26 April 2019
EMA/280661/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cabazitaxel Teva

International non-proprietary name: cabazitaxel

Procedure No. EMEA/H/C/004951/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

GMP	Good Manufacturing Practices
API	Active Product Ingredient
AR	Assessment report
AS	Active Substance
BE	Bioequivalence
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CMAs	critical material attributes
CMC	Critical micellar concentration
CQAs	Critical Quality Attributes
DP	Drug product
DS	Drug substance
EA	elemental analysis
EC	European Commission
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
EU	Endotoxin Units
EURD	European Union reference dates
EPAR	European Public Assessment Report
EWP	Efficacy Working Party
GC	Gas chromatography
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
GVP	Good Pharmacovigilance Practices
HPLC	High-Performance Liquid Chromatography
HR	Hazard Ratio
HRPC	Hormone-refractory prostate cancer
HS-GC	Head space gas chromatography
ICH	International Conference on Harmonization
INN	International non-proprietary name
IR	Infrared
IV	Intravenous
KF	Karl-Fischer
LC	Liquid Chromatography
LOQ	Limit of quantification
LoQ	List of questions
LT	Lower than
MAA	Marketing Authorisation Application (or Applicant)
MAC	Maximum additive concentration
MAH	Marketing Authorisation Holder
mCRPC	Metastatic castration-resistance prostate cancer
mHRPC	Metastatic hormone-refractory prostate cancer
MDR	Multidrug-resistant
MI	myocardial infarction
MS	Mass spectrometry
NAS	New Active Substance
ND	Not detectable

NMR	Nuclear magnetic resonance
NMT	Not more than
OC	Other concern
OR	Odds ratio
OS	Overall survival
P value	Probability value
PD	Pharmacodynamics
PE	Polyethylene
PEG	Polyethyleneglycol
PFS	Progression Free Survival
P-gp	P-glycoprotein
PI	Product Information
PL	Package leaflet
PSA	Prostate Specific Antigen
PVC	Polyvinyl chloride
QP	Qualified Person
QTPP	Quality target product profile
QWP	Quality Working Party
RH	Relative humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TLC	Thin Layer Chromatography
TTC	Threshold of Toxicological Concern
UV	Ultraviolet
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Teva B.V. submitted on 30 April 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Cabazitaxel Teva, through the centralised procedure under Article 3(3) of Regulation (EC) No. 726/2004– 'Generic/hybrid of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 14 December 2017.

The application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference medicinal product, as defined in Article 10(2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Cabazitaxel Teva 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.

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data, and literature references instead of bioequivalence, non-clinical and clinical data unless justified otherwise.

The chosen reference medicinal product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 6-10 years in the EEA:

- Product name, strength, pharmaceutical form: Taxotere
- Marketing authorisation holder: Aventis Pharma S.A.
- Date of authorisation: 29-11-1995
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation number: EU/1/95/002/001 - EU/1/95/002/002

Medicinal product authorised in the Union/Member State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Jevtana
- Marketing authorisation holder: Sanofi-Aventis Groupe
- Date of authorisation: 17-03-2011
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/11/676/001

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP were:

Rapporteur: Fátima Ventura

The application was received by the EMA on	30 April 2018
The procedure started on	24 May 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	14 August 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	04 September 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on:	20 September 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	19 December 2018
The Rapporteur circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	05 February 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on:	14 February 2019
The CHMP agreed on a list of outstanding issues to be sent to the applicant on:	28 February 2019
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	26 March 2019
The Rapporteur circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	10 April 2019
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a marketing authorisation to Cabazitaxel Teva on:	26 April 2019

2. Scientific discussion

2.1. Introduction

Teva B.V. (hereafter referred to as Teva) has filed a marketing authorisation application for Cabazitaxel Teva in accordance with Article 10(3) of Directive 2001/83/EC (hybrid medicinal product). The reference medicinal product is Taxotere (docetaxel). The application also refers to data submitted in support of the marketing authorisation (MA) of Jevtana (cabazitaxel) for which at the time of submission of the marketing authorisation application (MAA) for Cabazitaxel Teva data protection period was not yet expired.

Cabazitaxel Teva 10 mg/mL concentrate for solution for infusion (60 mg/6 mL) is claimed to be a hybrid medicinal product to Jevtana (cabazitaxel) containing the same active substance cabazitaxel but a different pharmaceutical form (concentrate for solution for infusion instead of concentrate and solvent for solution for infusion). Cabazitaxel Teva only requires a single dilution into infusion solutions prior to administration.

Cabazitaxel belongs to the family of taxanes, being an antineoplastic agent (L01CD04). Cabazitaxel acts by disrupting the microtubular network in cells. Cabazitaxel binds to tubulin and promotes the assembly of tubulin into microtubules while simultaneously inhibiting their disassembly. This leads to the stabilisation of microtubules, which results in the inhibition of mitotic and interphase cellular functions.

The applicant claimed the same indication as the one approved for Jevtana: *Cabazitaxel Teva 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*.

The proposed posology is the same as the one for Jevtana: the recommended dose of Cabazitaxel Teva is 25 mg/m^2 administered as a 1 hour intravenous infusion every 3 weeks in combination with oral prednisone or prednisolone 10 mg administered daily throughout treatment.

To demonstrate comparability between the proposed product and Jevtana after dilution, immediately before administration, the physicochemical characteristics were assessed and compared in numerous characterization studies using different analytical methods. To further support the similarity of Cabazitaxel Teva formulation and Jevtana, published literature was submitted. No bioequivalence (BE) study was provided as the product is administered intravenously and a biowaiver was claimed by the Applicant with reference to the *Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr* **) and the *Reflection paper on the pharmaceutical development of intravenous medicinal products containing active substances solubilised in micellar systems (EMA/CHMP/QWP/799402/2011)*.

The application did not include non-clinical study reports, but was based on published literature. The application also referred to the non-clinical data submitted in support of Jevtana (cabazitaxel).

No clinical data other than supporting literature were provided in the MAA. The application referred to the clinical data submitted in support of the MA of Jevtana (cabazitaxel).

Reference to data submitted in support of the MA Jevtana (cabazitaxel) (EMEA/H/C/002018), authorised on 17 March 2011, was justified by the applicant based on the claim that Jevtana falls within the same global marketing authorisation as Taxotere (docetaxel) authorised on 29 November 1995. This was justified by Teva on the basis that cabazitaxel and docetaxel should be considered the same active substance within the meaning of Article 10(2)(b) of Directive 2001/83/EC.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a concentrate for solution for infusion containing 10 mg/ml of cabazitaxel. The product contains the ethyl acetate solvate of cabazitaxel.

Other ingredients are citric acid, anhydrous ethanol, polysorbate 80 and macrogol 400.

The product is available in colourless glass vials (type I) closed with bromobutyl rubber stoppers sealed with aluminium caps with polypropylene disks, containing 6 ml of concentrate.

2.2.2. Active substance

General information

The chemical name of cabazitaxel ethyl acetate is (*2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS*)-12b-acetoxy-9-(((*2R,3S*)-3-((tert-butoxycarbonyl)amino)-2-hydroxy-3-phenylpropanoyl)oxy)-11-hydroxy-4,6-dimethoxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4] benzo[1,2-b]oxet-12-yl benzoate, ethyl acetate. It corresponds to the molecular formula $C_{45}H_{57}NO_{14}\cdot C_4H_8O_2$, its relative molecular mass is 924.04 g/mol and it has the structure shown in Figure 1.

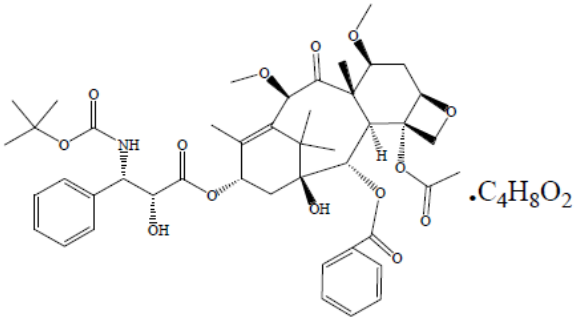


Figure 1. Structure of cabazitaxel ethyl acetate

The structure of the active substance (AS) was elucidated by a combination of elemental analysis (EA), mass spectrometry (MS), ultraviolet spectrometry (UV), infrared spectroscopy (IR), nuclear magnetic resonance spectroscopy (NMR), thermal analysis (TA) and X-ray powder diffraction (XRPD).

Cabazitaxel appears as a white or off-white non-hygroscopic crystalline powder. It is freely soluble in dichloromethane, soluble in absolute ethanol, and insoluble in water. Its partition coefficient (LogP) could not be determined due to the insolubility of cabazitaxel ethyl acetate solvate in water.

It has 11 chiral centres although there are only three potential isomers which can be formed as impurities during the manufacturing process. It has been shown that sufficient controls are in place at the specification of the starting material, the intermediate and the final AS. The active substance is one enantiomer and the specific stereochemistry is stated.

Cabazitaxel exhibits polymorphism. There are at least 18 known solid forms reported in the literature. The manufacturer developed and is producing cabazitaxel ethyl acetate solvate.

Manufacture, characterisation and process controls

Cabazitaxel ethyl acetate solvate is a semi-synthetic compound derivative of the 10-deacetyl Baccatin III (called 10-DAB III), which is extracted from European yew needles. The proposed starting materials have

been justified and are considered acceptable. The synthetic process comprises 11 convergent steps; 7 steps to prepare the intermediate and 4 steps to prepare the final AS.

Critical steps were identified and a suitable control strategy has been defined. Acceptable specifications and analytical methods were provided for in-process controls and for the control of the intermediates.

Potential and actual impurities were well discussed with regards to their origin and characterised. An analysis on the potential genotoxic impurities, based in the principles of the ICH M7 guideline was performed on all raw materials, reagents, solvents, the potential impurities and on the manufacturing process of the AS, including the manufacturing of key intermediate. From the above analysis, it was concluded that from all the compounds used or that are intermediates in the synthesis of the AS, one compound is classified as Class 1, two compounds are classified as Class 2 and six are classified as Class 3. All of these compounds are either purged or sufficiently controlled either in the intermediate or final AS specification.

Cabazitaxel ethyl acetate solvate is packaged into polyethylene (PE) bags, which are sealed by heat and put inside tightly sealed aluminum-plastic complex film bags. The specifications of the containers are described. It was confirmed that polyethylene bags comply with Commission Regulation (EU) No 10/2011 (as amended) on plastic materials and articles intended to come into contact with food.

