; version 2012)

The applicant 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 Koc >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 PECsediment. Applicable tests are those with Hyalella sp; Lumbriculus sp. (OECD 225) or Chironomus sp. (OECD 218 or 219).

The applicant made the following commitment: The committed studies (including reports) are anticipated to be available for submission by November 2019, with submission of an updated ERA by December 2019.

VI.3 Proposed list of conditions pursuant to Article 21a or specific obligations pursuant to article 22 of Directive 2001/83/EC

N/A

VI.4 Module I – Application related comments (including product name)

Product name
The proposed name in the RMS
Testavan 20mg/g gel voor transdermaal gebruik is acceptable.

VI.5 Summary of Product Characteristics (SmPC)

The SPC is considered acceptable.
See attachment.

VI.6 Package Leaflet (PL)

VI.6.1 Package Leaflet

The PL is considered acceptable.
See attachment

VI.6.2 Assessment of User Testing

Assessment of the User Testing is attached in the 'QRD Guidance and Checklist for the Review of User Testing Results'.

VI.7 Labelling

The labelling is considered acceptable. See attachment.

VII APPENDIX

QRD GUIDANCE AND CHECKLIST FOR THE REVIEW OF USER TESTING RESULTS

QRD GUIDANCE AND CHECKLIST FOR THE REVIEW OF USER TESTING RESULTS

[Disclaimer: This guidance has been set up to provide practical information on how to evaluate user testing reports which are based on the readability testing method as described in Annex 1 of the EC Readability Guideline. This does not exclude the submission and evaluation of user testing reports based on other methods than the one outlined above, for which specific assessment guidance may be issued once experience has been gained

Useful links: More detailed practical guidance can be found in the following documents:

- *EC Readability Guideline http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/c/2009_01_12_readability_guideline_final.pdf*
- *"Operational procedure on Handling of "Consultation with target patient groups" on Package Leaflets (PL) for Centrally Authorised Products for Human Use http://www.emea.europa.eu/htms/human/qrd/qrdplt/27737805en.pdf* "Consultation with Target Patient Groups-meeting the requirements of Article 59(3) without the need for a full test-Recommendations for Bridging" http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/Consulation_PatientsGroups/CMDh_100_2007_Rev1_clean_April09.pdf
- "Position paper on user testing of package leaflets" http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/Consulation_PatientsGroups/CMDh_234_2011.pdf
- *[MRP/DCP relevant document – link to be inserted]*

PRODUCT INFORMATION

Name of the medicinal product:	Testavan 20mg/g transdermal gel
Name and address of the applicant:	Ferring BV
Name of company which has performed the user testing:	Luto research Ltd
Type of Marketing Authorisation Application:	Decentralized procedure
Active substance:	testosterone
Pharmaco-therapeutic group (ATC Code):	
Therapeutic indication(s):	Testosterone replacement therapy

- Full user testing report provided ☒ yes ☐ no

- Bridging report provided ☐ yes ☐ no

(In case of bridging report, multiple bridging is, in principle, not acceptable. However, a maximum of 3 bridging procedures could be accepted for one product: e.g. first bridging to address the scientific content, a second one to address the device and a last one to address the layout of the PL).

- Grounds for bridging based on a sound justification:
  - ☐ extensions for the same route of administration
  - ☐ reference to test on same class of medicinal product
  - ☐ reference to test with same safety issues
  - ☐ other _____

Is the justification for bridging acceptable? ☐ yes ☐ no

(In case no full user testing or bridging report has been provided, a justification should be submitted.)

- Is the justification for not submitting a report acceptable? ☐ yes ☐ no

(The following are examples of what are not considered valid justifications for not performing User Testing:
- Administration in a hospital setting only,
- Administration by a healthcare professional only,
- Compliance with the QRD templates,

- Long established use of the product.

Reasons *[assessor's views on acceptability or not of the justification/bridging report – assessment of justification/bridging]*

_____

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1 TECHNICAL ASSESSMENT

1.1 Recruitment

- Is the interviewed population acceptable? ☒ yes ☐ no

Comments/further details__
Twenty participants were recruited and all fulfilled the entry criteria set out below.
Pre-study screening ensured that participants were eligible for the leaflet being tested.

Inclusion criteria

Inclusion criteria for each round of 10 participants were:
• majority of participants to be male, with 1 female in each round to represent possible carers or partners
• participants across the age range for the medicine. As the medicine can be used by men over 18 years of age, but is used less often in older men, at least 1 person from each of the following age groups: up to 30 years, 30s, 40s, 50s, 60s and 70s-plus. However, with no more than 1 person in their 70s and no more than 2 people in their 60s.
• no more than 3 higher education graduates
• at least 3 participants who completed their education by 16 years
• at least 2 participants who either do not use written documents as part of their work, or who are currently not working or are retired
• able to read and having reading glasses with them (as required)
• able to speak English to native standard
• able to grasp an understanding of what they were required to do during the interview and able to engage with the interviewer._____

