COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Testosteron undecanoaat SIT 1000 mg/4 ml solution for injection (testosterone undecanoate)

NL/H/5748/001/DC

Date: 27 August 2024

This module reflects the scientific discussion for the approval of Testosteron undecanoaat SIT 1000 mg/4 ml solution for injection. The procedure was finalised on 21 December 2023. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
POME	Pulmonary oil microembolism

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Testosteron undecanoaat SIT 1000 mg/4 ml solution for injection, from Laboratorio Farmaceutico SIT s.r.l.

The product is indicated for: testosterone replacement therapy for male hypogonadism, when testosterone deficiency has been confirmed by clinical features and biochemical tests (see section 4.4 of the SmPC).

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

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Nebido, 1000 mg/4 ml, solution for injection (NL RVG 30794) which has been registered in Austria by Grünenthal GmbH since 7 September 2004 (original product). In the Netherlands, Nebido has been registered since 2005 by the decentralised procedure FI/H/0313/001.

The concerned member states (CMS) involved in this procedure were Italy and Spain.

II. QUALITY ASPECTS

II.1 Introduction

Testosteron undecanoaat SIT is a solution for injection. It is a slightly yellow to yellow oily solution.

Each mL solution for injection contains 250 mg testosterone undecanoate corresponding to 157.9 mg testosterone.
Each ampoule or vial with 4 mL solution contains as active substance 631.5 mg of testosterone, as 1000 mg of testosterone undecanoate.

The excipients are benzyl benzoate and castor oil (refined).

4 mL of the solution for injection is either packed in a 5 mL type I amber glass ampoule or in a 5 mL type I amber glass vial with a bromobutyl rubber stopper and an aluminium cap.

II.2 Drug Substance

The active substance is testosterone undecanoate, an active substance which is not described in the European Pharmacopoeia. The active substance is a white to almost white waxy powder

and is practically insoluble in water. The active substance contains six chiral centres. The active substance exists in only one polymorphic form.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The manufacturing process consists mainly of one synthesis step, one purification step and one crystallisation step. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Quality control of drug substance

The active substance specifications are in line with the drug substance specification of the ASMF holder, with additional tests for microbiological purity and bacterial endotoxins. The proposed specifications are acceptable. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Stability data on the active substance have been provided for five batches in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 3 years when stored under the stated conditions. This aspect has been evaluated within the scope of the ASMF.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The development of the product has been described, the choice of excipients is justified, and their functions explained. The choices of packaging and manufacturing process are adequately justified based on the dosage form. The optimal composition and manufacturing process parameters have been investigated. Comparative studies (solubility, optimum benzyl benzoate composition, chemical, photo- and oxidative stability) have been performed.
Also, in support of bioequivalence, the viscosity and further rheological characterisation of both the drug product and the reference drug product demonstrate that the rheological behaviour and the comparative fatty acid composition are the same. Equivalence to the reference drug product has been sufficiently demonstrated by rheological characterisation of the reference drug product as the drug product. No difference in injectability and release profile are anticipated. The biowaiver is granted. Details are adequately described.

Manufacturing process

The product is manufactured by well-known manufacturing techniques. The process is concluded to be a non-standard manufacturing process due to the aseptic processing and the modified release characteristics of the drug product. The drug product is manufactured by compounding of the bulk solution in a vessel, sterilisation step and aseptic filling into amber glass vials including vial closure (stoppering) or ampoules. The method of sterilisation has been adequately justified.
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been submitted for three full-scale batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph.Eur. and in-house requirements. These specifications are acceptable.

Microbiological attributes

Sterilization filtration is adopted to sterilize the drug product; the provided justification is considered acceptable and sufficient. It is shown that the container closure system adequately protects the drug product from light and microbial contamination.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, solution clarity and opalescence, particle matter, identification, assay, related substances, sterility and bacterial endotoxins. Viscosity was added as an acceptance criterion, the proposed range is acceptable. The release and shelf-life limits are identical. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Appropriate tests for nitrosamine presence are performed on the final product. The risk for presence of nitrosamines in the drug product was considered negligible.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three batches stored at 30°C ± 2 °C /75% ± 5 % RH (12 months) and 40°C ± 2 °C/75% ± 5 % RH (6 months). The stability was tested in accordance with applicable European guidelines. Photostability studies were performed in accordance with ICH recommendations and the proposed drug product. On basis of the data submitted, a shelf life was granted of 2 years, with the specific storage condition that the product must be used immediately after first opening. No other specific storage conditions needed to be included in the SmPC or on the label.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

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

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Testosteron undecanoaat SIT has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Testosteron undecanoaat SIT is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Nebido which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Testosteron undecanoaat SIT 1000 mg/4 ml solution for injection is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence “5.1.6 parenteral solutions”, which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Testosteron undecanoaat SIT is entirely the same as the originator. Therefore, it may be considered as therapeutic

equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

IV.2 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 Testosteron undecanoaat SIT.

Table 1. Summary table of safety concerns as approved in RMP

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

The member states agreed that routine pharmacovigilance activities are sufficient for the risks and areas of missing information.
The additional risk minimisation measures of the originator product include educational material for health care professionals on the correct injection technique, recognition and management of pulmonary oil microembolism (Nebido Educational Brochure (Administration Guide for Nebido)). The educational material was updated by the MAH to include the additional risk minimisation measures for POME.
The additional risk minimisation measures are part of the routine practice and familiar to health care professionals. The information available in the SmPC and patient information leaflet is sufficient to reduce the impact of POME on the benefit-risk balance of the product and in line with the SmPC of the innovator.

IV.3 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Nebido. No new clinical studies were conducted. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.
The test consisted of: a pilot test with 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Testosteron undecanoaat SIT 1000 mg/4 ml solution for injection has a proven chemical-pharmaceutical quality and is a generic form of Nebido, 1000 mg/4 ml, solution for injection. Nebido is a well-known medicinal product with an established favourable efficacy and safety profile. Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary. A biowaiver has been granted.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Testosteron undecanoaat SIT with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 21 December 2023.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/5748/001 /IB/001	*Type IB - A.2.b* Change in the (invented) name of the medicinal product for Italy	Yes	26 August 2024	Approved	-