28 February 2019
EMA/202215/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pazenir

International non-proprietary name: paclitaxel

Procedure No. EMEA/H/C/004441/0000

Note

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

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List of abbreviations

5-FU	5 fluorouracil
ABC	ATP-binding cassette
ABI-007	Nab-paclitaxel; Albumin-bound paclitaxel; Protein-bound paclitaxel
API	Active Pharmaceutical Ingredient
ATP	Adenosine triphosphate
AUC	Area under the time-concentration curve
BCS	Breast-conserving surgery
CA	Carbohydrate antigen
CDP	Cytidine deaminase protein
CEP	Certificate of Suitability of the EP
CFU	Colony Forming Units
CEP	Certificate of Suitability of the EP
CFU	Colony Forming Units
CHMP	Committee for Medicinal Products for Human use
CIA	Collagen-induced arthritis
Cmax	Peak plasma concentration
CoA	Certificate of Analysis
COX	Cyclooxygenase
CR	Complete response
CrEL-P/C	CrEL-paclitaxel plus carboplatin
Cryo-TEM	Cryogenic transmission electron microscopy
CT	Computerized tomography
CYP	Cytochrome
DCR	Disease control rate
DFI	Disease-free interval
DLS	Dynamic light scattering
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
EDQM	European Directorate for the Quality of Medicines
EC	European Commission
EMA	European Medicines Agency
EOC	Epithelial ovarian cancer
ER	Oestrogen receptor (ER)/progesterone receptor
ESMO	European Society for Medical Oncology
ESO	European School of Oncology
ET	Endocrine therapy
EU	European Union
FDA	Food and Drug Administration
FOLFIRINOX	Folinic acid (leucovorin)/5-FU/irinotecan/oxaliplatin
GC	Gas Chromatography
GDP	Guanosine diphosphate
GLP	Good laboratory practice
Gp	Glycoprotein
GTP	Guanosine triphosphate
HAS	Human serum albumin
HER2	Human Epidermal Growth Factor Receptor 2
HMEC	Human mammary epithelial cells
HMVEC	Human M vascular endothelial cells

HMVEC-L	Human microvascular epithelial cells-lung
HPLC	High performance liquid chromatography
HSA	Human serum albumin
HUVEC	Human umbilical vein endothelial cells
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
ICP-OES	Inductively coupled plasma optical emission spectrometry
IFN	Interferon
IL	Interleukin
IPC	In-process control
IR	Infrared
IRAK	Interleukin receptor-associated kinase
IV	Intravenous
Km	Maximum reaction velocity
LC	Liquid Chromatography
LD10,50,90	Doses lethal to 10%, 50% and 90% of animals
LDM	Low-dose metronomic therapy
LABC	Locally advanced breast cancer
MAPK	Mitogen-activated protein kinase
MAP	Microtubule-associated protein
MBC	Metastatic breast cancer
MDT (MDR)	Multidrug resistance
MML	Monocyte-macrophage lineage
MKP	Protein kinase phosphatase
mRNA	Messenger ribonucleic acid
MTD	Maximum tolerated dose
Nab-P	*Nab*-paclitaxel
Nab-P/C	*Nab*-paclitaxel plus carboplatin
NBPs	Nitrogen-containing bisphosphonates
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NMT	Not more than
NOAEL	No observed adverse effect level
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PBSC	Peripheral blood stem cells
PDAC	Pancreatic ductal adenocarcinoma
PDE	Permitted Daily Exposure
PET	Positron-emission tomography
PFS	Progression free survival
P-gP	P-glycoprotein
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PMF	Plasma master file
ppm	Parts per million
PPTP	Pediatric preclinical testing program
PR	Partial response
PS	Performance status
PSCs	Pancreatic stellate cells
q3w	Every 3 weeks
q2w	Every 2 weeks

RECIST	Response Evaluation Criteria In Solid Tumours
RH	Relative Humidity
RMP	Reference medicinal product
ROS	Reactive oxygen species
RT	Radiation therapy
SCLC	Small cell lung cancer
SPARC	Secreted protein acid and rich in cysteine
SD	Stable disease
SDS-PAGE	Sodium dodecyl sulfate polyacrylamide gel electrophoresis
SmPC	Summary of Product Characteristics
TAMC	Total Aerobic Microbial Count
TSP-1	Thrombospondin-1
TNBC	Triple-negative breast cancer
TLR	Toll-like receptor
TSG	Tumor suppressor gene
TTE	Time to endpoint
TTP	Time to progression
TX	Thromboxane
TYMC	Total Combined Yeasts/Moulds Count
ULN	Upper limit of normal
UV	Ultraviolet
VEGF	Vascular endothelial growth factor
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Teva B.V. submitted on 28 July 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Pazenir, 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 28 April 2016.

