NEBIDO®
(Testosterone undecanoate)
EU Risk Management Plan

Part VI – Summary of Activities in the Risk Management Plan by Product

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Active substance(s) (INN or common name):	Testosterone undecanoate

Medicinal products to which this RMP refers:	1

Name of Marketing Authorisation Holder or Applicant:	Bayer AG

Data lock point for this module	31 DEC 2018

Version number of RMP when this module was last updated	3.2

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List of Abbreviations

EU	European Union
INN	International Nonproprietary Name
PBRER	Periodic Benefit-Risk Evaluation Report
POME	Pulmonary oil microembolism
PSUR	Periodic Safety Update Reports
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics

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1. Summary of Risk Management Plan (RMP) for Nebido (Testosterone Undecanoate)

This is a summary of the RMP for Nebido. The RMP details important risk of Nebido, how it can be minimised, and how more information will be obtained.

Nebido's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Nebido should be used.

Important new concerns or changes to the current ones will be included in updates of Nebido's RMP.

2. The Medicine and what It Is Used for

Nebido is authorised as testosterone replacement therapy for male hypogonadism (see SmPC for the full indication). It contains testosterone undecanoate as the active substance and it is given by intramuscular injection.

3. Risks Associated with the Medicine and Activities to Minimise or further Characterise the Risks

Important risk of Nebido together with measures to minimise it are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Nebido, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Nebido is not yet available, it is listed under ‘missing information’ below.

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3.1 List of Important Risks and Missing Information

Important risks of Nebido are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Nebido. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 3-1: Summary of safety concerns

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

3.2 Summary of Important Risks

Important identified risk: Pulmonary oil microembolism (POME)	
Evidence for linking the risk to the medicine	Nebido is formulated to contain 1,000 mg of testosterone undecanoate in a 4 ml oily solution. Pulmonary microembolism of oily solutions can lead to signs and symptoms such as cough, dyspnoea, malaise, hyperhidrosis, chest pain, dizziness, paraesthesia, or syncope. These signs and symptoms may occur during or immediately after the injection and are typically benign and transient. Cases suspected by the company or the reporter to represent oily pulmonary microembolism have been reported rarely in clinical trials (in ≥1/10,000 and <1/1,000 injections) as well as from post-marketing experience. POME is classified as an important identified risk, due to the recognised causal relationship with oily solutions injection procedure, requiring risk minimisation measures to reduce its occurrence and consequently reduce the impact on the benefit-risk balance of the product. Such measures include specific clinical actions recommended in the SmPC and additional educational brochure for health care professionals on the correct injection technique, recognition and management of POME. Evidence source: Integrated clinical trial database, post-marketing reports/ PBRERs/ PSURs, literature.
Risk factors and risk groups	Patients inadvertently injected intravascularly or too rapidly can be hypothesised to be at increased risk, although some reports describe occurrence of POME despite administration of Nebido as recommended in SmPC.

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Important identified risk: Pulmonary oil microembolism (POME)	
	A potential dose-dependency of this reaction cannot be determined due to its low frequency in the clinical trial program.
Risk minimisation measures	**Routine risk minimisation measures:** 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: • Nebido is a medicinal product subject to medical prescription, for use as directed by medical practitioner. **Additional risk minimisation measures:** • Nebido Educational Brochure (Administration Guide for Nebido).

PBRER = Periodic Benefit-Risk Evaluation Reports; POME = Pulmonary oil microembolism; PSUR = Periodic Safety Update Reports; SmPC = Summary of Product Characteristics.

Important potential risk: Thromboembolic risk secondary to haematocrit increase	
Evidence for linking the risk to the medicine	Polycythaemia, haematocrit increased, red blood cell count increased, and haemoglobin increased have been reported commonly in clinical trials (in ≥1/100 and <1/10 patients). Cardiovascular disorder has been reported uncommonly (in ≥1/1,000 and <1/100 patients). Recommendations for monitoring of haemoglobin and haematocrit in patients receiving long-term androgen therapy are provided in the SmPC. As the thromboembolic risk secondary to haematocrit increase requires routine risk minimisation recommendations for special clinical actions to reduce its impact on the benefit-risk balance, and because activities to further assess its relatedness and impact are being carried out, it is regarded as important potential risk. Evidence Source: Integrated clinical trial database, post-marketing reports/ PBRERs/ PSURs, literature.
Risk factors and risk groups	Stimulation of erythropoiesis is an expected pharmacodynamic effect of any testosterone replacement therapy [1]. Excessive increases in haematocrit and correspondingly increased risk for

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Important potential risk: Thromboembolic risk secondary to haematocrit increase	
	thromboembolism conceivable only with supraphysiological testosterone levels. Patients with additional risk factors for polycythaemia (e.g. chronic obstructive pulmonary disease), venous or arterial thromboembolism may be assumed to be at higher risk. Elderly patients might be at increased risk for the development of increased haematocrit under testosterone treatment [2, 3].
Risk minimisation measures	**Routine risk minimisation measures:** Routine risk communication: • SmPC sections 4.4, 4.8. 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: • Nebido is a medicinal product subject to medical prescription, for use as directed by medical practitioner. **Additional risk minimisation measures:** • None.

PBRER = Periodic Benefit-Risk Evaluation Reports; PSUR = Periodic Safety Update Reports;
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3.3 Post-authorisation Development Plan

3.3.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Nebido.

3.3.2 Other studies in post-authorisation development plan

There are no other studies in the post-authorisation development plan.

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References

1. Jockenhövel F, Schubert M. Male hypogonadism. 2nd ed. Bremen: Uni-Med; 2007. p. 118.

2. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, et al. Testosterone therapy in adult men with androgen deficiency syndromes: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2006;91(6):1995-2010.

3. Calof OM, Singh AB, Lee ML, Kenny AM, Urban RJ, Tenover JL, et al. Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. J Gerontol A Biol Sci Med Sci. 2005;60(11):1451-7.