30 April 2020
EMA/267872/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cabazitaxel Accord

International non-proprietary name: cabazitaxel

Procedure No. EMEA/H/C/005178/0000

Note

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

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Administrative information

Name of the medicinal product:	Cabazitaxel Accord
Applicant:	Accord Healthcare S.L.U. World Trade Center Moll de Barcelona S/N Edifici Est, 6ª Planta 08039 Barcelona SPAIN
Active substance:	CABAZITAXEL
International non-proprietary name/Common name:	cabazitaxel
Pharmaco-therapeutic group (ATC Code):	plant alkaloids and other natural products, taxanes (L01CD04)
Therapeutic indication(s):	Cabazitaxel Accord 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.
Pharmaceutical form(s):	Concentrate for solution for infusion
Strength(s):	20 mg/ml
Route(s) of administration:	Intravenous use
Packaging:	vial (glass)
Package size(s):	1 vial

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List of abbreviations

ABCC4	ATP-cassette binding protein 4
AP	Applicant's Part of an ASMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
AS	Active substance
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File
AST	Aspartate aminotransferase
AUC	Area under the curve
BSA	Body Surface Area
CEP	Certificate of Suitability of the Ph.Eur.
CFU	Colony Forming Units
CHMP	Committee for Medicinal Products for Human use
Cmax	Peak serum concentration
CMC	critical micelle concentration
CMS	Concerned Member State
CoA	Certificate of Analysis
CPP	Critical process parameter
CR	Complete response
CrCl	Creatinine clearance
CRS	Chemical Reference Substance (official standard)
CV	Coefficient of Variation
DCP	Decentralised Procedure
DD	Delivered Dose
DPI	Dry Powder Inhaler
DSC	Differential Scanning Calorimetry
EA	elemental analysis
EC	European Commission
ECG	Electrocardiogram
EDQM	European Directorate for the Quality of Medicines
EP	European Pharmacopoeia
EU	European Union
GC	Gas Chromatography
GMP	Good Manufacturing Practice
h	Hour(s)
HDL	High density lipoprotein
HDPE	High Density Polyethylene
HER 2	Human epidermal growth factor receptor-2
HPLC	High Pressure Liquid Chromatography
HR	Hazard ratio
IC50	50% inhibitory concentrations
ICH	International Conference on Harmonisation
IPC	In-process control test
IR	Infrared spectroscopy
IU	International Units
IUPAC	International Union of Pure and Applied Chemistry
IV	Intravenous
kg	Kilogram
L	Liter
LCMS	Liquid chromatography mass spectrometry
LDL	Low density lipoprotein
LDPE	Low Density Polyethylene
LOD	(1) Limit of Detection, (2) Loss on Drying
LOQ	(1) Limit of Quantification, (2) List of Questions
LT	Less than
MA	Marketing Authorisation
MAA	Marketing Authorization Application
MAH	Marketing Authorisation holder
mg	Milligram
mL	Milliliter
MS	Mass Spectrometry

MTD	Maximum tolerated dose
ND	Not detected
ng	Nanogram
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
OTC	Over the counter
PDE	Permitted Daily Exposure
PE	Polyethylene
P-gp	P-glycoprotein
Ph.Eur.	European Pharmacopoeia
PP	Polypropylene
ppb	parts per billion
PSA	Prostate specific antigen
PVC	Polyvinyl chloride
QOS	Quality Overall Summary
QWP	Quality Working Party
RH	Relative Humidity
RMS	Reference Member State
RP	Restricted Part of an ASMF
RRT	Relative retention time
RSD	Relative standard deviation
RVG #	Marketing Authorisation number in NL
SmPC	Summary of product characteristics
TAMC	Total Aerobic Microbial Count
TEAE	Treatment-emergent adverse events
TFS	Tumor-free survival
TGA	Thermo-Gravimetric Analysis
Tmax	Time taken for the drug to reach peak plasma concentration
TSE	Transmissible Spongiform Encephalopathy
TTC	Threshold of toxicological concern
TYMC	Total Combined Yeast/Mould Count
USP	United States Pharmacopoeia
ULN	Upper Limit of Normal
UV	Ultraviolet spectrometry
v/v	Volume/ volume
VLDL	Very low density lipoprotein
WHO	World Health Organization
XR(P)D	X-Ray (powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare S.L.U. submitted on 25 March 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Cabazitaxel Accord, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 18 October 2018.