The application concerns a generic medicinal product as defined in Article 10(2)(b) 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 in the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Pazenir monotherapy is indicated for the treatment of metastatic breast cancer in adult patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline containing therapy is not indicated.

Pazenir in combination with gemcitabine is indicated for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas.

Pazenir in combination with carboplatin is indicated for the first-line treatment of non-small cell lung cancer in adult patients who are not candidates for potentially curative surgery and/or radiation therapy.

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC)

The application submitted is composed of administrative information, complete quality data and comparative pharmacokinetic and demonstration of similarity of anti-tumour effects non-clinical studies with the reference medicinal product Abraxane.

The chosen reference product is:

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

- Product name, strength, pharmaceutical form: Abraxane, 5 mg/ml, powder for suspension for infusion
- Marketing authorisation holder: Celgene Europe B.V.
- Date of authorisation: 11-01-2008
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/07/428/001, EU/1/07/428/002

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

- Product name, strength, pharmaceutical form: Abraxane, 5 mg/ml, powder for suspension for infusion
- Marketing authorisation holder: Celgene Europe B.V.
- Date of authorisation: 11-01-2008

- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/07/428/001, EU/1/07/428/002

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Abraxane, 5 mg/ml, powder for suspension for infusion
- Marketing authorisation holder: Celgene Europe B.V.
- Date of authorisation: 11-01-2008
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/07/428/001, EU/1/07/428/002

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 submit a critical report addressing the possible similarity with authorised orphan medicinal products but subsequently withdrew the claimed indication that related to a condition for which there was an authorised orphan medicinal product for patent reasons.

Scientific advice

The applicant received Scientific Advice on the development relevant for the approved indication from the CHMP on 23 July 2015. The Scientific Advice pertained to the following: quality, non-clinical and clinical aspects of the dossier:

Questions on Quality development:

- Acceptability of the attributes for release testing of human serum albumin as well as completeness of the indicated attributes, current release requirements, test methods for release and stability testing of the drug product. The Scientific Advice also discussed the additional characterisation tests to demonstrate sameness of Pazenir 5 mg/ml Drug Product vs EU reference product (Abraxane), another nanoparticle albumin-bound paclitaxel.
- Acceptability of the manufacturing process for preparing Pazenir nanoparticles and combination of smaller sub-batches to receive a larger commercial batch size.

Multidisciplinary questions on Pharmaceutical and Clinical development:

- The multidisciplinary topics concerned the head-to-head *in vitro* physical and chemical characterisation studies and the suitability of their methodology to be used for the MAA submission to establish the comparability with Abraxane. Further, the discussion concerned the eligibility for a biowaiver of a bioequivalence study, based on the applicant's position that the products have same route of

administration (IV) and have the same qualitative and quantitative compositions, as well as nature and behaviour of the products.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Milena Stain

The application was received by the EMA on	28 July 2017
The procedure started on	17 August 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	3 November 2017
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	17 November 2017
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	29 November 2017
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 December 2017
The applicant submitted the responses to the CHMP consolidated List of Questions on	17 April 2018
The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	04 May 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	17 May 2018
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	31 May 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	26 June 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	12 July 2018
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	26 July 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	03 January 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	16 January 2019

The CHMP agreed on a list of outstanding issues to be sent to the applicant on	31 January 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	04 February 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	15 February 2019
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 Pazenir on	28 February 2019

2. Scientific discussion

2.1. Introduction

Pazenir 5 mg/ml powder for dispersion for infusion is a generic medicinal product containing the active substance paclitaxel. The reference medicinal product is Abraxane 5 mg/ml powder for suspension for infusion, authorised in the EU on 11th of January 2008.

The use of 'powder for dispersion for infusion' to describe the pharmaceutical form of Pazenir (instead of 'powder for suspension for infusion' as used for the reference product) is justified based on the decision from European Directorate for Quality of Medicines.

