LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Testosteronenantat SIT
(testosterone enantate)

SE/H/2435/01/DC

This module reflects the scientific discussion for the approval of Testosteronenantat SIT. The procedure was finalised on 2024-07-17. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Testosteronenantat SIT, 250 mg/mL, solution for injection.

The active substance is testosterone, testosterone enantate. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Testosteronenantat SIT, 250 mg/mL, solution for injection, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC. The Applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and the following countries as concerned member states (CMS): FR, IT.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Testoviron-Depot, 250 mg/mL, solution for injection, authorised in Sweden since 1955, with Schering AG as marketing authorisation holder.

European Reference Product (ERP)
A European Reference Product is used in CMS IT: Testoviron-Depot, 250 mg/mL, solution for injection, authorised in Sweden since 1955, with Schering AG as marketing authorisation holder. The justification to use this product is based on RMS's own files. The SE ERP information was circulated by RMS during the validation period.

Potential similarity with orphan medicinal products
Not applicable

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of testosterone are well known. As testosterone is a widely used, well-known active substance, no further studies are required, and the Applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
The justification for not submitting an ERA is not considered acceptable. Upon request, the Applicant submitted ERA sales data from the member states involved in the procedure. Based on the data presented, there was an increase in sales in all countries except RMS in the time period and the increases are considered significant in terms of environmental exposure.
Therefore, a tailored ERA for testosterone in accordance with the relevant guideline has been requested. The Applicant, EVER Valinject GmbH, commits to submit an Environmental Risk Assessment for the drug product Testosterons enantate 250 mg/mL solution for injection of current registration procedure, by the end of 2024. A commitment letter dated July 11 2024 has been submitted.

IV. CLINICAL ASPECTS

Pharmacokinetics
No bioequivalence studies were submitted.

Discussion and overall conclusion
The applied product is to be administered as an intramuscular solution containing the same active substance in the same concentration as the currently authorised product. The applied product also contains the same excipients in similar amounts as the reference product. For this type of product, no bioequivalence studies are required according to the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1).

A clarification on the guideline requirements for parenteral oily solutions were published December 2022 (EMA Q&A 3.12), stating that the test drug product's 'rheological behaviour' (e.g. viscosity but not exclusively) and other physiochemical properties (e.g. partition coefficient and injectability) should be equivalent to those of the reference product. The pharmaceutical equivalence to the reference product has been discussed in Quality part.

The absence of bioequivalence studies is acceptable.

Pharmacodynamics
Testosterone is a natural hormone responsible for the expression of masculine characteristics during foetal, early childhood, and pubertal development and thereafter for maintaining the masculine phenotype and androgen-dependent functions (e.g., spermatogenesis, accessory sexual glands). Decreased production of testosterone, a condition known as male hypogonadism, can occur with aging, certain medications, chemotherapy, hypothalamus-pituitary axis disorders, primary hypogonadism, cryptorchidism and orchitis, and with genetic disorders such as Klinefelter and Kallmann syndrome (Nassar GN, *et al*., 2023). Injectable testosterone esters are a commonly used

therapeutic option.

Testosterone enantate is an ester of the natural male sex hormone testosterone and exhibits all the pharmacological effects of the natural hormone. It is indicated for testosterone replacement therapy for male hypogonadism. Testosterone enantate has a depot effect and thus a longer duration of action (injected at doses of 200 to 250 mg per 14 days). Other commonly used formulations include the longer-acting ester testosterone undecanoate (Nebido®), which intended to provide depot release throughout months (~9-12 weeks). The efficacy and safety profile of testosterone enantate and testosterone undecanoate does not differ significantly (Handelsman DJ, 2016, Minnemann T, 2008).

The Applicant has not submitted any new pharmacodynamics data, which is acceptable considering that testosterone enantate is a compound with a well-known pharmacological profile.

Clinical efficacy
The Applicant has not provided any new clinical efficacy data and has instead provided a literature review on previously reported efficacy data from 11 clinical studies with testosterone enantate in male hypogonadism and other indications.

This is however considered acceptable as testosterone enantate is an effective and well-tolerated treatment for male hypogonadism with similar efficacy as substitution therapy as other marketed injectable solutions of testosterone.

Clinical safety
No new studies on clinical safety have been submitted.

No new safety data has been provided. In the published clinical studies submitted in support of the application, testosterone enantate shows a well-known safety profile consistent with its androgen effect. The emerged risks discussed are adequately covered by the risk minimization measures and are communicated in the product information.

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 Testosteronenantat SIT.

Part II Safety specification
The MAH has submitted the version 0.4 RMP dated 15/05/2024 and proposed the following summary safety concerns. The safety concerns are aligned with those of the originator product.