The application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted 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 Accord 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 study with the reference medicinal product Jevtana instead of non-clinical and clinical data.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 8 years in the EEA:

- Product name, strength, pharmaceutical form: Jevtana, 60 mg, concentrate and solvent for solution for infusion
- 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

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

- Product name, strength, pharmaceutical form: Jevtana, 60 mg, concentrate and solvent for solution for infusion
- 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 from the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and appointed by the CHMP were:

Rapporteur: Hrefna Gudmundsdottir

The application was received by the EMA on	25 March 2019
The procedure started on	23 May 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	9 August 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	27 August 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	19 September 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	23 December 2019
The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	04 February 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 February 2020
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	27 February 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	03 March 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	16 March 2020
The CHMP agreed on a second list of outstanding issues in writing to be	26 March 2020

sent to the applicant on	
The applicant submitted the responses to the CHMP List of Outstanding Issues on	07 April 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	15 April 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Cabazitaxel Accord on	30 April 2020

2. Scientific discussion

2.1. Introduction

This centralised application concerns Cabazitaxel Accord, concentrate for solution for infusion, 20 mg/ml, in 3 ml (60 mg vial).

This application is submitted in accordance with Article 10(3) of Directive 2001/83/EC as amended (hybrid application). The originator and reference product is Jevtana 60 mg concentrate and solvent for solution for infusion. The MA holder of Jevtana is Sanofi-Aventis groupe, France. It was authorised in the EU on 17-03-2011. The difference between Cabazitaxel Accord and Jevtana is in the pharmaceutical form.

Cabazitaxel Accord is supplied as a concentrate ready to be diluted into recommended diluents, compared to Jevtana with a 2-step dilution process. Jevtana is a concentrate for solution for infusion at 60 mg/1.5 ml, supplied with a solvent vial containing 4.5 ml of a 13% w/w aqueous solution of ethanol (96 per cent) for the preparation of an intermediate premix at 10 mg/ml, prior to dilution with 0.9 % sodium chloride solution or 5 % dextrose solution in an infusion bag.

Both Cabazitaxel Accord 20 mg/ml concentrate for solution for infusion (60 mg/3ml) and Jevtana 40 mg/ml concentrate and solvent for solution for infusion (60mg/1,5ml) contain the same active substance, cabazitaxel, which is an antineoplastic agent belonging to the taxane class. Cabazitaxel binds to tubulin promoting its assembly into microtubules while simultaneously inhibits microtubules disassembly leading to microtubules stabilization. It therefore promotes the disruption of the microtubular network in cells and by these means inhibits the mitotic and interphase cellular functions.

The applicant claimed the same indication as the one approved for Jevtana: Cabazitaxel Accord 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 recommended dose of cabazitaxel 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.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a concentrate for solution for infusion containing 20 mg/ml of cabazitaxel as the active substance.

Other ingredients are: polysorbate 80, citric acid and ethanol anhydrous, as described in section 6.1 of the SmPC.

The product is available in a clear glass vial (type I) closed with a grey siliconized rubber closure (type I) with teflon film and sealed by an aluminium cap covered with a violet plastic flip-off cap, containing 3 ml of concentrate, as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of cabazitaxel is (1S,2S,3R,4S,7R,9S,10S,12R,15S)-4-(acetyloxy)-15-{[(2R,3S)-3-{[(tert-butoxy)carbonyl]amino}-2-hydroxy-3-phenylpropanoyl]oxy}-1-hydroxy-9,12-dimethoxy-10,14,17,17-tetramethyl-11-oxo-6-oxatetracyclo [11.3.1.0^ {3,10}.0^ {4,7}] heptadec-13-en-2-yl benzoate. It corresponds to the molecular formula $C_{45}H_{57}NO_{14}$, its relative molecular mass is 835.93 g/mol and it has the structure shown in Figure 1.

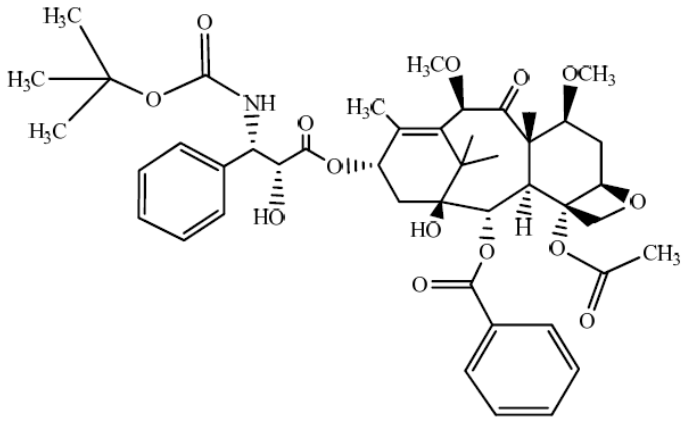

Figure 1. Structure of cabazitaxel

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) and ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy (NMR).

Cabazitaxel appears as a white or almost white slightly hygroscopic amorphous powder. It is freely soluble in dichloromethane, soluble in absolute ethanol, and insoluble in water.

Cabazitaxel is obtained as amorphous form by the proposed manufacturer and process. Polymorphism of cabazitaxel is of no significance as the AS is used for the manufacture of injectable dosage forms. Results by X-RPD on four batches demonstrate that the manufacturing process consistently results in the amorphous form. A test for the amorphous form is included in the AS specification.