The reference product Abraxane is a nanoparticle albumin-bound paclitaxel (also referred as nab-paclitaxel in this report). This formulation allows the administration of insoluble lipophilic agents, such as nab-paclitaxel, which is an amorphous and crystalline form of paclitaxel bound to albumin (at a concentration of 3–4%). Nanoparticle albumin-bound paclitaxel (nab-paclitaxel; nab-P) is Cremophor EL(CrEL)-free, consisting only of unmodified paclitaxel and human albumin. By eliminating CrEL from its formulation, nab-paclitaxel has a reduced risk of hypersensitivity reactions, does not require premedication and can be administered over a shorter period (30 min) of time without special IV tubing.

The first commercial product based on protein nanoparticles was a 130-nanometer albumin-bound paclitaxel, approved by the US Food and Drug Administration (FDA) in 2005 and by the European Commission in 2008 for the treatment of metastatic breast carcinoma, and later on for the treatment of metastatic pancreatic cancer (2013) and advanced non-small cell lung carcinoma (2015).

Pazenir consists of nanoparticles, which most likely consist of packages of paclitaxel-bound HSA (human serum albumin), which are attached together via non-covalent/hydrophobic interactions in the form of nanoparticles and fall apart upon dilution in vitro or in the systemic circulation. Upon intravenous administration, the paclitaxel albumin nanoparticles are expected to rapidly dissociate into soluble, albumin-bound paclitaxel complexes of approximately 10 nm in size. Albumin is known to mediate endothelial caveolar transcytosis of plasma constituents, and *in vitro* studies demonstrated that the presence of albumin enhances transport of paclitaxel across endothelial cells. It is hypothesised that this enhanced transendothelial caveolar transport is mediated by the gp-60 albumin receptor, and that there is enhanced accumulation of paclitaxel in the area of tumour due to the albumin-binding protein Secreted Protein Acidic Rich in Cysteine (SPARC) (SmPC Abraxane).

The safety and efficacy profile of nab-paclitaxel for the treatment of metastatic breast cancer, metastatic adenocarcinoma of the pancreas and non-small cell lung cancer has been demonstrated in several clinical trials for the reference medicinal product. In addition, there is a long-term post-marketing experience contributing to the knowledge of the clinical use of this active substance.

The claimed indications of Pazenir are as follows:

- Breast cancer: in monotherapy for the treatment of metastatic breast cancer in adult patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline containing therapy is not indicated.
- Non-small cell lung cancer: in combination with carboplatin for the first-line treatment of non-small cell lung cancer in adult patients who are not candidates for potentially curative surgery and/or radiation therapy.

The indication for pancreatic adenocarcinoma is not included. The application is for the 100 mg strength only and does not concern the 250 mg that is also approved for Abraxane.

To demonstrate comparability between the proposed generic product and the reference product Abraxane, the physicochemical characteristics and protein characterization of both products were compared. Integrity studies were also performed in order to demonstrate that the albumin present in the Pazenir formulation is comparable with the albumin present in the reference product and its integrity is not affected by the manufacturing process of Pazenir.

No bioequivalence studies have been conducted. The applicant justified that Pazenir was eligible for a biowaiver on the basis of qualitative and quantitative comparability with the reference product and based on the nature of the product, rapidly dissociating upon *in vivo* dilution and binding to endogenous albumin.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a powder for dispersion for infusion containing 5 mg/ml of paclitaxel as active substance.

Other ingredients are albumin (human), sodium caprylate, *N*-acetyl-DL-tryptophan, sodium chloride, hydrochloric acid and sodium hydroxide.

The product is available in type 1 glass vials with butyl rubber stoppers and aluminium overseals as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of paclitaxel is 5β,20-epoxy-1,7β-dihydroxy-9-oxotax-11-ene-2α,4,10β,13α-tetrayl 4,10-diacetate 2-benzoate 13-[(2*R*,3*S*)-3-(benzoylamino)-2-hydroxy-3-phenylpropanoate)] corresponding to the molecular formula $C_{47}H_{51}NO_{14}$. It has a relative molecular mass of 854 g/mol and the following structure:

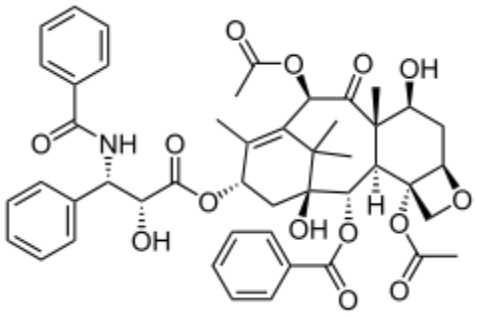

Figure 1: active substance structure

As there is a monograph of paclitaxel in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for paclitaxel which has been provided within the current marketing authorisation application.

Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the CEP.

