COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Trabectedine Teva 0.25 mg and 1 mg, powder for concentrate for solution for infusion

(trabectedin)

NL/H/5282/001-002/DC

Date: 9 February 2022

This module reflects the scientific discussion for the approval of Trabectedine Teva 0.25 mg and 1 mg, powder for concentrate for solution for infusion. The procedure was finalised at 7 January 2022. 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
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
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 Trabectedine Teva 0.25 mg and 1 mg, powder for concentrate for solution for infusion, from Teva B.V.

- The product is indicated for the treatment of adult patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients.

- The product in combination with pegylated liposomal doxorubicin (PLD) is indicated for the treatment of patients with relapsed platinum-sensitive ovarian cancer.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Yondelis 0.25 mg and 1 mg, powder for concentrate for solution for infusion which has been registered in the EEA by Pharma Mar S.A. since 17 September 2007 by centralised procedure (EU/1/07/417).

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Croatia, Denmark, France, Germany, Greece, Hungary, Italy, Luxembourg, Norway, Portugal, Romania, Slovakia, Slovenia, Spain and Sweden.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

Similarity assessment in view of the orphan drug legislation

The MAH provided a similarity report in which potential similarity between Trabectedine Teva 0.25 mg and 1 mg, powder for concentrate for solution for infusion and the orphan medicinal product under market exclusivity Zejula 100 mg, hard capsule, registered by GlaxoSmithKline (Ireland) Limited on 16 November 2017 by centralised procedure (EU/1/17/1235/001-3), was discussed. The MAH stated that currently Zejula, with the active substance niraparib, is the only approved orphan medicinal product under orphan market exclusivity, with an overlapping indication for ovarian cancer. This is agreed. There are several medicinal products which have been designated as orphan medicinal products, but have not yet been granted a marketing authorisation in the EU.

Further, the MAH provided data demonstrating the lack of similarity between the product at issue and Zejula, taking into account the therapeutic indication, the mechanism of action and chemical structure. With reference to the therapeutic indication, both medicinal products are indicated for the treatment of patients with relapsed platinum-sensitive ovarian cancer. However, Zejula is used as maintenance therapy in patients who are in response to platinum-based chemotherapy, while Trabectedine Teva is used in combination

with doxorubicin. Given these differences, the MAH stated that there is no overlap of the target populations of these indications. Zejula is also "indicated as monotherapy for the maintenance treatment of adult patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy". However, this indication concerns the use of Zejula as maintenance therapy in patients who are in response following completion of first-line platinum-based chemotherapy. Hence, there is also no overlap of the target populations when considering this indication.
Concerning the mechanism of action, the MAH stated that trabectedin binds to the minor groove of the deoxyribonucleic acid (DNA), which results in perturbation of the cell cycle. This mechanism is different from that of niraparib, as niraparib inhibits poly(ADP-ribose) polymerase (PARP) enzymes, which results in DNA damage, apoptosis and cell death.
Also, the MAH stated that Trabectedin and niraparib are not similar based on their different principle molecular structures.

Having considered the arguments presented by the MAH and with reference to article 8 of Regulation (EC) No 141/2000, Trabectedine Teva 0.25 mg and 1 mg powder for concentrate for solution for infusion is considered not similar (as defined in article 3 of Commission Regulation (EC) No. 847/2000) to Zejula. Therefore, the existence of any market exclusivity for Zejula in the treatment of ovarian cancer, does not prevent the granting of the marketing authorisation of Trabectedine Teva.

II. QUALITY ASPECTS

II.1 Introduction

Trabectedine Teva is a white to off-white powder, supplied in colourless glass vials, closed with a type I bromobutyl rubber stopper and sealed with an aluminium metallic flip-off cap with a coloured polypropylene disk. Each vial of powder contains 0.25 or 1 mg of the active substance trabectedin, respectively, depending of the strength. It is a powder intended for intravenous use. The strength after reconstitution is 0.05 mg of trabectedin per ml. Once reconstituted with water for injections, the solution must be further diluted with 0.9% sodium chloride solution for infusion or 5% glucose solution for infusion. The excipients are L-arginine hydrochloride, phosphoric acid (for pH-adjustment) and potassium hydroxide (for pH-adjustment).

The excipients and packaging are usual for this type of dosage form.

II.2 Drug Substance

The active substance is trabectedin, an active substance not described in the European or British Pharmacopeia (Ph. Eur. and BP), the United States Pharmacopeia, nor in the pharmacopeia of a member state. The active substance is practically insoluble in water,

soluble in N, N-dimethylformamide, methanol, ethanol or acetic acid. It is slightly soluble in acetone and sparingly soluble in dichloromethane or acetonitrile. Trabectedin is a single enantiomer with a total of seven stereogenic centres. The drug substance is a crystalline powder. No other polymorphic forms are identified.

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 of the synthesis of trabectedine in eleven reaction steps. The last stage of the manufacturing process includes salt formation. The process has been adequately described. Adequate specifications have been adopted for starting materials, solvents and reagents. The characterisation of the active substance is acceptable.

