COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

NL/H/5733/001/DC

Date: 30 September 2025

This module reflects the scientific discussion for the approval of Testosteron undecanoaat SUN 1000 mg/4 ml solution for injection. The procedure was finalised on 13 November 2024. 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
HPLC	High-Performance Liquid Chromatography
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
PDA	Photo Diode Array
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
POME	Pumonary Oil Microembolism
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Testosteron undecanoaat SUN 1000 mg/4 ml solution for injection, from Sun Pharmaceutical Industries Europe B.V.

The product is indicated as testosterone replacement therapy for male hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests.

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 Finland (procedure FI/H/0313/001) by Grünenthal GmbH (previously Bayer) since 2003.

The concerned member states (CMS) involved in this procedure were Belgium, Czechia, Finland, France, Germany, Greece, Hungary, Italy, Norway, Slovakia, Spain and Sweden.

II. QUALITY ASPECTS

II.1 Introduction

Testosteron undecanoaat SUN is a solution for injection.
Each ml solution for injection contains as active substance 157.9 mg testosterone, as 250 mg of testosterone undecanoate. Each vial with 4 ml solution for injection contains as active substance 631.5 mg testosterone, as 1000 mg of testosterone undecanoate.

The product is an oily, clear yellowish solution.
The excipients are benzyl benzoate and refined castor oil.

The solution is packed in 5 ml amber glass vial with a bromobutyl rubber injection stopper sealed with an aluminium flip-off cap containing a fill volume of 4 ml.

II.2 Drug Substance

The active substance is testosterone undecanoate, an established active substance not described in the European Pharmacopoeia (while related testosterone decanoate is described in the Ph.Eur.) 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 of testosterone undecanoate crude consists of three steps. The crude is further purified to obtain the testosterone undecanoate. 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 specification is considered adequate to control the quality. 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 four batches in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 60 months when stored under the stated conditions.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified, and their functions explained. The 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. Equivalence between the test and reference product has been demonstrated based on the similarity of the *in vitro* rheological profile.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three full-scale production batches in accordance with the relevant European guidelines. The method of sterilisation has been justified. The product is manufactured by well-known manufacturing techniques. The

manufacturing process is considered non-standard due to the aseptic processing and the modified release characteristics of the drug product.

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

Microbiological attributes
All involved sterilisation processes have been described and validated and microbial attributes are considered adequate.

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, colour of solution, particle matter, identification (by HPLC and PDA), extractable volume, viscosity, water content, acid value, uniformity of dosage units, assay, related substances, sterility and bacterial endotoxins. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release and shelf-life limits are identical. The MAH has tightened the limit for viscosity in the specification of the drug product.
An adequate nitrosamines risk evaluation report has been provided. All potential sources have been evaluated and the risk is considered low. This is acceptable.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from four 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 25°C±2°C/60% RH (6 months) and 40°C/75% RH (6 months), both in normal and inverted position. The stability was tested in accordance with applicable European guidelines. Photostability studies were performed in accordance with ICH recommendations, and the product was found to be photolabile. On basis of the data submitted, a shelf life was granted of two years. The labelled storage conditions are "*Store in the original package in order to protect from light*".

The medicinal product must be used immediately after first opening.

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 SUN 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 SUN 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

Testosterone undecanoate is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Testosteron undecanoaat SUN 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 SUN 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 quality of the excipients is of decisive influence on the controlled release of testosterone from the depot formulation. The MAH has provided data that show pharmaceutical equivalence between the test product and the reference product as the requirements in EMA clinical pharmacology and pharmacokinetics Q&A 3.12 have sufficiently been met. Therefore, the proposed product was considered bioequivalent to the reference product. Thus, a biowaiver has been granted.

IV.3 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 SUN. At the time of approval, the most recent version of the RMP was version 0.3, date of final sign-off 18 September 2024.

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

Important identified risks	• Pumonary 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. Besides routine risk minimisation measures, the MAH provided additional risk minimisation measures (aRMM) for the safety concern POME, as mentioned in Table 1. The aRMM consists of a Healthcare Professional Guide for administration of the product. These activities are considered acceptable.

IV.4 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 two 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 SUN 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 SUN with the reference product, and have therefore granted a marketing authorisation. The decentralised/mutual recognition procedure was finalised with a positive outcome on 13 November 2024.

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
-	-	-	-	-	-