Specification

The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph. The active substance specification used by the finished product manufacturer includes tests for appearance (visual), identity (IR, specific optical rotation, both Ph. Eur.), appearance of solution (clarity, colour, both Ph. Eur.), assay (HPLC), impurities (HPLC), residual solvents (GC), water content (Ph. Eur.), heavy metals (ICP-OES), microbial contamination (Ph. Eur.) and bacterial endotoxins (Ph. Eur.). In-house methods were adequately described and validated in accordance with the ICH guidelines. The microbial contamination methods were suitably validated. Suitable information has been provided on the reference standards used for assay, impurities and residual solvents testing.

Batch analysis data from 3 production scale batches of the active substance were provided. The results were within the specifications and consistent from batch to batch.

Stability

Stability data was assessed during evaluation of the CEP. No additional data were provided with the present application.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

Pazenir 5 mg/ml powder for dispersion for infusion (100 mg/vial) is a white to slightly yellow lyophilized cake, packaged in a 50 ml clear Type I glass vial closed with a bromobutyl fluorinated polymer coated stopper which is sealed by 20 mm aluminium overseal with a coloured polypropylene snap-cap.

The aim of the pharmaceutical development was to develop a generic medicinal product essentially similar to Abraxane 5 mg/ml powder for suspension for infusion. Pazenir has the same active substance, dosage form, strength, route of administration and conditions of use as the reference product.

Although the dosage forms are the same, there is a discrepancy between how these are described in the dossier, labelling, and product information. Abraxane is described as a "powder for suspension for infusion." However, this is no longer a valid standard term due to safety concerns with the concept of infusing a suspension, which implies solid particles. Therefore, the applicant describes the product as a "powder for dispersion for infusion," which was recommended by EMA during validation and is considered acceptable by CHMP.

Paclitaxel has poor solubility in aqueous media. Therefore, paclitaxel products aim to increase its solubility by use of excipients, for example, Cremophor. However this excipient has been known to cause hypersensitivity reactions. Abraxane uses human serum albumin (HSA) as an excipient to stabilise amorphous paclitaxel nanoparticles, preventing aggregation and improving dissolution characteristics once diluted with saline for intravenous infusion. HSA is a naturally occurring protein, which reduces the risk of any adverse effects during infusion. Once administered, the nanoparticles rapidly dissociate into soluble endogenous albumin-bound paclitaxel complexes, which are thought to be the major carriers of paclitaxel in blood, and also, to mediate tumour uptake. Sodium caprylate and *N*-acetyl-DL-tryptophan are added to stabilise the albumin, as per the reference product.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. HSA is supported by a plasma master file and its shelf-life is taken into account when determining the shelf-life of the formulated product. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The applicant considers the product to be eligible for a biowaiver on the basis of both qualitative and quantitative comparability with the reference product. It was stated that the paclitaxel dissociates rapidly upon *in vivo* administration and binds to endogenous albumin. Accordingly, it was argued that excipients do not alter the disposition of the product.

In order to demonstrate essential similarity to the reference product, numerous different characterization studies were carried out by using different analytical methods to compare the Pazenir and Abraxane formulations. The applicant has divided the characterization tests into 3 parts, namely physico-chemical characterization and *in vitro* dissociation, protein characterization (structural integrity of HSA), and sameness and nature of bond between paclitaxel and HSA. However, the initial data was not considered sufficient to grant a biowaiver and a multi-disciplinary major objection was raised. In particular, the qualitative and quantitative compositions immediately prior to administration had not been adequately compared, there were some differences in composition (apparent differences in excipient content and residual solvent content used to solubilise paclitaxel during formulation), and the particle size of reference product batches was slightly larger than the generic product on average, with inadequate discussion on how these differences might impact performance *in vivo*. Furthermore, the dissociation experiments had only been carried out in a set of media considered too limited to mimic *in vivo* conditions. In addition, comparison had only been carried out with one batch of reference product, which prevented any comparison of batch to batch variability.

In response, the applicant provided extensive additional data comparing relevant characteristics of Pazenir and the reference product. This included a demonstration that the differences in physico-chemical properties and excipient content were not significant once compared to the batch to batch variability. Protein characterization and integrity studies were performed to demonstrate that the albumin present in the test product formulation is comparable with the albumin present in the reference product and that its integrity is not affected by the

manufacturing process. Results of studies on binding characteristics of paclitaxel to HSA showed an identical binding site for paclitaxel and the affinity of the drug binding was also the same as for Abraxane. In addition, limits for residual solvents were tightened. It was adequately demonstrated that the products can be considered essentially qualitatively and quantitatively similar.