There are nine chiral centres in the taxol four fused ring skeleton and two chiral centres (2R, 3S) in the side chain of cabazitaxel structure. The four fused ring taxol skeleton is obtained by isolation from a natural source (taxus baccata leaves).

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Cabazitaxel is a semi-synthetic compound derivative of the 10-deacetyl Baccatin III (called 10-DAB III), which is extracted from Taxus baccata leaves. The proposed starting materials have been justified and are considered acceptable. The synthetic process comprises 7 steps including recrystallisation.

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. A discussion on mutagenic impurities was provided and in-line with ICH M7, potential mutagenic impurities are controlled according to the TTC of 1.5 µg/day considering a maximum daily dose of 25 mg/m2. The impurity profile of the AS has been adequately described and impurities resulting from the manufacturing process of the starting materials do not carry-forward to later stages of the GMP process. No Class 1 solvents are employed in the synthetic process, whereas those, which are potential contaminant in the solvents used throughout, are adequately controlled in the raw material specifications of the respective solvent.

Cabazitaxel is packaged in a transparent low density polyethylene (LDPE) bag inside a polybag and placed inside a triple laminated bag with silica gel pouches and stored inside a high density polyethylene (HDPE) drum. The primary packaging LDPE bags are in compliance with EU Regulation 10/2011 and amendments, as well as Ph. Eur. 3.1.3. Satisfactory specifications for the packaging materials are proposed.

Specification

Cabazitaxel active substance specification includes appropriate tests and limits for description (visual), solubility (Ph. Eur.), identification (IR, HPLC, XRD), water content (Ph. Eur.), sulfated ash (Ph. Eur.), specific optical rotation (Ph. Eur.), appearance of solution (Ph. Eur.), assay (HPLC), related substances (HPLC), methyltrifluoromethane sulphonate content (LCMS), bacterial endotoxins (Ph. Eur.), residual solvents (GC) and microbial limit (Ph. Eur.).

The maximum daily dose (MDD) for cabazitaxel is 50 mg/day (25 mg/m^2 and 2 m^2 of body surface). Therefore, the thresholds required by ICH Q3A for reporting, identification and qualification of impurities in the active substance are 0.05%, 0.10% and 0.15%, respectively. All impurities are controlled in-line with ICH Q3A and hence the proposed limits are acceptable. A limit for the potentially mutagenic impurity is included in the AS specification. The limit was set according to a TTC of 1.5 µg/day and a MDD of 40 mg (corresponding to 25 mg/m^2 and 1.6 m^2 of body surface. As cabazitaxel is not considered to fall within the scope of ICH M7 and is only administered once every three weeks, the slightly higher control of this impurity is not considered to be of any safety concern. Residual solvents are controlled in-line with ICH Q3C.

The analytical procedures have been sufficiently described. Non-compendial analytical methods have been successful 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 three commercial scale batches comply with the proposed specifications. No significant differences in any of the tested quality attributes are observable. The levels residual solvents detected are well below the acceptable ICH limits. Overall, the batch analyses data demonstrates that the active substance can be manufactured consistently within tight quality margins

Stability

Stability data on four production scale batches of active substance stored in the intended commercial packaging for up to 24 months under long term conditions (5 °C ± 3 °C), and for up to 6 months under accelerated conditions (25 °C ± 2 °C / 60% ± 5% RH) were provided according to the ICH guidelines. Stability studies conducted at 40 °C / 75% RH on one lab-scale batch demonstrated out-of-specification results after 1 month for water content. Therefore, it was considered acceptable to conduct stability studies under refrigerated conditions for long-term storage.

Samples were tested for description, identification, water content, specific optical rotation, related substances and assay. The stability of the polymorphic form was not investigated during the stability studies. As the active substance is fully dissolved during manufacture of the finished product, the polymorphic form is not considered to be a critical quality attribute and no further information is requested. Upon the request of the CHMP bacterial endotoxins and microbial quality were included as quality attributes in the stability program.

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, was conducted in solution (acidic, basic and oxidizing conditions), as well as solid state (heat and light). The highest degradation occurred under alkali and acidic conditions. Results from mass balance and peak purity demonstrate that the methods for assay and related substances are stability indicating. The AS showed signs of degradation after exposure to light without the protection of the primary packaging material.

Based on the presented stability data, the proposed re-test period of 24 months, with the special storage condition "*Preserve in air tight, light resistant container and store at 2 to 8°C*" in the proposed container closure system, is considered acceptable.

2.2.3. Finished medicinal product

Pharmaceutical development

Description of the product and pharmaceutical development

Cabazitaxel Accord 20 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. Each vial of 3 ml of concentrate contains 60 mg cabazitaxel.

Cabazitaxel Accord 20 mg/ml concentrate for solution for infusion is an abridged application (hybrid application) to the reference product, Jevtana 60 mg concentrate and solvent for solution for infusion. Each vial of the test product contains a total of 60 mg cabazitaxel the same as Jevtana.

