LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Testosterone Besins
(testosterone undecanoate, testosterone)

SE/H/2363/01/DC

This module reflects the scientific discussion for the approval of Testosterone Besins. The procedure was finalised on 2023-10-04. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Testosterone Besins, 1000 mg/4 ml, Solution for injection.

The active substance is testosterone undecanoate, testosterone. 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 Testosterone Besins, 1000 mg/4 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 BE, DE, FR, IE, LU as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Nebido, 1000 mg/4 ml, Solution for injection authorised in FI since 2003, with Bayer Oyas marketing authorisation holder.

Potential similarity with orphan medicinal products

According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

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 undecanoate are well known. As testosterone undecanoate 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 Applicant has presented a justification for the absence of a tailored environmental risk assessment of Testosterone Besins. Since the product is intended for generic substitution, it is not expected to cause increased exposure to the environment. This is further supported by provided consumption data for the last 4 years (until Q1 2022).

There are no objections to approval of Testosterone Besins solution for injection from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
No bioequivalence study has been submitted. The generic medicinal product Testosterone Besins has the same pharmaceutical form (solution for injection) with the same quantitative composition of the active substance as the reference medicinal product Nebido®. The product is a parenteral solution intended exclusively for intramuscular injection exclusively as the reference product Nebido®.

Pharmacokinetic properties of the active substance
Absorption: Following intramuscular injection of testosterone undecanoate as an oily solution, the compound is gradually released from the depot and is almost completely cleaved by serum esterases into testosterone and undecanoic acid. An increase in serum levels of testosterone above basal values may be seen one day after administration.
Steady-state conditions: After the 1st intramuscular injection of 1000 mg testosterone undecanoate to hypogonadal men, mean C_{max} values of 38 nmol/L (11 ng/mL) were obtained after 7 days. The second dose was administered 6 weeks after the 1st injection and maximum testosterone concentrations of about 50 nmol/L (15 ng/mL) were reached. A constant dosing interval of 10 weeks was maintained during the following 3 administrations and steady-state conditions were achieved between the 3rd and the 5^{th} administration. Mean C_{max} and C_{min} values of testosterone at steady-state were about 37 (11 ng/mL) and 16 nmol/L (5 ng/mL), respectively. The median intra- and inter-individual variability (coefficient of variation, %) of C_{min} values was 22% (range: 9- 28%) and 34% (range: 25- 48%), respectively.
Distribution: In serum of men, about 98% of the circulating testosterone is bound to sex hormone binding globulin (SHBG) and albumin. Only the free fraction of testosterone is considered as biologically active. Following intravenous infusion of testosterone to elderly men, the elimination half-life of testosterone was approximately one hour and an apparent volume of distribution of about 1.0 L/kg was determined.
Biotransformation: Testosterone which is generated by ester cleavage from testosterone undecanoate is metabolized and excreted the same way as endogenous testosterone. The undecanoic acid is metabolized by ß-oxidation in the same way as other aliphatic carboxylic acids. The major active metabolites of testosterone are oestradiol and dihydrotestosterone.
Elimination: Testosterone undergoes extensive hepatic and extrahepatic metabolism. After the

administration of radio-labelled testosterone, about 90% of the radioactivity appears in the urine as glucuronic and sulphuric acid conjugates and 6% appears in the faeces after undergoing enterohepatic circulation. Urinary medicinal products include androsterone and etiocholanolone. Following intramuscular administration of this depot formulation the release rate is characterised by a half life of 90±40 days.

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. In the case of other parenteral routes, e.g. intramuscular or subcutaneous, and when the test product is of the same type of solution (aqueous or oily), contains the same concentration of the same active substance and the same excipients in similar amounts as the medicinal product currently approved, bioequivalence studies are not required according to the Guideline on the investigation of Bioequivalence (CHMP/QWP/EWP/1401/98 Rev. 1).

The justification for not conducting a bioequivalence study is satisfactory from a pharmacokinetic perspective.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted, which is acceptable.

Risk Management Plan
In accordance with the requirements of Directive 2001/83/EC as amended, the Applicant has submitted a risk management plan (version 1.1, dated 28.04.2023), describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent and minimise risks relating to Testosterone Besins.

Part II. Safety specification
In accordance with the RMP of the originator, the Applicant proposes the following Summary of safety concerns (Module SVIII):

List of important risks and missing information	
Important identified risks	• Pulmonary oil microembolism (POME)
Important potential risks	• Thromboembolic risk secondary to haematocrit increase
Missing information	• None

Part III. Pharmacovigilance Plan
Beyond the routine pharmacovigilance activities of ADR reporting and signal detection, the Applicant has proposed two Specific Adverse Reaction Follow-up Questionnaires; one for pulmonary oil microembolism (POME) and one for thromboembolic risk secondary to hematocrit increase.
No additional pharmacovigilance activities were proposed by the Applicant.

Part V. Risk minimisation measures
Beyond the routine risk minimisation measures, the Applicant has proposed distribution of educational material (Administration guide) to health care professionals to widen their knowledge on events that might occur during or after the injection. This additional risk minimisation measure, associated with the identified risk of POME, is in accordance with the RMP of the originator. The Applicant has submitted a commitment, signed by the EEA QPPV, to present the educational material for assessment at national level once the common phase of this procedure is finalised.

No additional risk minimisation measures associated with the risk of thromboembolism secondary to haematocrit increase, is proposed.

The Applicant has provided the following tabulated *Summary of risk minimisation measures and pharmacovigilance activities*:

Safety concern	Risk minimisation activities	Pharmacovigilance activities
Important identified risk		
Pulmonary oil microembolism (POME)	Routine risk communication: SmPC sections 4.2, 4.4 and 4.8. Routine risk communication recommending specific clinical measure to address the risk: • Recommendations to monitor for symptoms during and immediately after each injection (to allow early recognition) and information on supportive treatment (e.g. by administration of supplemental oxygen) are provided in SmPC sections 4.4 and 4.8. Other routine risk minimisation measures beyond the Product Information: • Prescription only medicine. Additional risk minimisation measures: • Educational Brochure (Administration Guide)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific Adverse Reaction Follow-up Questionnaire for Pulmonary Oil Microembolism (POME) Additional pharmacovigilance activities: • None
Important potential risk		
Thromboembolic risk secondary to haematocrit increase	Routine risk communication recommending specific clinical measure to address the risk: • Recommendations on monitoring haemoglobin and haematocrit (SmPC section 4.4) Other routine risk minimisation measures beyond the Product Information: • Prescription only medicine. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific Adverse Reaction Follow-up Questionnaire for Thromboembolic risk secondary to haematocrit increase Additional pharmacovigilance activities: None

Part VI. Summary of the RMP
The Applicant has adequately summarised the proposed RMP.

Overall conclusion of the RMP assessment
The RMP version 1.1, dated 28.04.2023, 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 Nebido 1000 mg/4 ml, solution for injection. 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, Testosterone Besins, is found adequate. The absence of bioequivalence studies is found acceptable, and there are no objections to approval of Testosterone Besins from a non-clinical and clinical point of view. The product information is acceptable.

The benefit/risk is considered positive, and the application is therefore recommended for approval.

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

N/A

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

N/A

VII. APPROVAL

The decentralised procedure for Testosterone Besins, 1000 mg/4 ml, Solution for injection was positively finalised on 2023-10-04.

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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)

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