In addition, further studies conducted in relevant media were able to show that the differences in particle size of the lyophilized product didn't translate to significant differences following dilution and simulated infusion.

Further clarification was requested on the relative amounts of HSA-bound and unbound paclitaxel. The applicant explained that there is no non-destructive method available to separate the non-encapsulated paclitaxel from the paclitaxel-HSA nanoparticles to accurately measure unbound paclitaxel and therefore no reliable data on non-encapsulated paclitaxel could be generated. However, almost all HSA in the formulation is expected to be bound to paclitaxel molecules and the fraction of unbound HSA that does not contain paclitaxel is considered to be negligible. The conclusion that the percentage of non-encapsulated (unbound) HSA indirectly represents the percentage of non-encapsulated paclitaxel (which is bound to the non-encapsulated HSA) is accepted. The applicant further described that any free paclitaxel above the maximum solubility will precipitate and be removed during the final sterile filtration in the manufacturing process.

The importance of the dissociation of the nanoparticle has been emphasized throughout the procedure. In addition to initially-provided results, dissociation data was provided in comparison to an additional two batches of reference product in order to address the concerns about batch to batch variability. Statistical comparison of the relative dissociation kinetics showed sufficient overlap. Overall, it is considered that complete dissociation of the nanoparticles has been shown in human plasma (neat and diluted) at a clinically relevant paclitaxel concentration, (see clinical section, dissociation kinetics sub-heading). Although slight differences were observed between the exact time-points at which complete dissociation was achieved *in vitro*, these were adequately justified on the basis that they are on the scale of minutes.

Overall, it was demonstrated that differences between the test and reference formulations in terms of the parameters measured were insignificant, or unlikely to impact the performance of the products. Considering that the nanoparticles are expected to dissociate even faster *in vivo,* and bearing in mind the additional dilution effect upon slow intravenous infusion, these minor differences are not expected to have a clinical impact. Overall, the biowaiver was considered justified.

Development of the manufacturing process was considered critical in order to produce a product essentially similar to the reference product. The process is based on emulsification followed by solvent evaporation. A suitable organic solvent had to be chosen in order to first dissolve paclitaxel and subsequently evaporate on lyophilisation.

In order to optimise the process, various parameters were investigated. In addition, suitable lyophilisation conditions were determined in order to remove both water and residuals of used organic solvents. The description of the manufacturing process development is suitably detailed.

Given the nature of the product, it is not possible to conduct terminal sterilisation. Instead, sterile filtration of the bulk product is carried out prior to filling and lyophilisation under aseptic conditions. It was demonstrated that the filtration step does not impact the nature of the nano-particulate formulation.

Compatibility studies were conducted with the manufacturing equipment including the vessels, tubing and filter material. Following a risk assessment, extractables studies were designed in line with the intended duration of the manufacturing process but under exaggerated conditions. No extractables were observed above the applied evaluation thresholds, demonstrating compatibility of the manufacturing equipment with the formulation.

The primary packaging is type 1 glass vials with butyl rubber stoppers and aluminium overseals. 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 consists of multiple steps of which the main ones are: preparation of bulk solutions of albumin, saline, paclitaxel and albumin stabilizer solution; preparation of nano-emulsion followed by dilution to give a nano-suspension; evaporation of organic solvent, removal of large particles; diafiltration; addition of albumin stabilizer solution; sterile filtration; filling followed by lyophilisation; capping; labelling and packaging. Overages for paclitaxel and albumin are applied to compensate for losses during the manufacturing process. These have been adequately justified and a consistent loss has been observed during different unit operations during process validation. The process is considered to be a non-standard manufacturing process.

The following unit operations were defined as critical for the process: preparation of crude emulsion; homogenization (to ensure desired nano-emulsion droplet size); quenching (to maintain particle size); evaporation for removal of organic solvent; sterile filtration. The process parameters used to control these steps have been adequately defined. The extensive IPCs applied to the whole process, and in particular, the critical steps, are adequate for this type of manufacturing process and pharmaceutical form. Bioburden is tested prior to sterile filtration and the integrity of the filters is also tested. Holding times for individual operations have been defined and justified with data.