However, the test is a 20 mg /ml concentrate while the reference product contains 60 mg per 1.5 ml (i.e. 40 mg /ml) concentrate. Jevtana concentrate requires a further dilution with a solvent provided as a separate vial in the packaging and then a final dilution to the infusion solvent (not provided as part of the finished product). Cabazitaxel Accord requires only one dilution step directly into the infusion solvent (not provided as part of the finished product). For both test and reference products the concentration of the infusion solution should be between 0.10 mg/ml and 0.26 mg/ml (SmPC section 6.6).

Due to the differences in the pharmaceutical form (concentrate for solution for infusion vs concentrate and solvent for solution for infusion), concentration of the concentrate (20 mg/ml vs 40 mg /ml) and consequently in the SmPC instructions on Preparation for the intravenous administration (6.6) between the test and reference product respectively, the issue of "medication error" has been raised as a major Objection. Therefore, upon the CHMP request, the issue was included among the safety concerns in the RMP, as an important potential risk. The applicant was also requested to propose risk minimisation measures associated with this risk (see section 2.5 and 4 in this report). In addition the colour of the flip-off caps (initially proposed green for Cabazitaxel Accord as for the originator) is changed to violet to avoid the potential product mix-ups and ease of use for the end user.

The proposed composition of the concentrate is very similar to that of the reference medicinal product with respect to the excipients. The excipients selected are among the excipients present in reference product and are commonly used in parenteral formulation. The formulation has been developed considering the pH of the reference product on dilution.

The active substance is practically insoluble in water. The applicant discussed the solubility of cabazitaxel in the components of the finished product. The data sufficiently supports that there are no concerns about the solubility of the AS in the proposed formulation.

The essential similarity of the test and the reference product was established based on relevant comparisons of composition, pH, impurity profiles, micellar size, critical micellar concentration (CMC), *in vitro* release profile from the micelle for the final diluted solution of the reference product and the test product. The test and reference product (Cabazitaxel Accord vs Jevtana) could be considered "Similar formulations" in accordance to the Reflection Paper on the pharmaceutical development of intravenous medicinal products containing active substances solubilised in micellar systems (EMA/CHMP/QWP/799402/2011), as they contain the same surfactant, and are qualitatively the same in the final solution for infusion. No BE-study was presented (see section 2.4 in this report on the acceptability of the absence of a BE-study). The CHMP requested additional comparisons of important micellar properties in accordance with the Reflection paper on the pharmaceutical development of intravenous medicinal products containing active substances solubilised in micellar systems (EMA/CHMP/QWP/799402/2011). In this regard it has been sufficiently shown that the micelle size is comparable between the test and reference solutions. The applicant has also clearly demonstrated that the differences in micelle size were more instrument related, than product related. Data obtained on the same apparatus showed comparable sizes. Furthermore, the same concentrations are tested in the solution for infusion (as per the instructions of the SmPC). Consequently, it can be derived that the test and reference product have similar concentration of micellar entities. Hence, there are no concerns about the micelle size.

It has also been shown that the [free] vs [solubilised] fractions of the active substance between the test and reference products after dilution using recommended dilution fluids as per the SmPC were found comparable for filtered and unfiltered solutions for both the conditions tested (8 hrs at 15-30°C

and for 48 hrs at 2-8°C), which indicate that AS remains in micellar system (solubilized form) over a recommended time interval and at recommended dilution concentration and storage temperature. Thus there is adequate data concerning the micelle component in solutions immediately prior to injection/infusion according to the dilution/administration instructions in the SmPC.

In vitro data showed comparable *in vitro* dissolution between the two products and also the protein binding capabilities were comparable. Moreover, the fate of the micelles is supported by *in vitro* dissolution data and a protein binding study. These results support that the fate of the micelles is comparable between the test and reference product.

Therefore, from a quality point of view, the conditions of the Reflection paper on the pharmaceutical development of intravenous medicinal products containing active substances solubilised in micellar systems (EMA/CHMP/QWP/799402/2011) can be considered fulfilled and a biowaiver is thus considered acceptable.

A compatibility study was performed to evaluate the stability of Cabazitaxel Accord 20 mg concentrate for solution for infusion after dilution with the proposed solvents (0.9% NaCl Injection and 5% Dextrose Injection) in non-PVC bag with administration set at concentration of 0.10 mg/mL and 0.26 mg/mL for a period of 8 hrs at 15-30 °C (under normal light) and 48 hours at 2-8 °C (protected from light) as per the SmPC section 6.6.
The product met predetermined acceptance criteria for a period of 8 hrs at 15-30 °C and 48 hours at 2-8 °C and it can be concluded that the dilution study results are comparable to that of the reference product Jevtana.