Specification

Cabazitaxel ethyl acetate solvate active substance specification includes appropriate tests and limits for appearance (visual), solubility and appearance of solution (Ph. Eur., visual), identification (IR, HPLC), water content (Ph. Eur.), residue on ignition (Ph. Eur.), specific rotation (Ph. Eur.), microbial limits (Ph. Eur.), bacterial endotoxins (Ph. Eur.), related substances (GC, HPLC), residual solvents (HS-GC), ethyl acetate (GC) and assay (HPLC).

The proposed tests and limits are considered satisfactory. ICH M7 guideline concerning potential mutagenic impurities is not applicable since cabazitaxel is an active substance indicated in advanced cancer. However, the TTC approach stated in this guidance was generally used as a control strategy of potential mutagenic impurities and this is acceptable.

The analytical procedures have been sufficiently described. Non-compendial analytical methods have been successfully validated according to ICH guidance. In-house reference standards are used to qualify working standards of active substance and its impurities. Satisfactory certificates of analysis of reference and working standards of active substance and its impurities have been presented.

Batch analysis results of six commercial scale batches comply with the proposed specifications confirming the consistency and uniformity of the product.

Stability

Stability data on six production scale batches of active substance stored in the intended commercial packaging for up to 24 months under long term conditions (25 ºC ± 2 ºC/60% ± 5% RH), and for up to 6 months under accelerated conditions (40 ºC ± 2 ºC/75% ± 5% RH) was provided according to the ICH guidelines.

Samples were tested for appearance, solubility and appearance of solution, identification, water content, related substances, assay and polymorphic form. The test methods were the same as for release and are stability indicating. No significant changes to any of the measured parameters were observed under long term and accelerated conditions and all remained within specification. The stability of the polymorphic form was investigated during the stability studies and no conversion of the polymorphic form was observed.

Stress testing, including photostability testing, has been performed under the conditions set in the ICH Q1B guideline including light exposure, high temperature (100 ºC and 60 ºC), acidic, alkaline, oxidation, reduction and humidity conditions. The results obtained show that cabazitaxel hardly degrades under humidity, at 60 ºC, on exposure to light or under oxidative conditions. Cabazitaxel degrades slightly at 100 ºC, and under reductive and acidic conditions, and degrades extensively under alkaline conditions.

Based on the presented stability data, the proposed re-test period of 36 months, preserved in tight, light-resistant containers, is considered acceptable.

2.2.3. Finished medicinal product

Description of the product and pharmaceutical development

Cabazitaxel Teva 10 mg/ml concentrate for solution for infusion is a concentrate intended for intravenous infusion after dilution with either 0.9% sodium chloride solution for injection or 5% glucose solution for infusion. Cabazitaxel Teva 10 mg/ml concentrate for solution for infusion (60 mg/6 ml) has been developed as an alternative to the two vial formulation of the reference product Jevtana 60 mg concentrate and solvent for solution for infusion. The objective of the development of the product Cabazitaxel Teva 10 mg/ml concentrate for solution for infusion (60 mg/6 ml) was to obtain a sterile and stable ready-to-use solution containing cabazitaxel, suitable for intravenous infusion:

- One-vial formulation, the preparation of the infusion solution being simplified by eliminating the first dilution step;
- A medicinal product having identical content of active substance per vial to Jevtana 60 mg concentrate and solvent for solution for infusion, that gives reconstituted solutions 0.10 mg/ml cabazitaxel and 0.26 mg/ml cabazitaxel in 0.9% Sodium chloride solution for infusion and 5% Glucose solution for infusion, respectively;

The test product 60 mg/6 ml has the same dosage form as Jevtana and the same concentration of active substance. A solvent system containing polysorbate 80 and ethanol anhydrous, the excipients used for Jevtana is used. The proposed composition of the finished product is very similar to that of Jevtana with respect to the inactive ingredients. The only difference consists is the addition of polyethylene glycol 400, and a different amount of dehydrated alcohol. These excipients are widely used in many pharmaceuticals and safe for intravenous administration. The exposure levels are covered by clinical experience with other marketed medicinal products administered in humans (see discussion on clinical aspects). These differences are judged to be 'non-critical' with regard to their influence on micelle stability and bioavailability of the drug and to have no adverse impact on the efficacy and safety of the proposed medicinal product.

The finished product critical and non-critical quality attributes have been evaluated and the critical quality attributes (CQAs) have been identified. An initial risk assessment of the potential impact of active substance attributes on finished product CQAs and risk assessment justification, risk mitigation studies and applicable control strategies for cabazitaxel active substance CMAs were provided. The initial risk assessment also considered the potential impact of formulation variables on the finished product CQAs and risk assessment justification, risk mitigation studies and applicable control strategies for formulation variables. For the purpose of the pharmaceutical development, the stability and solubility of cabazitaxel drug substance were taken into account. Cabazitaxel is the 7,10-dimethoxy analogue of docetaxel, which is a member of the taxane family. Taxanes are liable to undergo degradation under various manufacturing and storage conditions, including temperature, acidic and alkaline media and light exposure. Cabazitaxel is more stable than docetaxel. It is also known that taxane family molecules show improved stability in the presence of citric acid.

Like docetaxel, cabazitaxel exhibits very low solubility in aqueous solutions and Jevtana was formulated using a docetaxel-like formulation in a non-aqueous system containing ethanol anhydrous and polysorbate 80. Due to stability issues, Jevtana requires two dilutions prior to intravenous infusion. Based on the dilution process for Jevtana, it was decided to use polysorbate 80 and ethanol anhydrous in the composition of the Cabazitaxel Teva.

Solutions with low pH were proposed to improve the stability of cabazitaxel in polysorbate 80. Citric acid was selected as an acidifying agent for cabazitaxel. As the amount of citric acid used in Jevtana is not disclosed in any public data, three batches of Jevtana were tested to determine the content of citric acid. Knowing that the main mechanism of cabazitaxel degradation is hydrolysis, the level of water content should be kept as low as possible.

Development of Cabazitaxel Teva 10 mg/ml was performed on a different strength of 40 mg/4 ml, but considering that the only difference from the target strength of 60 mg/6 ml is the fill volume, all results are considered representative.

Comparative study Cabazitaxel Teva vs Jevtana

The composition of the 10 mg/ml solution of Cabazitaxel Teva was compared with the 10 mg/ml Jevtana reconstituted solution was presented. In addition, the compositions following dilution of both formulations to 0.26 mg/ml and 0.10 mg/ml were also compared.

Physical testing (osmolarity, mOsmol/l, specific gravity, g/ml, surface tension, mN/m) was performed on diluted solutions (5% Glucose and 0.9% NaCl; 0.10 mg/ml and 0.26 mg/ml) of Cabazitaxel Teva and Jevtana and comparable results were obtained.

Cabazitaxel Teva has not undergone clinical studies during the pharmaceutical development phase but extensive studies have been conducted in support of the biowaiver justification. A series of head-to-head *in vitro* characterization studies were performed to demonstrate that the physical characteristics of the micelles and the solubility behaviour of the cabazitaxel active substance in the solutions for intravenous use are comparable.

The tested parameters were selected according to the recommendations from EMA/CHMP/QWP/799402/2011 Guideline - Reflection paper on the pharmaceutical development of intravenous products containing active substances in micellar systems and Guideline on the Investigation of Bioequivalence- CPMP/EWP/QWP/1401/98 Rev. 1/ Corr**.

Micelle size and Size distribution study

The conclusions of the above studies were presented and discussed. The results obtained for proposed test product and Jevtana in regards to micelle size distribution parameters indicate that both products are similar, a fact that is supported by the statistical analysis, which has demonstrated equivalence between the test product and Jevtana.

Additional stability studies were done for the diluted samples of test product to assess stability of the active substance encapsulated in the micelles under the storage conditions recommended for the product. As per the intended storage conditions, the tests were performed for diluted samples (0.10 and 0.26 mg/ml respectively), in both 0.9% Sodium chloride and 5% Glucose, kept for 96 hours at 2-8 °C and for 72 hours at 25 °C. There was no precipitation noted throughout the testing time, and the results obtained for micelle size and size distribution are comparable to those obtained for the three batches tested under normal conditions. This means that the micellar characteristics are preserved in the diluted solution, for up to 72 hr at room temperature and up to 96 hr when refrigerated.

Critical micellar concentration study

The critical micellar concentration (CMC) is a quantitative characteristic that shows the ability of the surfactant to form supramolecular aggregates. The micellar aggregates present in the diluted solution are responsible for the solubilization of the active substance. The micellar aggregates begin to assemble in the solution when the concentration of the surfactant is equal or greater than that of the CMC. Comparative CMC testing performed between the test product and Jevtana confirmed that the minor differences in formulations are non-critical in relation to their influence on micelle stability and bioavailability of the drug. In conclusion, the mean CMC values for the test product and Jevtana are similar and comparable with the results obtained for polysorbate 80, in both 0.9% Sodium chloride and 5% Glucose diluents. In addition, these CMC values are much lower than the polysorbate 80 concentration in the infusion solution prior to administration, which means that the active substance is solubilized in stable micelles in the diluted drug product. The results also demonstrate that the influence of the excipients (other than polysorbate) on micelle formation is not significant.

Maximum additive concentration study

According to the Reflection paper on the pharmaceutical development of intravenous medicinal products containing active substances solubilised in micellar systems (EMA/CHMP/QWP/799402/2011), for any micellar system, "it is useful to know its 'capacity' to solubilise the active substance. The maximum additive concentration (MAC) provides this assurance with regards to the active substance as the additive in question". MAC provides a quantitative measure that shows the ability of the micellar system (fixed concentration of surfactant Polysorbate 80) to solubilize the active substance in the supramolecular aggregates thus giving "an indication of how great is the margin of safety before the crystallisation of the drug becomes a possible danger for the patient". Comparative MAC testing was performed and confirmed that the minor differences in formulations are non-critical in relation to active substance solubility. It also showed similarity between test product and Jevtana, which confirms the equivalence of micellar enclosing capacity between the two tested products.

In vitro plasma protein binding

Comparison of the *in vitro* plasma protein binding of the test product and Jevtana and a statistical analysis to assess the relevance of the findings was done. Plasma protein binding information is required to aid in the evaluation of pharmacological and pharmacokinetic data. Considering the similarity in composition between test product and Jevtana, containing the same amount of polysorbate 80, a difference in rapid disassembly of the micelle on dilution was not expected and neither was a difference in the protein binding profile.