Major steps of the manufacturing process have been validated on 3 consecutive production scale batches of finished product. In addition, the sterile filter was tested in a microbial challenge study and demonstrated to be suitable for filtration of the bulk product. Media fill studies were carried out to demonstrate an acceptable level of aseptic processing. Overall, it has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including appearance (visual), identification (UPLC, UV), reconstitution time (visual), appearance of dispersion (visual), particulate matter (Ph. Eur.), pH (Ph. Eur.), osmolality (Ph. Eur.), particle size distribution (Ph. Eur.), bound/unbound albumin (in-house), closure integrity (dye ingress), water content (Ph. Eur.), uniformity of dosage units (Ph. Eur.), residual solvents (GC), related substances (UPLC), solid state form (XRPD), albumin oligomeric status (UPLC), albumin assay (UPLC), N-acetyl-DL-tryptophan assay (UPLC), caprylic acid assay (UPLC), paclitaxel assay (UPLC), sterility (Ph. Eur.) and bacterial endotoxins (Ph. Eur.).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented. Impurities present above the qualification limit have been adequately qualified. A risk assessment for elemental impurities was carried out according to ICH Q3D indicating low risk of contamination. Batch analysis data on 3 batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE.

Batch analysis results are provided for 3 production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the release specifications, through traditional final product release testing.

Stability of the product

Stability data from 3 production scale batches of finished product stored for up to 12 months under long term conditions (25 ºC / 60% RH), for up to 12 months under intermediate conditions (30 ºC / 75% RH), and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, reconstitution time, appearance of dispersion, pH, osmolality, particle size distribution, bound/unbound albumin, closure integrity, water content, related substances, solid state form, albumin oligomeric status, albumin assay, *N*-acetyl-DL-tryptophan assay, caprylic acid assay, paclitaxel assay, sterility, bacterial endotoxins and sub-visible particles. The analytical procedures used are stability indicating. No significant trends to any of the test parameters were observed under any of the storage conditions.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Product stored in the primary container only showed an increase in degradation products over time whereas product stored within the primary and secondary (cardboard box) containers did not show any difference from the dark control. Therefore, the product is photosensitive and should be stored in the outer carton to protect from light exposure.

In order to assess the stability of the product to short term changes in temperature and humidity which may be experienced during uncontrolled transportation or short-term storage outside of the recommended conditions, a short term excursion study (-20 ^{o}C to 60 ^{o}C / 75% RH) and a thermal cycling study (-20 ^{o}C to 40 ^{o}C / 75% RH) were conducted. No significant changes to any measured parameters were observed, meaning that it is not necessary to transport the product under controlled conditions.

An in-use stability study was conducted to evaluate the stability of the product reconstituted in the intended infusion fluid (0.9% NaCl) in the primary packaging and in the intended infusion bag. Product from the initial time-point and following 12 months' storage was reconstituted and tested following storage in the original vial, inside the carton, under refrigerated conditions or following storage in the infusion bag under ambient conditions. Stability was demonstrated in both formats for up to 8 hours although it is recommended to transfer the reconstituted dispersion from vial to bag immediately, and also to use the dispersion in the infuse bag immediately (see SmPC section 6.3).

Based on available stability data, the proposed shelf-life of 2 years with the vial stored in the outer carton to protect from light as stated in the SmPC (section 6.3 and 6.4) is acceptable.

<u>Stability of reconstituted dispersion in the vial:</u>

Chemical and physical in-use stability has been demonstrated for 8 hours at 2-8 °C when the vial is in the original carton, and protected from bright light. Alternative light-protection may be used in the clean room. From a microbiological point of view, unless the method of opening/reconstituting/dilution precludes the risks of microbial contamination, the product should be filled into an infusion bag immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Stability of the reconstituted dispersion in the infusion bag:

Chemical and physical in-use stability has been demonstrated for 8 hours not above 25 °C. From a microbiological point of view, unless the method of opening/reconstituting/dilution precludes the risks of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Adventitious agents

Human serum albumin, a plasma-derived product, is used as an excipient in the finished product. The HSA used by the manufacturer has a valid marketing authorisation in the EU, linked to a certified plasma master file (PMF). The PMF certificate of compliance has been provided, along with a letter of access.

2.2.4. Discussion on chemical, and pharmaceutical aspects

A CEP was presented for the active substance. Information on development, manufacture and control of the finished product has been presented in a satisfactory manner. It was demonstrated through an extensive array of studies that Pazenir is essentially similar to the reference product, Abraxane. The data provided justifies the biowaiver. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. 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

Not applicable

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical development was limited to comparative pharmacokinetics studies and demonstration of similarity of anti-tumour effects. Other information on pharmacology, pharmacokinetics and toxicology of paclitaxel has been derived from literature and other scientific publications available up to June 2017.