In addition, as part of the compatibility study, it has been confirmed that drug crystallisation does not occur over a time interval relevant to the preparation and administration process and at the temperatures likely to be encountered in use. However, this has only been measured in samples of 18 months old. As per the Reflection paper on the pharmaceutical development of intravenous medicinal products containing active substances solubilised in micellar systems, this study should be conducted using diluted infusion solutions prepared from undiluted samples during its shelf-life. Thus, a repeat of this study should be performed on samples at/close to the product end of shelf-life (36 months). The CHMP recommended to perform a micellar size distribution study on samples at/close to the product end of shelf-life (36 months) when samples of that age become available, as well as to discuss the clinical implications of the observed changes along with an appropriate action plan, such as the planned submission of appropriate variations.

Furthermore, it is noted that although the number and level of impurities in the test product are higher than those in the reference product, the results remain within limits and the currently available 36 months stability data does not show any trends for impurities formed.

The manufacturing process was based on the development of an already developed medicinal product, nevertheless the presented information sufficiently supports that there are no concerns about crystallisation of the active substance. Also, the preparation of the slurry in the commercial process is also sufficiently addressed. Hence, it is acceptable that the description of the manufacturing process development was brief.

As part of the manufacturing process development of the product a solubilisation of cabazitaxel in the bulk solution was conducted and showed complete solubilisation at process temperature. The choice of the sterilisation method has been adequately supported by data showing that the use of radiation, as defined in the Decision tree for sterilisation choices for dry powder products, non-aqueous liquid or semi-solid products in the Sterilization Guideline (EMA/CHMP/CVMP/QWP/850374/2015), is not suitable for the proposed product.

Hence, the choice of aseptic compounding is adequately justified. In addition, the type of filters (Filter Compatibility Study) has been investigated to check the compatibility of Cabazitaxel Accord in solution with the filters (including sterilizing grade filters) utilised in the manufacture of the finished product. The presented results support the suitability of the selected filters.

Further studies confirmed the proposed bulk holding times and surface and tubing compatibility with process components. The container closure system was selected based on the reference product's characterisation and based on stability data.

Nitrogen sparging and headspace flushing is proposed as a result of a relevant study showing a steep rise in impurities when oxygen was used.
A Freeze thaw study concluded that short term temperature excursion outside the proposed storage condition "Store at 25°C; excursions permitted between 15°-30 °C." will not affect the product adversely.

No overage is utilized. However, an overfill is proposed and justified based on the viscosity of the solution.

Accordingly, the scalability of the process was studied, and all critical parameters were satisfactorily evaluated and the manufacturing process has been finalized.

Leachables study results were presented for the rubber stoppers and glass vials as well as the employed filters and tubing. The results do not raise any concerns.

The primary packaging is a 6 mL clear glass vial (type I), closed with grey siliconized rubber stopper (type I) with teflon film on plug surface and sealed by aluminium green coloured flip off seal. The finished product glass vial is further wrapped with PharmaShield which is a system consisting of a superficial plastic sheathing around the vial, going from the reinforced Non-PVC base to the vial seal.

The glass complies with Ph. Eur. 3.2.1 Glass containers for Pharmaceutical use and USP. The rubber stoppers used for the product comply with the requirements as mentioned in European Pharmacopoeia under Rubber closures for container for aqueous parenteral preparations, for powders and for freeze dried powders, Ph. Eur. 3.2.9 and USP.

Manufacture of the product and process controls

The manufacturing process of Cabazitaxel Accord 20 mg/ml concentrate for solution for infusion consists of the following main steps: mixing of excipients and addition of active substance under nitrogen sparging, prefiltration, sterile filtration, vial filling, stoppering and sealing, visual inspection labelling and 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 suitable in-process controls were presented for each identified step, i.e. preparation of bulk solution; prefiltration; sterile filtration; vial filling; sealing; and visual inspection. Details regarding the holding times of the unfiltered and filtered bulk solution during manufacturing of the product were provided. Sterilisation and depyrogenation methods of glassware and other heat-resistant container materials e.g. aluminium crimps, as well as the sterilisation method of rubber stoppers has been described and are deemed satisfactory. The presented information is deemed satisfactory and suitable to guarantee appropriate quality of the finished product.

The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full scale batches. This data supports that the manufacturing process is adequately under control 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 description (visual), identification (HPLC), pH (Ph. Eur.), pH (Ph. Eur.), extractable volume (Ph. Eur.), content of ethanol (GC), assay of cabazitaxel (HPLC),related compounds (HPLC), colour and clarity of solution (Ph. Eur.), water content (Ph. Eur.), particulate matter (Ph. Eur.), bacterial endotoxins (Ph. Eur.) and sterility (Ph. Eur.). The specification has been set in accordance to the relevant ICH guidelines.

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. All the identified potential elemental impurities levels are less than the 30 % of Permitted Daily Exposure (PDE) limits as per ICH Q3D Option 2B & hence no further control action/testing is required.

The analytical methods used have been adequately described and validated in accordance with the ICH guidelines. 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. 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 at long term conditions 25±2 °C / 60±5% RH for up to 36 months and for 6 months at accelerated conditions 40±2 °C / 75±5% RH according to the ICH guidelines. The tested batches were packed in the container closure systems intended for marketing and stored in inverted and upright position.