The results obtained in the validation study showed no difference between the percentages of cabazitaxel protein binding in the presence of the dilution solvent 0.9% NaCl. The data obtained further allow the following conclusions to be drawn:

(a) The time needed for the dialysis process to reach equilibrium at ca. 37 ºC was 75 minutes;

(b) *In vitro* protein binding following equilibrium dialysis of spiked human plasma at concentration of 10 µg/ml was comparable between Cabazitaxel Teva and Jevtana;

(c) The extent of plasma protein binding and fraction of free drug (unbound) was similar between Cabazitaxel Teva and Jevtana;

(d) Statistical analysis showed no statistically significant differences.

In addition to the above studies, the following additional comparative *in vitro* studies between the test product and Jevtana were submitted: information on the pH solubility, pH partition coefficient, and pH stability profiles; zeta potential following dilution in the intended infusion solutions; *in vitro* release study

(bound and unbound micelle) using the dilution solvent 5% glucose; and 2-sample t-test performed on the cabazitaxel bound fraction.

Biowaiver conclusion

Despite the fact that according to the guideline on the investigation of bioequivalence ('*Guideline on the Investigation of Bioequivalence, CPMP/EWP/QWP/1401/98 Rev. 1/ Corr**2010*), micelle solutions for intravenous administration may be regarded as 'complex' solutions and therefore normally do not qualify for a biowaiver, according to the applicant the biowaiver is acceptable based on the dispositions of the "*Reflection paper on the pharmaceutical development of intravenous medicinal products containing active substances solubilised in micellar systems*", because:

- The test product and Jevtana have identical formulations;
- The product is not designed to control the release or the disposition of the active substance;
- Rapid disassembly of the micelle on dilution occurs once it is administered in blood;
- The method and rate of administration is the same for the test product and Jevtana;
- The excipients do not affect the disposition of the drug substance (the same surfactant/micelle forming system - polysorbate 80 – in the same amount is present in the proposed test formulation as in Jevtana);
- Small differences in the content of added co-solubilising substances such as PEG or ethanol are not likely to influence the capacity of the surfactant (polysorbate 80) to form micelles and thus, its ability to solubilize the drug substance in the infusion solution or to have a significant impact on the micellar stability or disposition of the drug *in vivo*, because of the extensive dilution in plasma upon administration);
- The similarity in the *in vitro* characteristics of the micelle component & free and bound active substance was demonstrated in the *in vitro* studies undertaken (micelle size and distribution, CMC, MAC and *in vitro* protein binding).

The primary packaging is a colourless type I glass vial, closed with type I bromobutyl rubber, Flurotec-coated serum stopper sealed by an aluminium metal cap with coloured polypropylene disk. The pack size is 1 single-use vial. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process of Cabazitaxel Teva 10 mg/ml concentrate for solution for infusion consists of seven main steps: cleaning and sterilization of all pieces of equipment; dispensing of ingredients; compounding; pre-filtration; sterile filtration I; sterile filtration II, aseptic filling, stoppering and capping; external vial washing/drying; and secondary packaging. Due to the aseptic processing step, the manufacturing process is regarded to be a non-standard process. The critical steps of the process were identified and in order to ensure that the process is sufficiently controlled in-process controls were presented for each identified step. The tests, acceptance criteria and frequency of the tests performed at each critical step of the manufacturing process were presented. Details regarding the holding times at various in-process stages during manufacturing of the drug product were also provided. The presented information is deemed satisfactory and suitable to guarantee appropriate quality of the finished product.

The applicant has provided information regarding the compatibility of the stopper with the finished product under in-use conditions, taking into account the requirements of the Ph. Eur. 3.2.9., highlighting the difficulties in the performance of the leachables studies. Also, the applicant has submitted the study

of toxicological evaluation on the primary packaging. From all the chemicals that could potentially be extracted from the primary packaging, an unknown compound was observed at a level that is estimated to lead to a theoretical human exposure of about 48 µg/day, which could be associated with a safety concern. However, taking into account the indication and the recommended posology, it is expected that the levels of this unknown compound at which the patient may be exposed do not constitute an additional risk besides the risk associated with the administration of cabazitazel. So, based upon a risk-based approach and the difficulties in performing a leachables study, the justification provided by the applicant for the acceptance of this potential extractable can be considered acceptable.

The process validation data provided on three commercial scale batches and three partial commercial scale (approximately 50 % of the full scale) batches of Cabazitaxel Teva show a good reproducibility as all presented data match the specifications and are in compliance with results obtained from finished drug product release testing. This data suggest that the process is adequately controlled, reproducible and robust, in order to obtain a product that complies with the specifications.

Product specification

The finished product release and shelf life specifications include appropriate tests and limits for appearance (visual), visible particles (Ph. Eur.), sub-visible particles (Ph. Eur.), colour and clarity of solution (Ph. Eur.), pH (Ph. Eur.), extractable volume (Ph. Eur.), assay of cabazitaxel (HPLC), assay of ethanol (GC), degradation products (HPLC), bacterial endotoxins (Ph. Eur.) and sterility (Ph. Eur.).

All known impurities listed in the active substance specification are process impurities from the drug substance synthesis and are controlled at the active substance; therefore they are not listed in the finished product specification as individual specified degradation products. Taking into consideration the literature available on the potential degradation of cabazitaxel, studies were performed in order to evaluate the formation of degradation impurities in the finished product. Based on the results obtained, it is not considered necessary to report those as specified degradation products in the finished product specification. The potential presence of elemental impurities in the finished product in line with the new ICH Q3D Guideline for Elemental Impurities has been assessed using a risk-based approach. In all tested batches of Cabazitaxel Teva 10 mg/ml concentrate for solution for infusion, the total elemental impurity contribution is less than the control threshold for all evaluated elemental impurities.

The analytical methods used have been adequately described and validated in accordance with the ICH guidelines. Validation data for the microbial contamination and bacterial endotoxin test methods was still to be provided at the time of this Opinion, but this issue is not considered as having an impact on the benefit-risk balance of the product. Satisfactory information regarding the reference standards used in the routine analysis of finished product has been presented.

Batch analysis data was provided for three commercial scale batches and for three smaller batches. The data demonstrate that all parameters are well within their specifications and therefore indicate consistent manufacture of the finished product.

Stability of the product

The stability studies were carried out on three commercial scale batches stored up to 36 months at 5 ºC ± 3 ºC, 25 ºC / 60% RH or 30 ºC / 65% RH or 30 ºC / 75% RH and for 6 months at 40 ºC / 75% RH according to the ICH guidelines. Additionally, stability studies have been initiated for three slightly smaller scale batches at 5 ºC ± 3 ºC, 25 ºC / 60% RH or 30 ºC / 65% RH or 30 ºC / 75% RH and 40 ºC / 75% RH, but only data at the initial time point is available so far. All of the tested batches were packed in the container closure systems intended for marketing.

Samples were tested for appearance, visible particles, sub-visible particles, colour, clarity, pH, assay of cabazitaxel, assay of ethanol, degradation products, bacterial endotoxins and sterility. No significant changes were observed and the results are found to be well within the specification limits.

Photostability studies were performed on three commercial scale batches of Cabazitaxel Teva according to ICH Q1B guideline. No significant differences were observed between the exposed samples in primary packaging and the non-exposed samples. It can therefore be concluded that the finished product in its primary packaging is photo-stable.

Freeze/thaw cycling studies were performed on four batches to evaluate the stability under shipment conditions. All results of the freeze-thaw cycling study were within the proposed specifications. This data shows that the product is physically and chemically stable after temperature excursions that may be encountered during shipment and/or storage.

In-use stability studies were performed on three commercial scale batches. The physical and chemical in-use stability after dilution, in 5 % glucose solution or sodium chloride 9 mg/ml (0.9 %) solution for infusion to final concentrations of approximately 0.10 mg/ml and 0.26 mg/ml of cabazitaxel, was performed at the end and at the beginning of shelf life. The microbial in-use stability after dilution in 5 % glucose solution for infusion to a final concentration of approximately 0.10 mg/ml of cabazitaxel was performed at the end and at the beginning of shelf life. Samples were tested for appearance, visible particles, sub-visible particles, colour, clarity, pH, assay of cabazitaxel and degradation products (physical and chemical in-use stability) and sterility and bacterial endotoxins (microbial in-use stability). Based on the in-use stability results, the claimed in-use shelf-life for the diluted solution at 0.10 mg/ml cabazitaxel and at 0.26 mg/ml cabazitaxel (in 5% glucose solution or 0.9% sodium chloride solution for injection) of 48 hours (including the 1-hour infusion time) after dilution when stored at room temperature and 72 hours (including the 1-hour infusion time) after dilution when stored at 2-8 °C is accepted.

Based on the overall stability data, the claimed shelf life of 36 months is acceptable. Although the data do not suggest that the product requires any special storage conditions, the applicant's proposal to maintain the storage conditions "Do not refrigerate" in line with the originator and the guideline on declaration of storage conditions is acceptable.

Adventitious agents

There are no excipients of human or animal origin used in the manufacture of Cabazitaxel Teva 10 mg/ml Concentrate for solution for infusion.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. Validation data for the microbial contamination and bacterial endotoxin test methods was still to be provided at the time of this Opinion but this issue is not considered as having an impact on the benefit-risk balance of the product. The manufacturing process for the finished product is non-standard – the required validation data has been provided. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that from a quality perspective the product should have a satisfactory and uniform clinical performance.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable and consistent. Physicochemical and biological

aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Introduction

No detailed non-clinical study reports were submitted. The non-clinical overview consisted of a review of literature data on the pharmacology, pharmacokinetics and toxicology, also referring to data submitted in support of the MA of Jevtana. The proposed non-clinical aspects of the SmPC were in line with the SmPC of Jevtana.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment studies were submitted. This was justified by the applicant as the introduction of Cabazitaxel Teva is considered unlikely to result in any significant increase in the combined sales volumes for all cabazitaxel containing products and the exposure of the environment to the active substance.

Cabazitaxel active-product-ingredient (API) consumption data covering the years 2014-2018 and 2019-2021 showed a significant increase (30%) of API consumption during the first period for the combined sales volume, remaining stable for the second period of time (forecast data). Considering that the increased consumption corresponds to a small amount of active substance being the PEC/PNEC ratio $\leqslant$1, the applicant did not submit a complete ERA.

2.3.3. Discussion and conclusion on non-clinical aspects

No non-clinical studies have been provided. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology was provided, which was based on scientific literature. The overview justified why there was no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The company also submitted a justification for the absence of ERA which has been considered acceptable.

The non-clinical dossier refers to studies submitted in support of the marketing authorisation of Jevtana. However, reference to such studies cannot be accepted on the basis that cabazitaxel and docetaxel cannot be considered the same active substance within the meaning of Article 10(2)(b) of Directive 2001/83/EC (see section 2.7). Consequently, no conclusion can be reached on the non-clinical aspects.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for 10 mg/mL concentrate for solution for infusion (60 mg/6 mL) containing cabazitaxel.