Guidance regarding Recruitment
The following points should be taken into consideration when assessing recruitment methods:

- Is the recruitment method well defined? Is it clear that serious thought was given to the composition of the test group? (e.g. in terms of variables such as sex, age, education, experience with the medicinal product, existing knowledge of the complaint, etc.)
- How has the test group been recruited? Are they new users or patients, parents or carers?
- Is it clear how many people were involved in the test/test rounds?
- Is that number sufficient? (The PL should be tested in minimum 2 rounds of 10 participants each)

1.2 Questionnaire

- Is the number of questions ____15___ sufficient? ☒ yes ☐ no
- Questions cover significant (safety) issues for the PL concerned? ☒ yes ☐ no

Comments/further details___
the questions covers the key messages for safe use of the product._____

Guidance regarding Questionnaire

The following points should be taken into consideration when assessing the questionnaire*:*

- Have the key messages for safe use been identified by the applicant

- Do the questions cover the key messages and the following areas:

=>General impressions of package leaflet;

=>"Diagnostic" part of PL (i.e. questions aiming to test whether the participants were able to find specific information quickly and easily in each section of the PL and to verify if they were able to understand this information correctly; the questionnaire should primarily concentrate on safety and correct use of the medicinal product and understanding of the participant to assure safe use –it must be ensured that key safety messages have been addressed);

=>Aspects such as design and layout of PL.

- Is the number of questions sufficient? (too few or too many –e.g. 12- 15)

- Do the questions address "wording" aspects? Can respondents easily understand the text they are reading?

- Do the questions provide open or pre-defined answers? Respondents should not be provided with ready-made answers, thus increasing the possibility of positive results. Questions should be open, should be ordered randomly to see how patients use the PL and should not be leading. However, it is good practice to start with an easy question to ease the participant. Questions that require self-assessment (example: in your opinion, is paragraph X clear?) should not be used. Questions that require a long list of answers to be given (example: "what are the adverse events of this medicinal product?") should also not be used..

1.3 Time aspects

- Is the time given to answer acceptable? ☒ yes ☐ no
- Is the length of interview acceptable? ☒ yes ☐ no

Comments/further details_____

Guidance regarding Time aspects

The following points should be taken into consideration when assessing the time aspects*:*

- Is it clear how long the test lasted?

- Was the time given for respondents to read and answer the questions adequate? How long did the interview last? [The test should be designed in a way to last no more than 45 minutes, to avoid tiring participants]

1.4 Procedural aspects

- Rounds of testing including pilot __3_____

Comments/further details___
All of the items of information on the Testavan leaflet passed the User Testing criteria. That is, at least 90% of participants were able to find each item of information and of these, at least 90% understood it correctly._____

Guidance regarding Procedural aspects
The following points should be taken into consideration when assessing the procedural aspects:

- *Is the test based on different testing rounds? (minimum two test rounds, each involving 10 participants, are required: As this is an iterative process more rounds may be required in order to satisfy the success criteria; a pilot test (including 2 to 3 persons) could precede to assure the questionnaire is understood and major gaps are precluded. The PL after changes should then be tested on 20 participants in total. However, one single testing round may also be considered sufficient and acceptable on a case-by-case basis)*

A satisfactory test outcome for the method outlined above is when 90% of literate adults are able to find the information requested within the PL, of whom 90% can show they understand it, i.e. each and every question must be answered correctly by at least 81% of the participants

- *Does it make use of modification phases in-between the testing rounds in order to maximise readability?*
- *Do interviewers use scenarios or live demonstrations (e.g. in order to increase the efficiency of the test, if appropriate.*

1.5 Interview aspects

- Was the interview conducted in well structured/organised manner? ☒ yes ☐ no

Comments/further details_____

Guidance regarding Interview aspects
The following points should be taken into consideration when assessing the interview aspects:
- *Are there clear instructions for the test instructor(s)? (e.g. instructions on how to get more information from the consumers test, whether or not help should be given, etc.)*
- *Do interviewers let respondents show where information on the medicinal product can be found in the leaflet?*
- *Do they ask respondents to give their answer in their own words and not to rely on memory?*

2 EVALUATION OF RESPONSES

2.1 Evaluation system

- Is the qualitative evaluation of responses acceptable? ☒ yes ☐ no
- Does the evaluation methodology satisfy the minimum prerequisites? ☒ yes ☐ no

Comments/further details_____

Guidance regarding Evaluation system
The following points should be taken into consideration when assessing the evaluation system:

- Is the assessment based on a check list covering the following 3 basic areas:
Whether the respondent was able:
*⇒ **To find** the information (e.g. can a respondent easily find the information on dosage?)*
*⇒ **To understand** the information (e.g. can a respondent say in his/her own words what the proper dosage and the instructions for use are?)*
*⇒ **To use** the information (e.g. "imagine you are in situation X and Y happens, what must you do?")*

2.2 Question rating system

- Is the quantitative evaluation of responses acceptable? ☒ yes ☐ no

Comments/further details_____

Guidance regarding Questions rating system
The following points should be taken into consideration when assessing the questions rating system:
- How are answers evaluated? (e.g. 1= no answer, 2=wrong answer, 3=incomplete answer, 4=ambiguous answer, 5=complete and correct answer)

3 DATA PROCESSING

- Are data well recorded and documented? ☒ yes ☐ no

Comments/further details_____

Guidance regarding Data processing
The following points should be taken into consideration when assessing the data processing:

- Is it clear how the data are recorded?