Samples were tested for description, pH, ethanol content, assay, related substances, colour of solution, clarity of solution, particulate matter, bacterial endotoxins, and sterility. No significant changes were observed, and the results are found to be well within the specification limits.

A photostability study was carried out as per ICH requirement on a pilot batch. The presented data showed that the finished product is sensitive to light. In addition, it has been shown that the proposed marketing package is able to protect the finished product from light. Consequently, the additional storage condition "store in the original packaging in order to protect from light" has been added to the SmPC section 6.4.

A freeze thaw study was conducted including three thermal/freeze thaw cycles. No changes were observed in product quality. Hence it was concluded that short term temperature excursion outside the proposed storage condition will not affect the product adversely.

In-use stability was investigated as part of product development and included compatibility of the diluted solution with tubing and materials used for administration. The results of in-use stability show that the product is stable when prepared in accordance with the instructions in the SmPC. The results on the oldest samples available at the time were presented. The CHMP recommended to perform a micellar size distribution study on samples at/close to the product end of shelf-life (36 months) when samples of that age become available and notifying the authorities if the product´s micelle size shows significant changes, as well as to discuss the clinical implications of the observed changes along with an appropriate action plan, such as the planned submission of appropriate variations. Based on the in-use stability results, the claimed in-use shelf-life for the infusion solution as stated in SmPC section 6.3 is accepted.

Based on the overall stability data, the claimed shelf life of 36 months without any special temperature storage conditions but stored in the original package in order to protect from light, as stated in SmPC sections 6.3 and 6.4, is acceptable.

Adventitious agents

There are no excipients of human or animal origin used in the manufacture of Cabazitaxel Accord 20 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. The manufacturing process for the finished product is non-standard and 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. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

-to perform a micellar size distribution study on samples at/close to the product end of shelf-life (36 months) when samples of that age become available and notifying the authorities if the product´s micelle size shows significant changes, as well as to discuss the clinical implications of the observed changes along with an appropriate action plan, such as the planned submission of appropriate variations.

2.3. Non-clinical aspects

2.3.1. Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of cabazitaxel are well known. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile was considered acceptable. Therefore, the CHMP agreed that no further non-clinical studies are required.

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 Accord manufactured by Accord Healthcare S.L.U. 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. Thus, the ERA is expected to be similar. However, this was not considered sufficient and, the Applicant is recommended to perform a calculation of the predicted environmental exposure using the consumption data as a justification for not providing ERA data (post authorisation measure).

2.3.3. Discussion on non-clinical aspects

The non-clinical overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetic and toxicology data.

2.3.4. Conclusion on the non-clinical aspects

The CHMP considered that the non-clinical overview is based on up-to-date and adequate scientific literature. It is agreed that no further non-clinical studies are required. The Applicant is recommended to perform a calculation of the predicted environmental exposure using the consumption data as a justification for not providing ERA data (post authorisation measure).

2.4. Clinical aspects

2.4.1. Introduction

This is an application for 20 mg/mL concentrate for solution for infusion (60 mg/3 mL) containing cabazitaxel. Cabazitaxel Accord is different from the reference product Jevtana in the pharmaceutical form. Cabazitaxel Accord is a concentrate for solution for infusion while Jevtana is a concentrate and solvent for solution for infusion.

The applicant did not receive CHMP Scientific Advice pertinent to the clinical development.

No clinical studies were submitted. Since the product is administered intravenously, the Applicant claimed a biowaiver. The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of cabazitaxel based on published literature. The SmPC is in line with the SmPC of the reference product.
Due to a patent that was granted to the MAH of Jevtana for its use in patients with moderate hepatic impairment, the relevant dose adjustment/reduction was removed from the SmPC and replaced with appropriate warnings and contraindication (see SmPC sections 4.2, 4.3 and 4.4).

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."

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. 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, in vitro characterization studies have been performed to prove its equivalence to the reference product, Jevtana. In the applied indication, cabazitaxel is administered as a 1-hour intravenous infusion after dilution in a sterile 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 containing Polysorbate 80. The rapid esterase-sensitive breakdown of Polysorbate 80 in plasma is well known from the literature.

Therefore, considering that:

a) Cabazitaxel Accord 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 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,

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

Clinical studies

No clinical studies were submitted. Since the product is administered intravenously, the Applicant

claimed a biowaiver.

2.4.2. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.3. Discussion on clinical aspects

According to the Guideline on the Investigation of Bioequivalence, micelle formulations may be considered eligible for a biowaiver in cases where for example the critical micelle concentration, the solubilisation capacity of the formulation, free and bound active substance and micelle size are similar between the reference product and the proposed product. The Applicant has submitted the results which support that the fate of the micelles is comparable between the test and reference product. Therefore, the biowaiver for the applied product is considered justified. The differences in formulation and concentration with the reference product raised concerns about potential medication errors. Therefore, additional risk minimisation activities are required beyond those included in the product information. A DHPC at product launch was agreed. Additionally, regular 6-monthly safety updates on the cases of medication errors should be submitted (see RMP).