This application is based on a biowaiver claim. The applicant provided a clinical overview outlining the pharmacokinetics, pharmacodynamics, clinical efficacy and safety of cabazitaxel based on published literature. This application refers to clinical data submitted in support of the marketing authorisation of

Jetvana. The proposed SmPC is in line with the SmPC of Jevtana.

Exemption

Based on the intravenous route of administration of this medicinal product, a bioequivalence study is not required, as per the *Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1 Corr**)* which states the following for parenteral solutions:

"*Bioequivalence studies are generally not required if the test product is to be administrated as an aqueous solution containing the same active substance as the currently approved product*."

Furthermore, according to the guideline on the investigation of bioequivalence ('*Guideline on the Investigation of Bioequivalence, CPMP/EWP/QWP/1401/98 Rev. 1/ Corr***), micelle solutions for intravenous administration may be regarded as 'complex' solutions and therefore normally do not qualify for a biowaiver. However, in accordance with EMA/CHMP/QWP/799402/2011 "*Reflection paper on the pharmaceutical development of intravenous products containing active substances in micellar systems*" micelle formulations may be considered eligible for a biowaiver when certain conditions are fulfilled.

These conditions included: (a) rapid disassembly of the micelle on dilution occurs and the drug product is not designed to control release or disposition, (b) the method and rate of administration is the same as the currently approved product, and (c) the excipients do not affect the disposition of the drug substance. In those cases satisfactory data demonstrating similar physicochemical characteristics to the approved product could be regarded as sufficient and allow for a biowaiver. Consequently, head-to-head *in vitro* characterization studies have been performed to get better knowledge of the proposed product and to prove its equivalence to Jevtana.

In the applied indication, cabazitaxel is administered as a 1 hour intravenous infusion after dilution in a sterile PVC-free container of either 5% dextrose or 0.9% sodium chloride solutions for infusion. Once diluted in an infusion solution, cabazitaxel is present in solution entrapped in the hydrophobic core of the micelles formed by the surfactant polysorbate 80. In human plasma, the polysorbate 80 micelles are rapidly cleared as polysorbate 80 is sensitive to dilution effects during intravenous infusion. It is rapidly metabolized and does not have a long half-life in plasma, as declared in the "*Reflection paper on the pharmaceutical development of intravenous products containing active substances in micellar systems, EMA/CHMP/QWP/ 799402/2011*".

The same phenomenon was observed for other drug products containingpPolysorbate 80. The rapid esterase-sensitive breakdown of polysorbate 80 in plasma is well known from the literature.

Therefore, considering that:

a) Cabazitaxel Teva is not designed to control the release or the disposition of the active substance;

b) A rapid disassembly of the micelle on dilution occurs once it is administered in blood;

c) The method and rate of administration is the same for the test product and Jevtana;

d) The excipients do not affect the disposition of the active substance since:

- the same surfactant/micelle forming system - polysorbate 80 – in the same amount is present in proposed test formulation as in Jevtana;
- small differences in the content of added co-solubilising substances such as macrogol or ethanol are not likely to influence the capacity of the surfactant (polysorbate 80) to form micelles and thus its ability to solubilize the drug substance in the infusion solution (diluted solution); or to have a significant impact on the micellar stability or disposition of the drug *in vivo*, because of the extensive dilution in plasma upon administration;

- the similarity in the *in vitro* characteristics of the micelle component & free and bound active substance was shown in the *in vitro* studies undertaken (micelle size and distribution, CMC, MAC and *in vitro* protein binding),

the Applicant considers that demonstrating the comparability of micellar characteristics and the physicochemical similarity of Cabazitaxel Teva and Jevtana are adequate and sufficient to support the biowaiver claim.

2.4.2. Discussion and conclusion on clinical aspects

The change in formulation and the difference in excipients between the proposed product and Jevtana are characterized by the published literature and comparative quality data. Those differences are not expected to have adverse impact on the efficacy and safety of the proposed drug product. The biowaiver is considered acceptable.

The clinical dossier refers to studies submitted in support of the marketing authorisation of Jevtana. However, reference to such studies cannot be accepted on the basis that cabazitaxel and docetaxel cannot be considered the same active substance within the meaning of Article 10(2)(b) of Directive 2001/83/EC (see section 2.7). Consequently, no conclusion can be reached on the clinical efficacy and safety aspects.

2.5. Risk Management Plan

Safety concerns

List of important risks and missing information	
Important identified risks	• Neutropenia and associated clinical events (febrile neutropenia, neutropenic infection, neutropenic sepsis, sepsis, septic shock) • Gastro-intestinal disorders (vomiting and diarrhea, hemorrhage and perforation; colitis, enterocolitis, gastritis, neutropenic colitis; and ileus and intestinal obstruction) and associated complications (dehydration and electrolyte imbalance) • Renal failure • Peripheral neuropathy • Anaemia
Important potential risks	• Cardiac arrhythmia (ventricular arrhythmia and cardiac arrest) • Hepatic disorders • Lens toxicity • Effects on male fertility • Respiratory disorders (acute respiratory distress syndrome, interstitial pneumonia/pneumonitis, interstitial lung disease, and pulmonary fibrosis)
Missing information	• Drug-drug interaction (concomitant administration with CYP3A substrates or with inducers/ inhibitors of CYP3A) • Use in patients with hepatic impairment • Use in patients with moderate and severe renal impairment

Pharmacovigilance plan

No additional pharmacovigilance activities are proposed.

Risk minimisation measures

No additional risk minimisation measures are proposed.

Conclusion

The CHMP and PRAC, having considered the data submitted in the application was of the opinion that due to the concerns identified with this application, the risk management plan cannot be agreed at this stage.

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

Not applicable.

2.7. Claim of same active substance

The marketing authorisation application for Cabazitaxel Teva was submitted in accordance with Article 10(3) of Directive 2001/83/EC. The active substance of Cabazitaxel Teva is cabazitaxel.

In the application, the identified reference medicinal product which is or has been authorised for not less than 10 years in the EEA is Taxotere. The active substance of Taxotere is docetaxel.

The claim is made in the application that "In the absence of clinically significant data to show that cabazitaxel and docetaxel do differ significantly in properties with regard to safety and/or efficacy the two medicinal products should be considered to be the same active substance for the purposes of Article 10(2)(b) of the Directive" .

Article 10(2)b of Directive 2001/83/EC provides that "(…) The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy. In such cases, additional information providing proof of the safety and/or efficacy of the various salts, esters or derivatives of an authorised active substance must be supplied by the applicant".

The scientific evaluation of the claim submitted by the applicant in light of the applicable provision of Directive 2001/83/EC is presented below.

The assessment took into account the principles of

- the *Reflection paper on the chemical structure and properties criteria to be considered for the evaluation of new active substance (NAS) status of chemical substances* (EMA/CHMP/QWP/104223/2015), which describes the chemical structure and properties criteria to be taken into account to qualify a chemical active substance as NAS, as well as the required elements to be submitted by applicants.
- the *Reflection paper on considerations given to designation of a single stereo isomeric form (enantiomer), a complex, a derivative, or a different salt or ester as new active substance in relation to the relevant reference active substance* (EMA/651649/2010).

The applicant has provided support to their claim based on two experts' opinions on published data from non-clinical and clinical studies and by making reference to the European Public Assessment Report of Jevtana.

2.7.1. Quality aspects

Cabazitaxel belongs to the family of taxanes, being an antineoplastic agent (L01CD04). According to the Jevtana Public Assessment Report (EMA/CHMP/66633/2011), cabazitaxel is a semi-synthetic derivative from 10-deacetyl Baccatin III, which is extracted typically from European yew needles.

For the purpose of the assessment of whether cabazitaxel and docetaxel are to be considered as the same or different active substances, in the meaning of Article 10(2)(b) of Directive 2001/83/EC, cabazitaxel is, from a pure chemical perspective, a third generation, semi-synthetic 7,10-dimethoxy analogue of docetaxel and specifically an ether (7,10-dimethoxy analogue) of docetaxel. The difference is that two hydroxyl groups in docetaxel are substituted with methoxy side chains in cabazitaxel which increases its lipophilicity.

The differences in patients' exposure to the respective active moieties are discussed from the non-clinical and clinical perspective, including the relevance of any identified differences, with regard the safety and/or efficacy profiles of either active substance under sections 2.7.2 and 2.7.3.

2.7.2. Non-clinical aspects

The following information regarding the comparison between cabazitaxel and docetaxel was provided by the applicant:

- Cabazitaxel was engineered as a dimethyloxy derivative of docetaxel offering two advantages over its predecessor. The primary benefit provided by the extra methyl groups is the elimination of the P-glycoprotein (P-gp) affinity characteristic of docetaxel, enabling cabazitaxel to be effective against docetaxel-refractory prostate cancer. The extra methyl groups also provide cabazitaxel with an uncommon capacity among chemotherapy agents, i.e the ability to cross the blood–brain barrier.
- The cytotoxicity of cabazitaxel was compared with docetaxel in several murine and human cell lines. In docetaxel-sensitive cell lines, including P388 (murine leukemia), HL-60 (human leukemia), KB (human epidermoid carcinoma) and Calc18 (human breast carcinoma), cabazitaxel showed potent anti-tumour activity comparable to docetaxel. However, the compound was also active in cancer cell lines with acquired resistance to docetaxel, including P388/DOX, P388/TXT, P388/VCR, HL60/TAX, Calc18/TXT and KBV1. Resistance factor ratios ranged from 1.8 to 10 for cabazitaxel, whereas comparable values were 4.8-59 for docetaxel. Furthermore, cabazitaxel showed greater cytotoxicity compared to docetaxel against the human colon adenocarcinoma Caco-2 cell line, which exhibits primary resistance to taxanes.
- *In vitro*, cabazitaxel stabilized microtubules as effectively as docetaxel but was 10-fold more potent than docetaxel in chemotherapy-resistant tumour cells. Cabazitaxel was active in tumours poorly sensitive or innately resistant to docetaxel (Lewis lung, pancreas P02, colon HCT-8, gastric GXF-209, mammary UISO BCA-1) or with acquired docetaxel resistance (melanoma B16/TXT). The effects of cabazitaxel and docetaxel were compared on MCF7 human breast cancer cells expressing fluorescent tubulin. Results from this study indicate that the potency of cabazitaxel in docetaxel-resistant cells and tumours is due to stronger suppression of microtubule dynamics, faster drug uptake, and better intracellular retention than the one which occurs with docetaxel.
- *In vivo* studies were conducted to examine the potential activity of cabazitaxel against a variety of tumour types in tumour implant models. When treatment with cabazitaxel was compared directly to treatment with docetaxel, cabazitaxel had similar activity to docetaxel in the subcutaneous models and enhanced activity in the intracranial tumour models. In a human docetaxel-resistant breast tumour model, cabazitaxel treatment of implanted SCID mice resulted in a significant delay in tumour growth compared to either docetaxel or ixabepilone. Taken together, the *in vivo* studies suggest that cabazitaxel may have similar or superior activity compared to docetaxel in a variety of therapeutic settings. Although the anti-tumour activities of cabazitaxel and docetaxel were generally similar, the results from different *in vitro* and *in vivo*

primary pharmacodynamics studies indicate that cabazitaxel may also be active against tumour cell lines with acquired resistance to docetaxel.