The following *in vivo* non-clinical studies were submitted:

- Study 2215-003: PK study in non-tumour bearing rats with 40L scale development batch in comparison with EU and US-sourced Abraxane

- study MDA-MB231-e461: PK/PD study in tumour bearing mice with a production scale development batch in comparison with EU-sourced Abraxane.

Study No. 2215-03

72 male jugular vein-cannulated Sprague-Dawley [Crl:CD (SD)] rats were assigned to six groups (four test formulations and 2 batches of Abraxane). The test batches included in study 2215-003 were manufactured at different stages of scale-up ranging from early to mid-development. Two batches of Abraxane (EU-sourced and US-sourced) were included in the study for comparison with the test formulations.

Each test and reference product was prepared at a target concentration of 2 mg paclitaxel/mL and administered at a dose volume of 5 ml/kg to achieve a dose level of 10 mg paclitaxel/kg. Each group of rats was divided into 2 cohorts (6 animals per cohort) that were bled at the following alternating collection intervals: 0.033 (2 minutes), 0.083 (5 minutes), 0.25 (15 minutes), 0.5 (30 minutes), 1, 2, 4, 6, 8, and 12 hours post dose. All animals were bled at 24 hours post dose. Total (i.e. unbound plus bound) and unbound paclitaxel concentrations were determined in plasma via HPLC with MS/MS detection.

Results from the PK analysis are presented below.

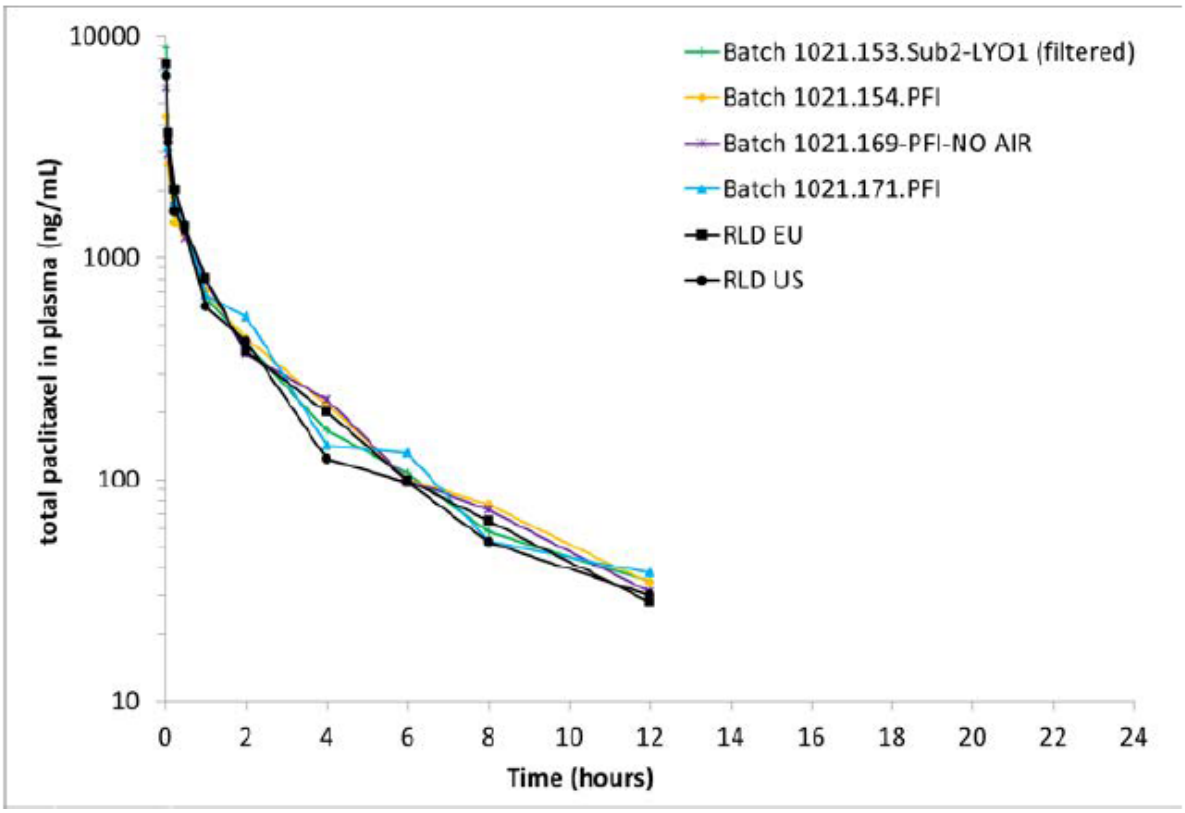

Figure 2: Levels of total paclitaxel in rat plasma after i.v bolus injection of nab-paclitaxel (10 mg paclitaxel/kg b.w.). Nominal quantitation range 20.0 – 20000 ng/mL