2.4.4. Conclusions on clinical aspects

Since the product is administered intravenously, the Applicant claimed a biowaiver. No clinical studies were submitted. This was agreed.

Due to a patent that was granted to the MAH of Jevtana for its use in patients with moderate hepatic impairment, the relevant dose adjustment/reduction was removed from the SmPC and replaced with appropriate warnings and contraindications for patients with moderate hepatic impairment (see SmPC sections 4.2, 4.3 and 4.4).

2.5. Risk management plan

Safety concerns

Table 1 - Summary of the safety concerns

Important identified risks	• Neutropenia and associated clinical events (febrile neutropenia, neutropenic infection, neutropenic sepsis, sepsis, septic shock) • Gastro-intestinal disorders (vomiting and diarrhea; gastrointestinal hemorrhage and perforation; colitis, enterocolitis, gastritis, neutropenic colitis; and ileus and intestinal obstruction) and associated complications (including dehydration and electrolytes imbalance) • Renal failure

	• Peripheral neuropathy • Anemia • Respiratory disorders (acute respiratory distress syndrome, interstitial pneumonia/pneumonitis, interstitial lung disease, and pulmonary fibrosis) (based on potential class effect) • Use in severe hepatic impairment
Important potential risks	• Cardiac arrhythmia (ventricular arrhythmia and cardiac arrest) • Hepatic disorders (based on potential class-effect) • Lens toxicity (observed in a non-clinical study in rats) • Effect on male fertility (based on nonclinical studies) • Use in non-evaluated indications • Drug-drug interaction (concomitant administration with inducers or with inhibitors of CYP3A) • Mild and moderate hepatic impairment • Teratogenicity (nonclinical studies) • Medication error
Missing information	• Ethnicity other than Caucasian

Pharmacovigilance plan

Table 2 - Summary of the safety concerns

Summary Table of additional Pharmacovigilance activities

Study; **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones** (required by regulators)	**Due dates**
Short title: Review of cases reported with "medication error" (Category 3 Study) Status: Planned	To minimize the risk of "medication error"	Medication error	Review of cases reported with "medication error" for cabazitaxel shall be performed six-monthly during routine signal management activity.	The 6-monthly safety updates on the cases of "medication errors" shall be submitted to the agency within 60-days of DLP, after the date of marketing authorisation.

Risk minimisation measures

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Important identified risk: Neutropenia and associated clinical events (febrile neutropenia, neutropenic infection, neutropenic sepsis, sepsis, septic shock)	Sections 4.2, 4.4, 4.8 and 5.1 of Accord Cabazitaxel SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures include; the labelling; and the prescription only status of the product. <u>Additional risk minimisation measures:</u> None	Routine pharmacovigilance activity: As summarized in RMP Part III Additional pharmacovigilance activity: None
Important identified risk: Gastro-intestinal disorders (vomiting and diarrhea; gastrointestinal hemorrhage and perforation; colitis, enterocolitis, gastritis, neutropenic colitis; and ileus and intestinal obstruction) and associated complications (including dehydration and electrolytes imbalance)	Sections 4.2, 4.4, 4.8, 4.9 and 5.1 of Accord Cabazitaxel SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures include; the labelling; and the prescription only status of the product. <u>Additional risk minimisation measures:</u> None	Routine pharmacovigilance activity: As summarized in RMP Part III Additional pharmacovigilance activity: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk: Renal failure	Sections 4.2, 4.4 and 4.8 of Accord Cabazitaxel SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures include; the labelling; and the prescription only status of the product. Additional risk minimisation measures: None	Routine pharmacovigilance activity: As summarized in RMP Part III Additional pharmacovigilance activity: None
Important identified risk: Peripheral neuropathy	Sections 4.2, 4.4, 4.8 and 5.1 of Accord Cabazitaxel SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures include; the labelling; and the prescription only status of the product. Additional risk minimisation measures: None	Routine pharmacovigilance activity: As summarized in RMP Part III Additional pharmacovigilance activity: None
Important identified risk: Anemia	Sections 4.4, 4.8 and 5.1 of Accord Cabazitaxel SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures include; the labelling; and the prescription only status of the product. Additional risk minimisation measures: None	Routine pharmacovigilance activity: As summarized in RMP Part III Additional pharmacovigilance activity: None
Important identified risk: Respiratory disorders (acute respiratory distress syndrome, interstitial pneumonia/pneumonitis, interstitial lung disease, and pulmonary fibrosis) (based on potential class effect)	Sections 4.4 and 4.8 of Accord Cabazitaxel SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures include; the labelling; and the prescription only status of the product. Additional risk minimisation measures: None	Routine pharmacovigilance activity: As summarized in RMP Part III Additional pharmacovigilance activity: None
Important identified risk: Use in severe hepatic impairment	Sections 4.2, 4.3, 4.4 and 5.2 of Accord Cabazitaxel SmPC and corresponding sections of PIL have information on this safety concern.	Routine pharmacovigilance activity:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Other routine risk minimisation measures include; the labelling; and the prescription only status of the product. Additional risk minimisation measures: None	As summarized in RMP Part III Additional pharmacovigilance activity: None
Important Potential Risk: Cardiac arrhythmia (ventricular arrhythmia and cardiac arrest)	Sections 4.4 and 4.8 of Accord Cabazitaxel SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures include; the labelling; and the prescription only status of the product. Additional risk minimisation measures: None	Routine pharmacovigilance activity: As summarized in RMP Part III Additional pharmacovigilance activity: None
Important Potential Risk: Hepatic disorders (based on potential class-effect)	Sections 4.2, 4.3, 4.4 and 5.2 of Accord Cabazitaxel SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures include; the labelling; and the prescription only status of the product. Additional risk minimisation measures: None	Routine pharmacovigilance activity: As summarized in RMP Part III Additional pharmacovigilance activity: None
Important Potential Risk: Lens toxicity (observed in a non-clinical study in rats)	Section 5.3 of Accord Cabazitaxel SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures include; the labelling; and the prescription only status of the product. Additional risk minimisation measures: None	Routine pharmacovigilance activity: As summarized in RMP Part III Additional pharmacovigilance activity: None
Important Potential Risk: Effect on male fertility (based on nonclinical studies)	Sections 4.6 and 5.3 of Accord Cabazitaxel SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures include; the labelling; and the prescription only status of the product. Additional risk minimisation measures:	Routine pharmacovigilance activity: As summarized in RMP Part III