The applicant also presented the opinion of a non-clinical expert on the data published for cabazitaxel and docetaxel. The non-clinical expert noted that the non-clinical evidence for clinically relevant differences was not compelling due to absence of direct comparative non-clinical studies evaluating cabazitaxel versus docetaxel in prostate cancer and absence of evidence of clinical data.

Discussion on non-clinical aspects

Limited information in terms of non-clinical comparative data have been provided in regards to the applicant's justification for the claim that cabazitaxel is to be considered the same active substance as docetaxel.

Docetaxel is a metabolite of cabazitaxel. According to Jevtana's EPAR, cabazitaxel metabolism was investigated *in vitro* and *in vivo* in the different animal species used in toxicological studies (Crl:CD-1(ICR)BR and C3H/HeN mouse, Sprague Dawley rat, New Zealand White rabbit, Beagle dog and Cynomolgus monkey). During these studies, it was shown that cabazitaxel can suffer biotransformation by: (1) 10-O-demethylation, leading to RPR123142 metabolite (16% dose); (2) 7-O-demethylation, leading to RPR112698 metabolite (24% dose); (3) hydroxylation on t-butyl moiety in the lateral chain, followed by cyclisation of the lateral chain giving rise to oxazolidine-type compounds (21% of the dose); and (4) cleavage of cabazitaxel, leading to the loss of the taxane ring (<0.1% of dose). Numerous combinations of these metabolic pathways were observed. However, *in vivo*, the parent drug was the main circulating compound in mouse, rat and dog plasma (≥ 65% of the total radioactivity).

The above studies also revealed that the metabolic ratio of docetaxel versus cabazitaxel was 3.6% in tumour bearing mice after single administration, while docetaxel was detected at only one sampling time at the highest dose tested (10 mg/kg) in the single toxicity study in rats and was not detected in rabbits in the dose range finding toxicity study or in dogs in the single dose, 5-day and single-cycle toxicity studies. Therefore, the contribution of docetaxel and its active metabolites for the efficacy and safety properties of cabazitaxel seems to be limited (see also discussion on clinical aspects).

The applicant argued that the evidence for clinically relevant differences was not compelling due to absence of direct comparative non-clinical studies evaluating cabazitaxel versus docetaxel in prostate cancer and absence of evidence from clinical studies. However, direct comparative data were obtained in other tumour types and are considered relevant for the prostate cancer setting. This is also in line with ICH S9 guideline which states that a medicinal product does not need to be studied in the same tumour type intended for clinical evaluation.

During the review of the present application, observations were received from Sanofi-Aventis Groupe and summarized here below. In particular, reference was made to studies using *in vivo* CNS disease models, which showed a greater activity for cabazitaxel than docetaxel. Cabazitaxel has been shown to be able to cross the blood–brain barrier, rapidly penetrating in the brain, with a similar brain-blood radioactivity exposure relationship across different animal species. Sémiond and co-workers (2013) described superior activity to similar dose levels of docetaxel and cabazitaxel both at early (before blood–brain barrier disruption) and at advanced stages of intracranial human glioblastoma models, consistent with higher brain penetration. *In situ* brain perfusion using wild-type mice also showed a two- to threefold greater brain penetration with cabazitaxel than with paclitaxel or docetaxel.

Cabazitaxel and docetaxel have also shown different affinities for a range of efflux transporters that protect the brain tissue from toxic insult, including P-glycoprotein (P-gp). Cabazitaxel is known to be a P-glycoprotein substrate. In a paper from Duran and co-workers (2018) cabazitaxel's affinity for the P-gp transporter was compared to first-generation taxanes in multidrug-resistant (MDR) cells. The results obtained indicated that the maximum intracellular drug concentration was achieved faster with

[^{14}C]-cabazitaxel (5 min) than [^{14}C]-docetaxel (15-30 min) and that the MDR cells accumulated twice as much cabazitaxel than docetaxel. Moreover, these levels could be restored to parental levels in the presence of the P-gp inhibitor PSC-833 (valspodar). In conclusion, these studies confirmed that cabazitaxel is more active in ABCB1(+) cell models due to its reduced affinity for P-gp compared to docetaxel. Furthermore, cabazitaxel showed a greater activity compared to first-generation taxanes in a number of taxane-resistant tumor models, including the melanoma model B16/TXT with acquired resistance to docetaxel.
In respect to mode of action, the taxane family shares, in general, the same mode of action, i.e. binding to tubulin and thereby disrupting the cancer cells division. *In vitro* data, obtained with a cell line not overexpressing P-glycoprotein (PgP), showed that cabazitaxel suppressed microtubule dynamic instability significantly more strongly than docetaxel. It was also taken up more quickly and can be retained longer in cells.

These observations complemented with information gathered from literature were consistent with the non-clinical information provided by the applicant.

Conclusion on non-clinical aspects

Overall, the published results from different *in vitro* and *in vivo* non-clinical primary pharmacodynamics studies available from various models (e.g. murine and human cell lines) and diverse tumour types (e.g. leukemia, melanoma, lymphoma, epidermoid carcinoma, breast carcinoma), indicate that cabazitaxel may also be active against tumour cell lines with acquired resistance to docetaxel. Additionally, cabazitaxel was more active than docetaxel in intracranial tumour models. Moreover, differences in non-clinical pharmacokinetics between the two molecules are also noted including the ability to cross the blood-brain barrier and a reduced affinity for the efflux transporter P-gp for cabazitaxel versus docetaxel.

Taken together, the available non-clinical data did not support the applicant's claim that cabazitaxel does not significantly differ with regard safety and/or efficacy from docetaxel.

2.7.3. Clinical aspects

Clinical pharmacology

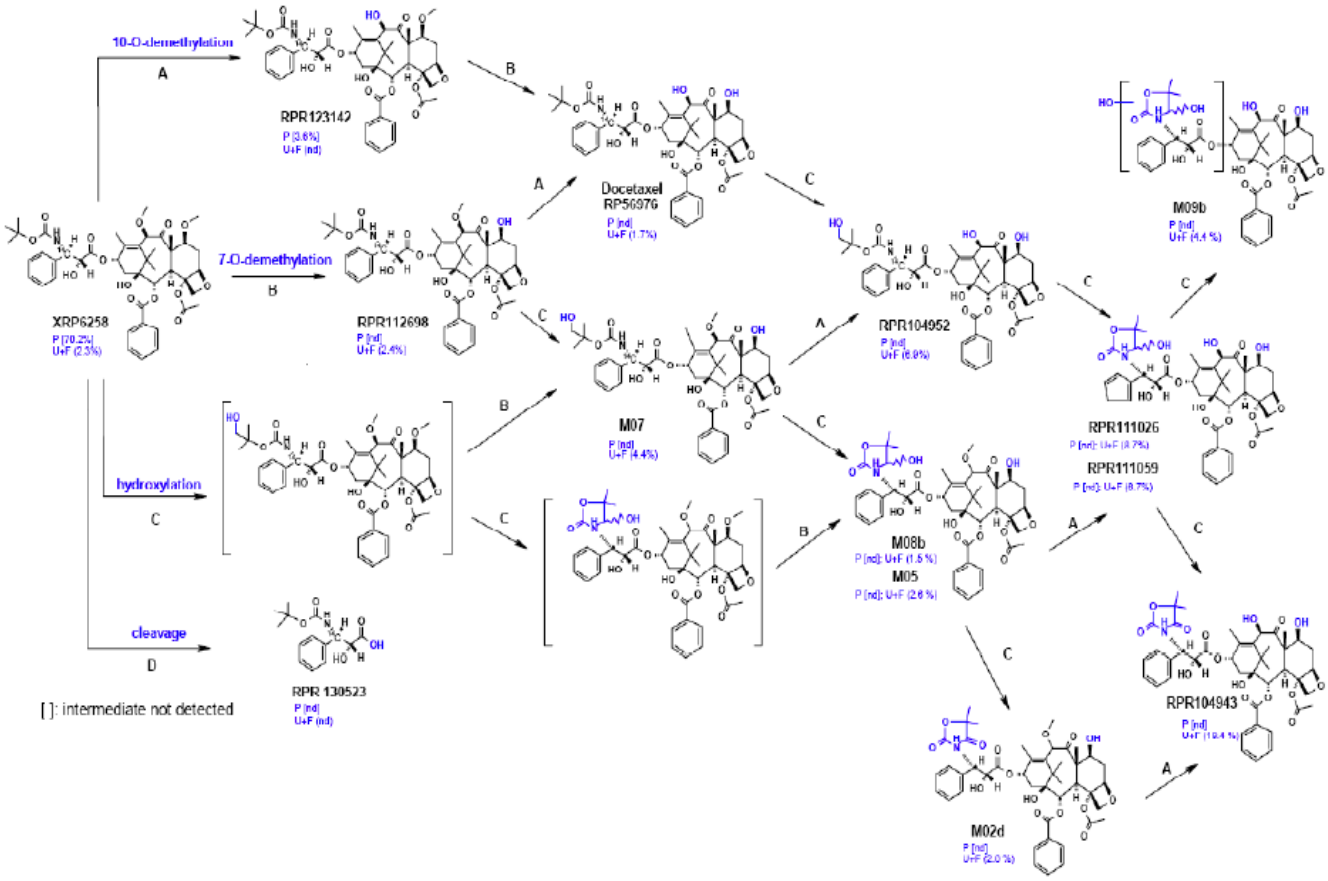
With reference to the Jevtana EPAR, the applicant claimed that no evidence has been provided that cabazitaxel has a different therapeutic moiety to docetaxel.

