COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Cabazitaxel MSN 60 mg concentrate and solvent for solution for infusion (cabazitaxel)

NL/H/4862/001/DC

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This module reflects the scientific discussion for the approval of Cabazitaxel MSN 60 mg concentrate and solvent for solution for infusion. The procedure was finalised on 5 November 2021. 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 Cabazitaxel MSN 60 mg concentrate and solvent for solution for infusion, from Vivanta Generics s.r.o.

The product in combination with prednisone or prednisolone is indicated for the treatment of adult patients with metastatic castration resistant prostate cancer previously treated with a docetaxel-containing regimen.

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 Jevtana 60 mg concentrate and solvent for solution for infusion which has been registered in the EEA by Sanofi-Aventis Groupe since March 2011 by the procedure EU/1/11/676.

The concerned member states (CMS) involved in this procedure were Czech Republic, Hungary, Poland, Romania and Slovakia.

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

II. QUALITY ASPECTS

II.1 Introduction

Cabazitaxel MSN is a concentrate and solvent for solution for infusion (sterile concentrate).

The concentrate is a clear colourless to pale yellow viscous solution practically free from particles.

The solvent is a clear and colourless solution practically free from particles.

One ml of concentrate contains 40 mg cabazitaxel.
One vial of 1.5 ml (nominal volume) of concentrate contains 60 mg cabazitaxel.
After initial dilution with the entire solvent, each ml of solution contains 10 mg cabazitaxel.

Note: Both the Cabazitaxel MSN 60 mg/1.5 ml concentrate vial (fill volume: 73.2 mg of cabazitaxel/1.83 ml) and the solvent vial (fill volume: 5.67 ml) contain an overfill to compensate for liquid loss during preparation. This overfill ensures that after dilution with

the entire contents of the accompanying solvent, there is solution containing 10 mg/ml cabazitaxel.

One pack contains one vial of concentrate and one vial of solvent and are packed in:

- Concentrate: 1.5 ml of concentrate is packed in a 15 ml clear glass vial (type I) closed with a chlorobutyl rubber closure sealed by an aluminium cap covered with a plastic flip-off cap.

- Solvent: 4.5 ml of solvent is packed in a 15 ml clear glass vial (type I) closed with a chlorobutyl rubber closure sealed by an aluminium cap covered with a plastic flip-off cap.

The excipients are:

- Concentrate: polysorbate 80 comprising traces citric acid up to pH 3.5 (in 5% aqueous solution) and
- Solvent: ethanol (96%) and water for injection

II.2 Drug Substance

The active substance is cabazitaxel, not described in any pharmacopeia. The drug substance cabazitaxel is a white to off-white powder, which is freely soluble in acetone and soluble in dichloromethane, however, insoluble in water. Cabazitaxel contains eleven chiral centres, it therefore exhibits optical isomerism. In addition, the drug substance exhibits polymorphism. With the manufacturing process as proposed, the amorphous form of Cabazitaxel is produced. Cabazitaxel is slightly hygroscopic.

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 is adequately described and consists of four chemical steps. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Quality control of drug substance

There is currently no Ph. Eur. monograph or any other pharmacopoeial monograph available. The manufacturer applies the same drug substance specifications as the ASMF-holder. The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided

for five batches. The drug substance will be dissolved in the manufacturing process for the drug product, therefore, a test on particle size is not required.

Stability of drug substance

Stability data on the active substance have been provided for three commercial scale batches stored at 25°C/60% RH (48 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. Storage under long-term and accelerated conditions showed no upward or downward trends, all results remain within specification up to 48 months. Based on the data submitted, a retest period could be granted of 48 months when stored in the original package and is therefore protected from light.

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 development of the proposed product is strongly based on the observed composition of the originator product Jevtana. According to the MAH the proposed compositions of the generic product for the concentrate and the solvent are highly similar with those of Jevtana. According to the EPAR of the originator product Jevtana, the active substance cabazitaxel is almost totally micelle-solubilised for infusion solutions. As requested, the MAH performed comparative studies between the proposed generic product and reference product in plasma.

It is concluded that the comparative studies of the proposed generic product and the reference product have been performed in line with the *Reflection paper on the pharmaceutical development of intravenous medicinal products containing active substances solubilised in micellar systems*, EMA/ CHMP/QWP/799402/2011, and that sufficient data have been provided demonstrating that both the proposed generic product and the reference product will behave similarly *in vivo*.
In view of sensitivity of cabazitaxel to base and acid, a strict pH control is applied. This specific acidified grade supports this pH regulation.

The proposed release and shelf-life specifications on water content can be accepted.

The drug substance appears to be light sensitive. However, the proposed container closure system, including the primary and secondary packaging, provides adequate protection when the drug product is stored in this final container pack. This justification is supported by the observation that for the innovator product Jevtana – in many respects highly comparable with the proposed product – also an additional storage label for light protection is not included in the (publicly accessible) SmPC.