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	None	Additional pharmacovigilance activity: None
Important Potential Risk: Use in non-evaluated indications	None proposed in Accord Cabazitaxel SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures include; the labelling; and the prescription only status of the product. Additional risk minimisation measures: None	Routine pharmacovigilance activity: As summarized in RMP Part III Additional pharmacovigilance activity: None
Important Potential Risk: Drug-drug interaction (concomitant administration with inducers or with inhibitors of CYP3A)	Sections 4.2, 4.4 and 4.5 of Accord Cabazitaxel SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures include; the labelling; and the prescription only status of the product. Additional risk minimisation measures: None	Routine pharmacovigilance activity: As summarized in RMP Part III Additional pharmacovigilance activity: None
Important Potential Risk: Mild and moderate hepatic impairment	Sections 4.2, 4.4 and 5.2 of Accord Cabazitaxel SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures include; the labelling; and the prescription only status of the product. Additional risk minimisation measures: None	Routine pharmacovigilance activity: As summarized in RMP Part III Additional pharmacovigilance activity: None
Important Potential Risk: Teratogenicity (nonclinical studies)	Section 4.6 and 5.3 of Accord Cabazitaxel SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures include; the labelling; and the prescription only status of the product. Additional risk minimisation measures: None	Routine pharmacovigilance activity: As summarized in RMP Part III Additional pharmacovigilance activity: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Potential Risk: medication error	Specific statements regarding difference in concentration in vials of Cabazitaxel Accord compared to other cabazitaxel products and the need to appropriately dilute the product before use – in Sections 4.4, 6.3 and 6.6 of the SmPC. Additional risk minimisation measures: Communication Plan (DHPC letter) to ensure healthcare professionals and pharmacies using oncology agents are aware of the key messages regarding different concentration.	Routine pharmacovigilance activity: As summarized in RMP Part III Specific adverse reaction follow-up questionnaires have been proposed for Medication error. Additional pharmacovigilance activity: Routine pharmacovigilance with specific query for cases where symptoms and signs of overdose have occurred to determine if medication error has occurred. Review of cases reported with "medication error" (Category 3 Study)
Missing Information: Ethnicity other than Caucasian	Section 5.2 of Accord Cabazitaxel SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures include the labelling; and the prescription only status of the product. Additional risk minimisation measures: None	Routine pharmacovigilance activity: As summarized in RMP Part III Additional pharmacovigilance activity: None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.4 is acceptable.

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

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. 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 60 mg concentrate and solvent for solution for infusion and Zoledronic Acid Accord 4 mg/5 ml concentrate for solution for infusion. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a hybrid medicinal product, Cabazitaxel Accord (cabazitaxel, 20 mg/ml concentrate for solution for infusion). The reference product Jevtana (cabazitaxel, 60 mg concentrate and solvent for solution for infusion) 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 Accord 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 studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance. The applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient. The exemption from the necessity to conduct a bioequivalence study has been adequately justified.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

Due to concerns about potential medication errors additional risk minimisation activities are required beyond those included in the product information. A DHPC at product launch was agreed. Additionally, regular 6-monthly safety updates on the cases of medication errors should be submitted (see RMP).

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus decision that the benefit-risk balance of Cabazitaxel Accord is favourable in the following indication:

Cabazitaxel Accord 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 CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.