The applicant provided different arguments based on published data, clinical expert's opinion and referring to the FDA review of Jevtana as follows:

a) Cabazitaxel and docetaxel, as taxanes, have the same mode of action binding to tubulin and thereby disrupting cancer cells division through the involvement of the sidechain on R2 which is the same in the two molecules and minimal involvement of the sidechains on R7 and R10, specific for cabazitaxel;

b) By direct hepatic metabolism, a significant part of cabazitaxel is degraded towards docetaxel and its metabolites; the metabolic pathway of cabazitaxel and docetaxel is the same. Cabazitaxel is metabolized through 4 possible pathways (A – D)(see figure below, Source: FDA's Clinical Pharmacology Review of Jevtana) responsible for 16%, 24%, 21% and < 0.1% of the dose administered, leading to the metabolites RPPR123142 (10-O-demethyl cabazitaxel) and RPPR112698 (7-O-demethyl cabazitaxel), oxazolidine-type (from the hydroxylation of the t-butyl moiety of the lateral chain and its cyclization) and loss of taxane moiety (through the cleavage of cabazitaxel). Pathways A and B, and pathways B and C, both converge to formation of docetaxel; Among the about 20 metabolites excreted after cabazitaxel administration the main 4 metabolites (oxazolidinedione derivative of docetaxel, 19.4% of the dose; two

hydroxyoxazolidine derivatives of docetaxel, 8.7% and 6.7% of the dose; and hydroxyl-docetaxel, 6.9% of the dose) are also docetaxel metabolites; Only a limited amount of cabazitaxel dose leads to different individual metabolites than docetaxel dose;



c) *In vitro*, after 2h post-incubation, almost 80% of cabazitaxel dose is converted into docetaxel or its metabolites and the same occurs in patients;

Discussion on clinical pharmacology

The cabazitaxel clinical pharmacology BEX6702 study [intended to assess PK (excretion balance), metabolism, and safety], confirmed that after a 1-hour IV administration of [^{14}C]- cabazitaxel, the unchanged drug was the major component circulating in plasma (86%) (Jevtana's EPAR).

Based on what is known on the metabolism of cabazitaxel, it is clear that when patients receive cabazitaxel they are mainly exposed to the unchanged drug in addition to the RPR123142 and RPR112698, which are cabazitaxel's metabolites not formed when docetaxel is administered, as they are precursors of docetaxel. These cabazitaxel metabolites, RPR123142 and RPR112698, have shown comparable cytotoxic activity IC50 values in P388 cell line after 4 days of continuous exposure with regard to cabazitaxel and may also contribute to the pharmacologic activity of cabazitaxel (Jevtana's EPAR).

Thus, although cabazitaxel is hydrolysed *in vitro* and *in vivo*, patients will not be exposed to the same levels and to the same therapeutic moieties as when receiving docetaxel. When patients are treated with cabazitaxel they are mainly exposed to the non-metabolised parent compound, which has its own pharmacological activity and not just to docetaxel and it's metabolites. Furthermore, the lower dose administered in the case of cabazitaxel (25 mg/m^2) *vs* the dose administered in the case of docetaxel (75 mg/m^2) are also indicators that the pharmacological activity comes from cabazitaxel and not from docetaxel.

Furthermore, in the observations received during the review of the present application by Sanofi-Aventis Groupe, Cabazitaxel is indicate to have a longer terminal half-life, higher plasma clearance (population PK estimate 48.5 L/h; 26.4 L/h/m^2), and greater mean volume of distribution at steady state (population PK estimate 4,870 L; 2,640 L/m^2) compared to docetaxel.

The cabazitaxel pharmacokinetic profile is described as being consistent with a 3-compartment pharmacokinetic model characterised by rapid initial and intermediate phases with population half-lives of 4.4 minutes and 1.6 hours, respectively, and by a long terminal phase with a half-life of 95.1 hours (Jevtana's EPAR) as compared with 12 hours for docetaxel (Jevtana's EPAR).

Furthermore, cabazitaxel exhibited a large volume of distribution in all species suggestive of a large diffusion of the drug in the body [gastrointestinal tract, kidneys, liver, in hematopoietic organs and various glandular structures (pancreas, pituitary, submaxillary gland, ovaries, prostate and adrenals)]. These data were corroborated by data from clinical studies TED 6188 (Dose-finding, safety, pharmacokinetics, efficacy) and TED 6190 (Dose-finding (IV) & oral bioavailability, safety, PK, efficacy) (Jevtana's EPAR).

PK modelling also showed the presence of a deeper peripheral compartment for cabazitaxel than for docetaxel, which is in slow equilibrium with the central compartment and was the main contributor to the very large steady-state volume of distribution and very long elimination half-life of cabazitaxel (Sanofi-Aventis group's observation).

These data suggest that cabazitaxel is eliminated more slowly than docetaxel and this might be the reason why is more distributed in the body. This is corroborated from mass balance studies in humans that suggested that excretion is slightly slower for cabazitaxel (76% of the administered dose of ^{14}C was recovered in faeces, while approximately 4% recovered in the urine over 2 weeks) than for docetaxel (80% of the administered dose of ^{14}C was excreted in the faeces, with approximately 5% recovered in the urine over 7 days). Moreover, no relevant metabolites were observed in plasma (i.e. AUC of main metabolite is $\leq$5% of the parent drug AUC). It was found that after administration of cabazitaxel at a therapeutic dose, the amount metabolised to docetaxel amounts to 0.15% of the plasma exposure expected after administration of docetaxel at therapeutic approved doses (Sanofi-Aventis group's observation).

On a pharmacodynamic aspect docetaxel and cabazitaxel are different based on the prominent feature of cabazitaxel compared to the other taxanes (namely docetaxel and paclitaxel) that is its minimal recognition with P-gp (multidrug resistance protein), and related activity in tumour models insensitive to chemotherapy including docetaxel. Due to this feature, cabazitaxel can be used in cases of resistance frequently observed following treatment with other Taxanes.

Cabazitaxel and docetaxel inhibited cell proliferation with a slight different extent (IC50s, cabazitaxel, 0.4 - 0.1 nmol/L, docetaxel, 2.5 - 0.5 nmol/L), cabazitaxel suppress microtubule dynamic instability significantly more potently than docetaxel (overall dynamicity by 83% vs. 64%), and is taken up into cells significantly faster than docetaxel (intracellular concentration of 25 mmol/L within 1 hour versus 10 hours for docetaxel) likely due to cabazitaxel higher lipophilicity than docetaxel (logP 3.9 versus 3.2).[Azarenko *et al*., 2014] These data provide a rationale for the activity of cabazitaxel in docetaxel-resistant tumors.

The metabolism of cabazitaxel may explain the non-clinical differences (see discussion on non-clinical aspects) and clinical differences also described in the literature for cabazitaxel versus docetaxel (see also discussion on clinical efficacy and safety).

Clinical efficacy and safety

No clinical studies other than supporting literature were provided in the present MAA.

To support their claim that docetaxel and cabazitaxel do not differ significantly with regard to safety and/or efficacy, the applicant referred to the EPAR of Jevtana (cabazitaxel), more precisely, the acknowledgement in the EPAR that cabazitaxel and docetaxel are derivatives, and the absence in the report of efficacy/safety data comparing docetaxel and cabazitaxel.

The claim is also based on an expert's clinical experience, literature review and the results (or interim results) of the following clinical trials:

- Cabazitaxel (XRP6258) Plus Prednisone Compared to Mitoxantrone Plus Prednisone in Hormone Refractory Metastatic Prostate Cancer ("TROPIC");
- Randomized, Open Label, Multi-Center Study Comparing Cabazitaxel at 25 mg/m^2 and at 20 mg/m^2 in Combination with Prednisone Every 3 Weeks to Docetaxel in Combination with Prednisone in Patients with Metastatic Castration Resistant Prostate Cancer Not Pretreated ith Chemotherapy ("FIRSTANA");
- A multicentre, phase II randomised controlled trial evaluating cabazitaxel versus docetaxel re-challenge for the treatment of metastatic Castrate Refractory Prostate Cancer, previously treated with docetaxel at inception of primary hormone therapy ("CANTATA").

The TAXYNERGY study Randomized, non-comparative, Phase II Trial of Early Switch From Docetaxel to Cabazitaxel or Vice Versa, With Integrated Biomarker Analysis, in Men With Chemotherapy-Naïve, Metastatic, Castration-Resistant Prostate Cancer (https://clinicaltrials.gov/ct2/show/NCT01718353 accessed by Rapporteur on the 13/08/2018), was also discussed.

TROPIC trial

The trial EFC6193 "TROPIC" was the pivotal trial submitted in support of Jevtana's marketing authorization. This was a multicenter, multinational, randomised, open-label phase III study comparing the efficacy and safety of cabazitaxel plus prednisone (or prednisolone) versus mitoxantrone plus prednisone (or prednisolone), in patients with hormone refractory metastatic prostate cancer (mHRPC) previously treated with a Taxotere (or docetaxel)-containing regimen.

Mitoxantrone was chosen as comparator as there was no consensus/approved drugs/combination therapies approved in second line mHRPC.

The main efficacy results are summarized in the Table below (Pean et al. 2012). In the primary analysis, the superiority of cabazitaxel over mitoxantrone was observed, with a 2.4-month longer median OS time and a 30% lower risk for death.

Table 2. Summary of efficacy results: phase III EFC6193 study

Measure	MTX + PRED (n = 377)	CBZ + PRED (n = 378)	HR[a] (95% CI)	p-value[b]
Median (95% CI) survival, mos	12.7 (11.6–13.7)	15.1 (14.1–16.3)	0.70 (0.59–0.83)	<.0001
Median (95% CI) PFS, mos	1.4 (1.4–1.7)	2.8 (2.4–3.0)	0.74 (0.64–0.86)	<.0001
Median (95% CI) tumor progression free, mos	5.4 (4.7–6.5)	8.8 (7.4–9.6)	0.61 (0.49–0.76)	<.0001
Median (95% CI) PSA progression free, mos	3.1 (2.2–4.4)	6.4 (5.1–7.3)	0.75 (0.63–0.90)	.001
Median (95% CI) pain progression free, mos	–	11.1 (8.0-.)	0.91 (0.69–1.19)	.52

[a]The HR was estimated using a Cox proportional hazards regression model. An HR <1 indicates a lower risk with CBZ + PRED than with MTX + PRED.
[b]p-value from stratified log-rank test, stratifying by Eastern Cooperative Oncology Group performance status and measurable disease at baseline.
Abbreviations: CBZ, cabazitaxel; HR, hazard ratio; MTX, mitoxantrone; PRED, prednisone or prednisolone; PFS, progression-free survival; PSA, prostate-specific antigen.