Quality control of drug substance

The active substance specification is in line with the specification of the drug substance of the ASMF and includes requirements for appearance, specific rotation, solubility, identification, assay, related substances, water content, elemental impurities, microbial contamination and bacterial endotoxins. Batch analytical data demonstrating compliance with this specification have been provided for three commercial scaled batches.

Stability of drug substance

Stability data on the active substance have been provided for three commercial scaled batches in accordance with applicable European guidelines, demonstrating the stability of the active substance under accelerated and long-term conditions for 6 and 24 months, respectively. Based on the data submitted, a retest period of 24 months has been accepted.

II.3 Medicinal Product

Pharmaceutical development

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 justified in relation to the innovator. The choice of sterilisation method has been adequately discussed. Compatibility studies between the drug product and the stainless-steel container materials and the tubing system and a study to justify the lack of overfill are adequately described. In general, the pharmaceutical development of the product has been adequately performed. Overall, the safety assessment of extractables from the vial, tubing and stopper submitted by the applicant is endorsed.

Manufacturing process

The manufacturing process consists of bulk solutions preparation, two sterilisation steps by filtration, aseptic filling, lyophilisation, vial closing, capping and secondary packaging. The manufacturing process is considered a non-standard process since the manufacturing includes a lyophilisation step. In general, the manufacturing process has been adequately described and validated according to relevant European guidelines. Process validation data on the product have been presented for three commercial batches per strength and are in accordance with the relevant European guidelines. The proposed holding time is acceptable.

Control of excipients

The excipients comply with the Ph. Eur. requirements. These specifications are acceptable.

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, identification, water content, uniformity of dosage units, assay of trabectedin, degradation impurities, uniformity of content, bacterial endotoxins and sterility for the powder as well as reconstitution time, colour clarity, visible particles, sub-visible particles and pH for the reconstituted solution in water for injection (0.05 mg/ml). The requirements are identical at release and shelf-life except for identification by UV, water content, uniformity of dosage units by mass variation, assay and degradation impurities. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. A risk evaluation concerning the presence of nitrosamine impurities in the drug product has been provided in line with the Notice EMA/189634/2019.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data on 3 commercial-scaled batches per strength from the proposed production site have been provided, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided on three commercial scaled batches of the 0.25 mg strength and two commercial batches of the 1 mg strength, stored at 2-8°C for 18 months and at 25°C/60% RH for 6 months. An additional commercial scaled batch of the 1 mg strength has been tested under long-term and accelerated stability studies for 12 and 6 months, respectively. The conditions used in the stability studies are according to the ICH stability guideline for products intended to be stored in a refrigerator. The batches were stored in type I glass vial, closed with a type I bromobutyl rubber stopper and sealed with an aluminium metallic flip-off cap with a coloured polypropylene disk. All results have been found within the proposed shelf life limits.

On basis of the data submitted, a shelf life for unopened vials was granted of 2 years. The labelled storage conditions are “Store in the refrigerator (2°C to 8°C)”.

Photostability studies were performed on three batches of each strength in accordance with ICH recommendations and showed that the product is stable when exposed to light.

In-use stability data has been provided on two batches per strength after reconstitution of the drug product in water for injections (0.05 mg/ml) and further diluted in 0.9% sodium chloride injection and 5% dextrose injection at two different concentrations (0.026 and 0.0026 mg/ml). The studies have been conducted at room temperature for 30 hours. Compliance with the specification of the reconstituted drug product has been demonstrated. The studies were performed according to the SmPC of the reference product and the same in-use shelf lives have been demonstrated. On the basis of the data, in-use stability of 30 hours up to 25ºC in polyethylene bag, PVC bag and glass container could be granted for both strengths.

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 Trabectedine Teva has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

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

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Yondelis which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is 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

Trabectedin is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

A bioequivalence study has not been performed. This is in line with the EMA Guideline on Investigation of bioequivalence, which states that bioequivalence studies are generally not required for parenteral solutions if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product. The lack of bioequivalence study is, in this particular case, acceptable since the generic drug product is intended to be administered as an aqueous solution and the active substance and strengths are the same as in the innovator. In addition, the proposed excipients are well known and do not have an impact on the pharmacokinetics of the drug substance.

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 Trabectedine Teva.

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

Important identified risks	• Capillary Leak Syndrome (CLS) • Injection site reaction
Important potential risks	• Acute Myelogenous Leukemia (AML)/ Myelodysplastic Syndrome (MDS) • Cardiac dysfunction • Pancreatitis, lipase and/or amylase increased.
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Yondelis. 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 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

Trabectedine Teva 0.25 mg and 1 mg, powder for concentrate for solution for infusion has a proven chemical-pharmaceutical quality and is a generic form of Yondelis 0.25 mg and 1 mg, powder for concentrate for solution for infusion. Yondelis 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.

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 Trabectedine Teva with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 7 January 2022.

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