Table SVIII.1: Summary of safety concerns

Important identified risks	– Pulmonary oil microembolism (POME)
Important potential risks	– Thromboembolic risk secondary to haematocrit increase
Missing information	– None

Part III Pharmacovigilance Plan
Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for individual case safety reports received for the safety concerns “POME” and “Thromboembolic risk secondary to haematocrit increase”:

Follow-up questionnaires are in place to obtain structured information on all individual case safety reports received for the safety concerns described above. These follow-up questionnaires are provided in Annex 4 of the RMP and are in line with the originator product.

Part V Risk minimisation measures
The MAH updated their RMM of the risk management plan and propose routine and additional RMM as followed:

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Pulmonary oil microembolism (POME)	Routine risk communication: SmPC • *Sections 4.4, 4.8* PL • *Sections 4, 6* Restricted medical prescription Additional risk minimisation measures: Educational brochure for health care professionals on the correct injection technique, recognition and management of POME.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire for individual case safety reports received for the safety concern "POME" Additional pharmacovigilance activities: *None.*
Thromboembolic risk secondary to haematocrit increase	Routine risk communication: SmPC • *Sections 4.4, 4.8* PL • *Sections 2, 4, 6* Restricted medical prescription Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire for individual case safety reports received for the safety concern "Thromboembolic risk secondary to haematocrit increase" Additional pharmacovigilance activities: *None*.

Part VI Summary of the RMP
The submitted Risk Management Plan, version 0.4 signed 15/05/2024, is endorsed.

Conclusion RMP assessment
The MAH has satisfactorily responded to the questions raised and updated the RMP accordingly.
Issue is resolved.

The submitted **Risk Management Plan, version 0.4 signed 15/05/2024** is 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.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to a) Testoterone undecanoate solution for injection authorised in procedure NL/H/5745/01 (lay-out and content), b) Testosterone enantate solution for injection, authorised by the MHRA since 1996 (content only).
The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Testosteronenantat SIT, is found adequate. There are no objections to approval of Testosteronenantat SIT, from a non-clinical and clinical point of view. The absence of bioequivalence studies is acceptable. The product information is acceptable. The benefit/risk ratio is considered positive, and the application is therefore recommended for approval.

For conditions pursuant to Article 21a of Directive 2001/83/EC and a commitment to be reported back to the Member States within predefined timeframes, see section below.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

Post approval commitments

Description	**Due date**
A tailored ERA in agreement with guideline for the drug product Testosterons enantate 250 mg/mL solution for injection for current registration procedure.	End of 2024

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

- Additional risk minimisation measures (including educational material)

The educational material should contain the following key elements:

 Check the Summary of Product Characteristics for any contraindications and special warnings before administering the injection;
 Injection Procedure:

o Do not inject refrigerated solution;
o Use a 20G (0.9mm), 21G2,3 (0.8mm) or 22G (0.7mm) needle to ensure slow intramuscular injection and deposition of Nebido;
o Lay the patient down, place hands under the head, and remain still during the injection;
o The preferred site for intramuscular injection is the gluteus medius muscle, located in the upper outer quadrant of the buttock;
o Care must be taken to prevent the needle from hitting the superior gluteal artery and sciatic nerve. Nebido should not be split into portions and it should never be administered into the upper arm or the thigh;
o After cleansing the area with antiseptic, insert the needle into the skin at a 90° angle to ensure it is deeply embedded in the muscle; and inject very slowly (over approximately 2 minutes).
 Pulmonary oil microembolism can occur following direct vascular or lymphovascular delivery of oil-based preparations. Signs and symptoms, such as cough, dyspnoea, malaise, hyperhidrosis, chest pain, dizziness, paraesthesia or syncope, can occur during or immediately after the injection and are reversible. Sometimes these symptoms may be difficult to distinguish from an allergic reaction. Treatment is usually supportive, e.g. by administration of supplemental oxygen.

The Educational Brochure (Administration Guide) is included in the submitted RMP V0.4, signed 15 May 2024, and is in line with the originator product. As requested, and in accordance with GVP module XVI addendum, the following statement has been included in RMP section V.2.: *"The methods for dissemination and the target audience in each Member State are determined at national level by the respective competent authority of the Member State."*

- Obligation to conduct post-authorisation measures in accordance with Article 21a of Directive 2001/83/EC

N/A

- Specific obligation to complete post-authorisation measures for the marketing authorisation under Exceptional circumstances in accordance with Article 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Testosteronenantat SIT, 250 mg/mL, solution for injection was positively finalised on 2024-07-17.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se