Previous docetaxel exposure is detailed in the table below:

Table 17: Summary of Taxotere-containing regimens prior to the trial - ITT population

		MTX+PRED (N=377)	CBZ+PRED (N=378)
Months from last Taxotere dose to randomisation of this trial	Median	3.7	4.1
	Mean (SD)	5.7 (6.8)	6.2 (6.7)
Number of patients randomised	Within 6 months since last Taxotere dose	270 (71.6%)	234 (61.9%)
	More than 6 months since last Taxotere dose	107 (28.4%)	143 (37.8%)
	Missing	0	1 (0.3%)
Months from last Taxotere dose to progression	Median	0.7	0.8
	Mean (SD)	2.2 (4.4)	2.1 (4.4)
Number of patients progressed	During last Taxotere treatment	104 (27.6%)	115 (30.4%)
	<3 months since last Taxotere dose	181 (48.0%)	158 (41.8%)
	3 months to < 6 months after last Taxotere dose	50 (13.3%)	58 (15.3%)
	≥ 6 months since last Taxotere dose	40 (10.6%)	44 (11.6%)
	Missing	2 (0.5%)	3 (0.8%)
Number of regimen containing Taxotere			
	1	327 (86.7%)	316 (83.6%)
	2	43 (11.4%)	53 (14.0%)
	3 or more	7 (1.9%)	9 (2.4%)
Total prior Taxotere (mg/m²)			
	Median	529.2	576.6
	Min	0	22
	Max	2999	3089
Number of patients received total Taxotere			
	<225 mg/m²	30 (8.0%)	29 (7.7%)
	>=225 to 450 mg/m²	112 (29.7%)	94 (24.9%)
	>=450 to 675 mg/m²	105 (27.9%)	112 (29.6%)
	>=675 to 900 mg/m²	57 (15.1%)	74 (19.6%)
	>=900 mg/m²	68 (18.0%)	66 (17.5%)
	Missing	5 (1.3%)	3 (0.8%)

MTX+PRED: Mitoxantrone + Prednisone/Prednisolone
CBZ+PRED: Cabazitaxel + Prednisone/Prednisolone

CANTATA study:

The CANTATA study was prematurely closed on April 2016 due to poor accrual. The accrual was 15 patients, of a target number of 138, not enough patients to justify any form of formal statistical analysis.

FIRSTANA study:

The FIRSTANA study is ongoing, but not recruiting participants. The current results have been published (J Clin Oncol. 2017 Oct 1;35(28):3189-3197. doi: 10.1200/JCO.2016.72.1068. Epub 2017 Jul 28.)[1]. (https://clinicaltrials.gov/ct2/show/results/NCT01308567?sect=X4012356 accessed 17/08/2017). The primary objective of the trial was:

- "To demonstrate the superiority of cabazitaxel plus prednisone at 25 mg/m^2 (Arm A) or 20mg/m^2 (Arm B) versus docetaxel plus prednisone (Arm C) in term of overall survival (OS) in participants with metastatic castration resistant prostate cancer (mCRPC) and not previously treated with chemotherapy."

Secondary objectives included:

"To compare efficacy of cabazitaxel at 20 mg/m^2 and 25 mg/m^2 to docetaxel for:

- Progression Free Survival (PFS) (RECIST 1.1)
- Tumor progression free survival (RECIST 1.1)
- Tumor response in participants with measurable disease (RECIST 1.1)
- PSA response
- PSA-Progression free survival (PSA-PFS)
- Pain response in participants with stable pain at baseline
- Pain progression free survival
- Time to occurrence of any skeletal related events (SRE)".

Between May 2011 and April 2013, 1,168 patients were randomly assigned to docetaxel 75 mg/m^2 (D75); cabazitaxel 20 mg/m^2 (C20) or 25 mg/m^2 (C25). Baseline characteristics were similar across cohorts. Median OS was 24.5 months with C20, 25.2 months with C25, and 24.3 months with D75. Hazard ratio for C20 versus D75 was 1.01 (95% CI, 0.85 to 1.20; P = 0.997), and hazard ratio for C25 versus D75 was 0.97 (95% CI, 0.82 to 1.16; P = 0.757). Median PFS was 4.4 months with C20, 5.1 months with C25, and 5.3 months with D75, with no significant differences between treatment arms. Radiographic tumor responses were numerically higher for C25 (41.6%) versus D75 (30.9%; nominal P = 0.037, without multiplicity test adjustment). Rates of grade 3 or 4 treatment-emergent adverse events were 41.2%, 60.1%, and 46.0% for C20, C25, and D75, respectively. Febrile neutropenia, diarrhea, and hematuria were more frequent with C25; peripheral neuropathy, peripheral edema, alopecia, and nail disorders were more frequent with D75.

The authors concluded that C20 and C25 did not demonstrate superiority for OS versus D75 in patients with chemotherapy-naïve mCRPC. Tumor response was numerically higher with C25 versus D75; pain PFS was numerically improved with D75 versus C25. Cabazitaxel and docetaxel demonstrated different toxicity profiles, with overall less toxicity with C20.

No difference was found regarding efficacy in chemo-naïve mCRPC patients. The survival benefit for cabazitaxel over mitoxantrone shown in TROPIC and the heterogeneous use of active drugs after progressing on study treatment might have lessened any study treatment OS difference.

FIRSTANA Study **Supplemental Table 1**. Most frequent anticancer systemic therapies administered after study treatment (in >5% of patients in either arm)

	Cabazitaxel		
	20 mg/m² N=389	25 mg/m² N=388	Docetaxel N=391
Any anticancer therapy	287 (73.8)	273 (70.4)	301 (77.0)
Docetaxel	154 (39.7)	142 (36.6)	49 (12.5)
Abiraterone/abiraterone acetate	152 (39.1)	154 (39.6)	181 (46.3)
Enzalutamide	71 (18.3)	69 (17.8)	64 (16.4)
Prednisone/prednisolone	23 (5.9)	28 (7.2)	37 (9.5)
Cabazitaxel	24 (6.2)	21 (5.4)	103 (26.3)
Mitoxantrone	15 (3.9)	16 (4.1)	20 (5.1)

Toxicity profiles of cabazitaxel and docetaxel differed, with patients treated with docetaxel D75, versus cabazitaxel C25 or C20, experiencing higher levels of any grade peripheral sensory neuropathy (25.1% vs 12.3% vs 11.7%, respectively) and stomatitis (13.7% vs 6.6% vs 4.9%, respectively). Meanwhile, patients treated with cabazitaxel C25, versus those treated with cabazitaxel C20 and docetaxel D75, experienced more diarrhea (49.9% vs 32.5% vs 37%, respectively), febrile neutropenia (12% vs 2.4% vs 8.3%, respectively), and hematuria (25.1% vs 20.3% vs 3.6%, respectively). The rates of nausea, fatigue, and asthenia were similar across the three treatment arms.

The results show that there is limited difference in adverse events between docetaxel and cabazitaxel. However, there is a slight difference in the rate of total serious adverse events – with cabazitaxel in a 25mg/m^2 having a higher rate of serious adverse events (although cabazitaxel 20mg/m^2 and docetaxel are comparable).

The only differences identified in the other adverse events profiles (rather than SAE profiles) that may not be as a result of dosage or population profiles are the adverse events profiles of the skin and subcutaneous tissue disorders, specifically alopecia, nail disorders, and skin rashes (shown below):

	Docetaxel 75	Cabazitaxel 20	Cabazitaxel 25
Skin and subcutaneous tissue disorders			
Alopecia [†1]			
# participants affected / at risk	151/387 (39.02%)	33/369 (8.94%)	51/391 (13.04%)
Nail disorder [†1]			
# participants affected / at risk	35/387 (9.04%)	1/369 (0.27%)	3/391 (0.77%)
Rash [†1]			
# participants affected / at risk	23/387 (5.94%)	3/369 (0.81%)	5/391 (1.28%)

TAXYNERGY study:

The TAXYNERGY trial evaluated clinical benefit from early taxane switch and circulating tumor cell (CTC) biomarkers to interrogate mechanisms of sensitivity or resistance to taxanes in men with chemotherapy-naïve, metastatic, castration-resistant prostate cancer. Patients were randomly assigned 2:1 to docetaxel or cabazitaxel. Men who did not achieve ≥ 30% prostate-specific antigen (PSA) decline by cycle 4 (C4) switched taxane. The primary clinical endpoint was confirmed ≥ 50% PSA decline versus historical control (TAX327).

Sixty-three patients were randomly assigned to docetaxel (n = 41) or cabazitaxel (n = 22); 44.4% received prior potent androgen receptor–targeted therapy. Overall, 35 patients (55.6%) had confirmed ≥ 50% PSA responses, exceeding the historical control rate of 45.4% (TAX327). Of 61 treated patients, 33

(54.1%) had ≥ 30% PSA declines by C4 and did not switch taxane, 15 patients (24.6%) who did not achieve ≥ 30% PSA declines by C4 switched taxane, and 13 patients (21.3%) discontinued therapy before or at C4. Of patients switching taxane, 46.7% subsequently achieved ≥ 50% PSA decrease. Median composite progression-free survival was 9.1 months (95% CI, 4.9 to 11.7 months); median overall survival was not reached at 14 months. Common grade 3 or 4 adverse events included fatigue (13.1%) and febrile neutropenia (11.5%).

Discussion on clinical efficacy and safety aspects

In terms of efficacy and safety, docetaxel and cabazitaxel have different indications. Docetaxel is used as a first line treatment, cabazitaxel as a second line treatment (in patients previously exposed to docetaxel) of prostate cancer.

Differences pertaining to specific aspects of cabazitaxel clinical efficacy may be shown for example in sub-populations with relevant characteristics, namely resistance to docetaxel.

In the TROPIC trial the target population includes mHRPC patients previously treated with docetaxel .

Most of the patients (72%) had progressed during or within 3 months since their last docetaxel dose and 14.9% of the patients had received two or more regimens of prior docetaxel-based chemotherapy. A minimum previous exposure to docetaxel was set, and patients with previous treatment with a <225 mg/m^2 cumulative dose of docetaxel were not eligible for the trial (following protocol amendment).

The efficacy results of cabazitaxel in the treatment of mHRPC patients, previously treated with docetaxel can be regarded as sufficient evidence to show that the two substances differ significantly with regard to efficacy.

Two retrospective studies published (Pezaro et al., 2014; Al Nakouzy et al., 2015) also support the anticancer activity of cabazitaxel after docetaxel and abiraterone or enzalutamide.

It is acknowledged that direct comparison is the preferred way according to the EMA's guidance to demonstrate that the two molecules differ significantly in terms of efficacy and/or safety (*Reflection paper on considerations given to designation of a single stereo isomeric form (enantiomer), a complex, a derivative, or a different salt or ester as new active substance in relation to the relevant reference active substance*).