- Is the way in which they are recorded satisfactory?
- Have the data been processed satisfactorily? (e.g., is it clear how verbal assessments have been converted into graded answers?)
- Has the assessor been provided with the patient leaflets used during (different rounds of) testing?
- Are the revisions in the PL explained/justified? Is it also clear which comment from the participants were ignored and why?

4. QUALITY ASPECTS

4.1 Evaluation of diagnostic questions

- Does the methodology follow Readability guideline Annex 1? ☒ yes ☐ no
- Overall, each and every question meets criterion of 81% correct answers ☒ yes ☐ no

Comments/further details_____

4.2 Evaluation of layout and design

- Follows general design principles of Readability guideline ☒ yes ☐no
- Language includes patient friendly descriptions ☒ yes ☐ no
- Layout navigable ☒ yes ☐ no
- Use of diagrams acceptable ☐ yes ☐ no

Comments/further
details_____

Guidance regarding Quality aspects
The following points should be taken into consideration when assessing the quality aspects:

- Is the report complete?
- Does the report clearly distinguish between quantitative and qualitative results?
- Is the medicinal product and the company concerned clearly indicated?
- Based on EC guidelines, are "diagnostic" questions (see 1.2) scoring satisfactorily?
- Do respondents find the layout and design of the package leaflet satisfactory?
Special focus should be given to the following elements:
- *Writing style (simple language, short sentences, use of bullets)*
- *Type face (font size, italics/underlining, lower/upper case)*
- *Layout (spacing, white space, contrast, left justified, columns)*
- *Headings (consistent location, stand out)*
- *Use of colour (present, adequate contrast)*

- Pictograms should be subject to user testing as it is well known that these can confuse patients.
- Do respondents encounter difficulties in locating and using correctly (if appropriate) the information provided in the PL?

5. DIAGNOSTIC QUALITY/EVALUATION

- Have any weaknesses of the PL been identified? ☐ yes ☒ no
- Have these weaknesses been addressed in the appropriate way? ☐ yes ☐ no

Comments/further details__Some questions wee more difficult to answer. However no changes were proposed to the PL.

Guidance regarding Diagnostic quality/evaluation
The following points should be taken into consideration when assessing diagnostic quality/evaluation:

- Are the results (as far as possible) related to actual passages of text?
- Is an attempt made to explain that readers' problems arose because of certain characteristics of those passages (e.g. something was difficult to find because of a badly chosen heading; or a passage could not be understood because of a double negative; or specific information could not be applied properly because certain terms were unclear)?
- Was a second round revision carried out?
- Have weaknesses of the first round been clearly identified and addressed in the appropriate way? (e.g. questions that scored low led to modifications on the PL => introduction of stylistic changes to improve readability or removal of redundant and confusing information)
- Is it clear which passages have been revised and how and on the grounds of what observations in the first round?
- Is it also clear what observations were ignored in making the revision and why?
- Have modifications been tested and proved to improve readability?

6. CONCLUSIONS

- Have the main objectives of the user testing been achieved? ☒ yes ☐ no
- Is the conclusion of applicant accurate? ☒ yes ☐ no
- Overall impression of methodology ☒ positive ☐ negative
- Overall impressions of leaflet structure ☒ positive ☐ negative

CONCLUSION / OVERVIEW

The User Test of 20 people from the target population, in structured individual interviews, showed that the leaflet for Testavan enabled at least 90% of participants to find, and at least 90% of those to understand, each item of information tested.
These results confirm that the Package Leaflet for Testavan complies with current EU requirements for User Testing.
The user test is acceptable.

Guidance regarding Conclusions

A general view on the user testing performed and on the overall readability /quality of the PL should be provided here *[to be used in the DCP day 70/ day 120 overview assessment report as appropriate– the complete evaluation report of the user testing results should only be included as an Annex of the Day 70 or Day 120 overview assessment report, as appropriate]*

The following points should be taken into consideration when drafting the conclusions:

Objectives:
1. To ensure the final PL reflects the results of testing with patients to make sure it meets their needs and can enable the patient to use the medicinal product safely and effectively
2. To assess the readability of the PL
3. To identify problems regarding comprehensibility and usefulness of information
4. To describe possible changes in the leaflet in order to improve the readability of the leaflet

- Does the report make it clear on what test results specific conclusions are based?
- Do the conclusions match the results or, given the actual results, is too favourable a picture painted?
- Are the conclusions clear, concise and well organised?
- Have the recommendations and conclusions also been incorporated in any revision of the text?