All equipment needed has been indicated. The results of the bulk concentrate solution (after filtration) were meeting the set requirements for description, pH, assay, bacterial endotoxins, and sterility. All process parameters and manufacturing controls for filtration

have been defined. In a similar way the pivotal process parameters for the solvent manufacturing process and the filtration parameters for the solvent have been defined.

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 batches in accordance with the relevant European guidelines.

Control of excipients

The four excipients used all meet the requirements of the respective Ph.Eur. monograph. Certificates of analysis have been provided. These specifications are acceptable.

Quality control of drug product

Concentrate

The finished product specifications for the concentrate are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification of cabazitaxel, pH, particulate matter (visible particles, sub-visible particles), uniformity of dosage units, water content, assay, related substances, bacterial endotoxins test, sterility test, colour absorbance at 420 nm (Ph. Eur. 2.2.25), % transmittance (Ph. Eur. 2.2.25), and extractable volume. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

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

Solvent

The finished product specifications for the solvent are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification of ethanol, pH, particulate matter (visible particles, sub-visible particles), assay, bacterial endotoxins test, sterility test, and extractable volume. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

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

Stability of drug product

Stability data on the concentrate have been provided for three batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months) in accordance with applicable guidelines. The MAH provides stability data for the concentrate product in the vials in the upright and inverted position: three and six months (accelerated study) and 3, 6, 12, 24 and 36 months (long-term) test points test both positions, and all other test points in inverted position. All accelerated and long-term stability data meet the set requirements. On basis of the data

submitted, a shelf life was granted of 36 months for the unopened vials. According to the results from the photostability studies and freeze-thaw studies, this concentrate product does not require any special storage conditions.

Stability data on the solvent have been provided for three batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. On basis of the data submitted, a shelf life was granted of three years (unopened vials). According to the results from the photostability studies and freeze-thaw studies, this product does not require any special storage conditions.

Based on this data, the shelf-life of the opened product after dilution of the concentrate with the solvent is considered acceptable. Chemical and physical in-use stability has been demonstrated for 1 hour at ambient temperature (15°C-30°C). From a microbiological point of view, the concentrate solvent mixture should be used immediately. If not used immediately, in use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hour at 2°C – 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

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

The following post-approval commitments were made:

- A new batch of Cabazitaxel is added to the stability program every year. If any new batch is not available at the scheduled time, the new batch is introduced into the stability program when-ever it is available. In case of any major changes in the manufacturing process, batches from the modified process are added to the stability program. One batch of the re-processed batch if available is also added to the stability program.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Cabazitaxel MSN 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 Jevtana 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

Cabazitaxel 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. For this generic application, the MAH has submitted no bioequivalence study.

IV.2 Pharmacokinetics

Cabazitaxel MSN 60 mg concentrate and solvent for solution for infusion 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 authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Cabazitaxel MSN 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.

Biowaiver

As a micellar solution (with polysorbate 80), a biowaiver is possible based on BE guideline and also the reflection paper regarding micellar solution (EMA/CHMP/QWP/799402/2011). According to the BE guideline (CPMP/EWP/QWP/1401/98 Rev. 1**), “Bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved

product." therefore a biowaiver can be applied in this case, and the requested justification in the reflection paper for micellar solution has been provided.

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 Cabazitaxel MSN.

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

Important identified risks	• Neutropenia and associated clinical events (febrile neutropenia, neutropenic infection, neutropenic sepsis, sepsis, septic shock) • Gastrointestinal disorders (vomiting and diarrhea; gastrointestinal hemorrhage and perforation; colitis, enterocolitis, gastritis, neutropenic colitis; and ileus and intestinal obstruction) and associated complications (including dehydration and electrolytes imbalance) • Renal failure • Peripheral neuropathy • Anemia • Drug preparation errors, i.e., reconstitution errors • Respiratory disorders (acute respiratory distress syndrome, interstitial pneumonia/pneumonitis, interstitial lung disease, and pulmonary fibrosis) (based on potential class effect) • Use in severe hepatic impairment
Important potential risks	• Cardiac arrhythmia (ventricular arrhythmia and cardiac arrest) • Hepatic disorders (based on potential class effect) • Lens toxicity (observed in a nonclinical study in rats) • Effect on male fertility (based on nonclinical studies) • Use in non-evaluated indications • Drug-drug interaction (concomitant administration with inducers or with inhibitors of CYP3A) • Mild and moderate hepatic impairment • Teratogenicity (nonclinical studies)
Missing information	• Ethnicity other than Caucasian

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 Jevtana. No new clinical studies were conducted. The MAH demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. 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

Cabazitaxel MSN 60 mg concentrate and solvent for solution for infusion has a proven chemical-pharmaceutical quality and is a generic form of Jevanta 60 mg concentrate and solvent for solution for infusion. Jevanta 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 Cabazitaxel MSN with the reference product, and have therefore granted a marketing authorisation. The decentralized procedure was finalised with a positive outcome on 5 November 2021.

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