The CANTATA trial was designed by University of Birmingham and Cancer Research UK to evaluate cabazitaxel *versus* a docetaxel rechallenge for the treatment of metastatic Castrate Refractory Prostate Cancer, previously treated with docetaxel at inception of primary hormone therapy. This trial was closed prematurely due to poor accrual. Of note, this trial population is very different from the population in the TROPIC trial. The inclusion criteria was mCRPC "previously treated with up to 6 cycles of docetaxel as part of the STAMPEDE trial", i.e. that had docetaxel for 6 cycles when initiating first line hormone therapy for metastatic castration sensitive prostate cancer. The research question compares cabazitaxel to docetaxel later on, when the disease becomes castrate-resistant.

The CANTATA study cannot be argued on the feasibility of a head-to-head comparison between docetaxel and cabazitaxel with a population matching the TROPIC trial inclusion criteria as most of the population in the TROPIC trial is not suitable for docetaxel rechallenge. Suggested eligibility criteria for docetaxel rechallenge (Petrioli et al., 2015) include a favorable response to first-line docetaxel and a progression-free interval (PFI) of > 6 months. It was reported that PFI < 3 months was associated with no benefit from docetaxel rechallenge, probably because of early development of complex mechanisms of resistance to the drug (Seruga et al., 2011).

In the FIRSTANA study, no difference was found regarding efficacy in chemo-naïve mCRPC patients. However, the proposed efficacy advantage of cabazitaxel is to overcome docetaxel resistance. The result

of FIRSTANA could be due to lack of previous exposure, as in the TROPIC trial no advantage was shown for patients with a previous exposure to docetaxel <225 mg/m^2 (Jevtana's EPAR). An alternative explanation could be related to the effect of systemic therapies administered after study treatment.

The results show that there is limited difference in adverse events between docetaxel and cabazitaxel. However, there is a slight difference in the rate of total serious adverse events – with cabazitaxel 25 mg/m^2 having a higher rate of serious adverse events (although cabazitaxel 20 mg/m^2 and docetaxel are comparable).

Although in the FIRSTANA study the overall lesser toxicity with cabazitaxel C20 may be explained by dose, the difference in the adverse events profiles of the skin and subcutaneous tissue disorders, specifically alopecia, nail disorders, and skin rashes is unlikely to be justified only by external factors, implying that cabazitaxel may have a different safety profile compared to docetaxel.

The TAXYNERGY trial was a non-comparative trial and no conclusions can be made on the comparison between docetaxel and cabazitaxel but rather on the basis that the majority of switches were from docetaxel to cabazitaxel. This supports an effect of cabazitaxel salvaging in some patients whose disease has become resistant to docetaxel (Zhang et al., 2017).

The CHMP furthermore noted that the role of cabazitaxel in the post docetaxel setting is recognized by clinical experts, which include this molecule in current guidelines for the treatment of prostate cancer, as the ones published by the European Society of Medical Oncology (ESMO)(Parker et al., 2015) and the European Association of Urology (Prostate cancer. EAU Guidelines. T. Van den Broeck, M. Cumberbatch, N. Fossati, et al., Available online at http://uroweb.org/guideline/prostate-cancer/#11).

In a retrospective analysis by Oudard et al. 2015 it is described that docetaxel rechallenge plus prednisone is a management option for responders to docetaxel with a progression-free interval (PFI) of > 6 months, but did not prolong survival versus mitoxantrone plus prednisone. On the opposite, survival was significant longer with cabazitaxel compared to mitoxantrone (15.1 months versus 12.7 respectively), with a 30% reduction in the risk of death compared to mitoxantrone.

In addition, in the current treatment paradigm for mCRP where most of the patients receive at least one novel hormonal agents prior chemotherapy, any comparison between docetaxel and cabazitaxel should consider data of cross-resistance largely reported in literature (Mezynski et al., 2012, Pezaro et al., 2014, Al Nakouzy et al., 2015, va Soest et al., 2015; Van Soest et al., 2017) between these novel androgen receptor targeted agents and these taxanes, which seem to affect less the antitumor effect of cabazitaxel.

Conclusion on clinical efficacy and safety

From a clinical pharmacodynamics perspective, docetaxel and cabazitaxel are considered significantly different regarding resistance profile. Cabazitaxel has shown to be active in mCRPC patients progressing during or <3 months after docetaxel treatment. Although a head-to-head comparison has not been made in this setting, available evidence suggests these patients are unlikely to respond to a docetaxel rechallenge. A survival benefit has been shown for cabazitaxel in docetaxel treated mCRPC unlikely to respond to docetaxel re-treatment, and on this basis it can be concluded that cabazitaxel provides a clinically relevant benefit over docetaxel. These findings are in line with the pre-clinical and pharmacodynamic data.

2.8. Product information

2.8.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Jevtana. The bridging report submitted by the applicant has

been found acceptable.

3. Benefit-risk balance

This application concerns a hybrid medicinal product containing cabazitaxel as active substance. The reference product for the calculation of the data protection period is Taxotere (docetaxel) based on the applicant's claim that cabazitaxel and docetaxel should be considered the same active substance within the meaning of Article 10(2)(b) of Directive 2001/83/EC, i.e. that the substances do not differ significantly with regard to safety and/or efficacy. The application otherwise makes reference to Jevtana (cabazitaxel, 60 mg concentrate and solvent for solution for infusion) which is indicated in combination with prednisone or prednisolone for the treatment of adult patients with metastatic castration resistant prostate cancer previously treated with a docetaxel-containing regimen.

The quality of the product is considered to be acceptable and consistent. The differences in formulation between Cabazitaxel Teva and Jevtana are in general fully and satisfactorily characterized by the published literature and comparative quality data required, and those differences are expected to have no adverse impact on the efficacy and safety of the proposed drug product.

No nonclinical and clinical studies have been provided for this application. Exemption from the necessity to conduct a bioequivalence study is considered adequately substantiated.

However, in order to use Taxotere as reference medicinal product and to rely on the dossier of Jevtana on the basis of the claim that Jevtana falls within the same global marketing authorisation as Taxotere, the applicant also submitted a justification to demonstrate that cabazitaxel and docetaxel do not differ with regards to properties in efficacy or safety.

The assessment of the claim that cabazitaxel and docetaxel are to be considered the same active substance have been performed within the meaning of Article 10(2)(b) of Directive 2001/83/EC and is to be informed by the principles of the following CHMP reference documents:

- "*Reflection paper on the chemical structure and properties criteria to be considered for the evaluation of new active substance (NAS) status of chemical substances" (EMA/CHMP/QWP/104223/2015)*;
- "*Reflection paper on considerations given to designation of a single stereo isomeric form (enantiomer), a complex, a derivative, or a different salt or ester as new active substance in relation to the relevant reference active substance*" (EMA/651649/2010).

Non clinical studies indicate the capacity of cabazitaxel to cross the blood-brain barrier, to have a reduced affinity for the efflux transporter P-gp for cabazitaxel versus docetaxel together with indication that cabazitaxel may also be active against tumour cell lines with acquired resistance to docetaxel. In clinical pharmacokinetic settings as well, cabazitaxel indicates a different pharmacokinetics profile in regards to metabolic aspects which expose patients mainly to unchanged active substance in addition to two other active metabolites which are not present in the docetaxel treatment. Cabazitaxel is also described as having a longer terminal half-life and a large volume of distribution suggesting a slower elimination. In clinical studies cabazitaxel shows efficacy in the treatment of patients with metastatic castration resistant prostate cancer previously treated with a docetaxel containing regimen. In terms of safety clinical studies indicate that cabazitaxel present with a different profile compared to docetaxel.

Therefore, in light of the above mentioned guidelines and considering the above discussed findings, it cannot be concluded that cabazitaxel and docetaxel do not differ significantly in properties with regard to safety and/or efficacy and hence that both active substances are the same. Subsequently, as it has not been demonstrated that docetaxel and cabazitaxel may be considered as the same active substance, the reference made to Taxotere, a medicinal product containing docetaxel, is not scientifically justified in an

application for a medicinal product containing cabazitaxel. It follows that Taxotere cannot be used as reference medicinal product in support of this application. Consequently, the data referred to, to support the safety and efficacy of Cabazitaxel Teva, cannot be used.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy for Cabazitaxel Teva in combination with prednisone or prednisolone indicated for the treatment of adult patients with metastatic castration resistant prostate cancer previously treated with a docetaxel-containing regimen, the CHMP considers by consensus that:

[a] the safety and efficacy in regards to the claim of same active substance for cabazitaxel and docetaxel in the submission of the above mentioned medicinal product is not sufficiently demonstrated, and

[b] particulars or documents provided in accordance with Article 6 of Regulation (EC) No 726/2004 are incorrect,

and therefore recommends the refusal of the granting of the marketing authorisation for the above mentioned medicinal product.

The CHMP considers that:

- The marketing authorisation application for Cabazitaxel Teva was submitted under Article 10(3) of Directive 2001/83/EC making reference to Taxotere (docetaxel), which was granted marketing authorisation on 27 November 1995 as reference medicinal product. The applicant also refers to the data submitted in support of Jevtana (cabazitaxel).
- In order to use these data in an application for a medicinal product containing the active substance cabazitaxel, the applicant submitted information in support of the claim that docetaxel and cabazitaxel do not differ significantly in properties with regard to safety and/or efficacy. This claim was then analysed during the scientific assessment.
- While cabazitaxel, from a pure chemical perspective, is a dimethoxy derivative of docetaxel, patients receiving cabazitaxel are mainly exposed to the unchanged parent compound in addition to two metabolites, which are not formed when docetaxel is administered. Furthermore, differences between cabazitaxel and docetaxel have been observed in non-clinical studies showing that cabazitaxel can cross the blood-brain barrier, has less affinity for the efflux transporter P-gp and supporting activity of cabazitaxel in docetaxel resistant tumours. These findings are further supported by a survival benefit of cabazitaxel over mitoxantrone observed in a clinical trial in patients with metastatic castration resistant prostate cancer previously treated with a docetaxel containing regimen, whereas literature data suggest absence of such advantage for docetaxel rechallenge. Clinical data also showed differences in the safety profiles.
- Based on these findings, it cannot be concluded that cabazitaxel and docetaxel do not differ significantly in properties with regard to safety and/or efficacy and hence that both active substances are the same.
- Subsequently, as it has not been demonstrated that docetaxel and cabazitaxel may be considered as the same active substance, the reference made to Taxotere, a medicinal product containing docetaxel, is not scientifically justified in an application for a medicinal product containing cabazitaxel. It follows that Taxotere cannot be used as reference medicinal product in support of this application.

- Consequently, the data referred to, to support the safety and efficacy of Cabazitaxel Teva, cannot be used.