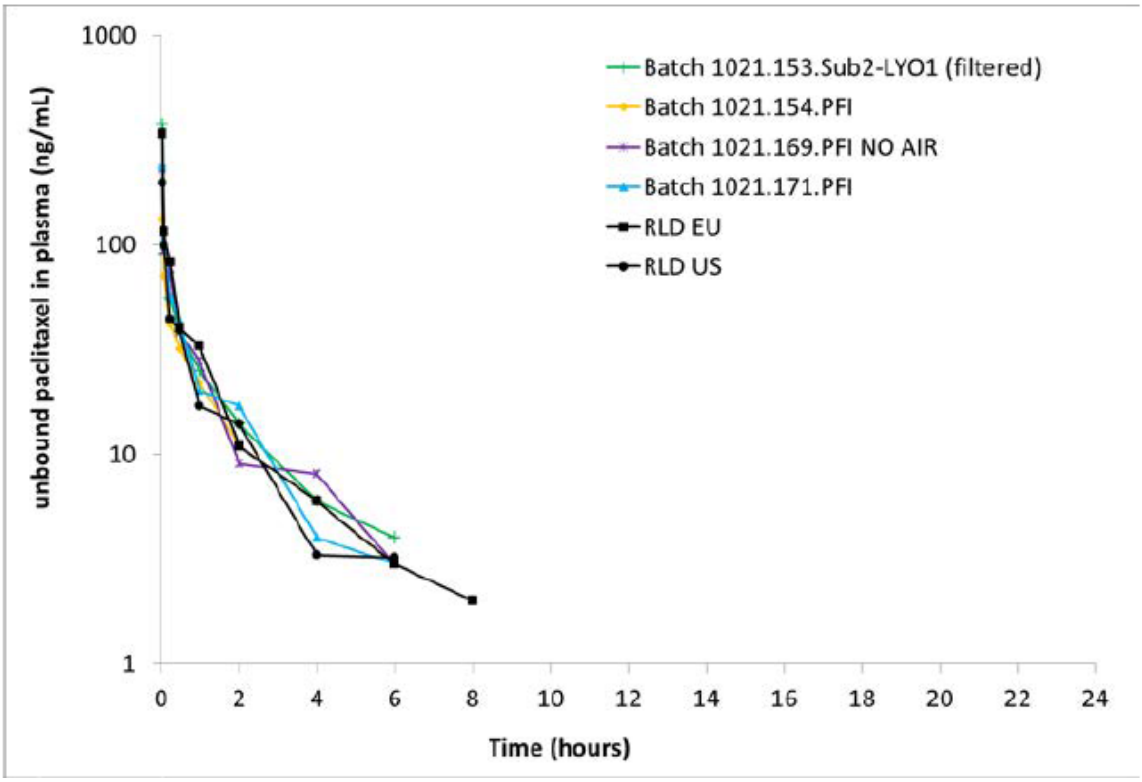

Figure 3: Levels of unbound paclitaxel in rat plasma after i.v. bolus injection of nab-paclitaxel (10 mg paclitaxel/kg b.w.). Nominal quantitation range 2.00 – 2000 ng/mL

No deaths were observed and all doses were well-tolerated; no signs of systemic toxicity following administration of a single intravenous bolus dose at a dose level of 10 mg/kg were noted.

Study MDA-MB231-e461

The anticancer effect of Pazenir 5 mg/ml powder for dispersion for infusion was studied in female athymic nude mice transplanted with MDA-MB-231 human breast carcinoma cells, in comparison with EU-sourced Abraxane. The study was conducted as a combined pharmacokinetics (PK)/pharmacodynamics (PD) study.

The study was performed in the human xenograft MDA-MB231 breast carcinoma model in female NCr nu/nu mice. Nude mice were inoculated with MDA-MB231 tumour cells in the flank. For the PD groups (groups 1-5; vehicle and two paclitaxel dose levels), a pair match was performed when tumours reached an average size of 100 – 150 mm3 followed by dosing of the animals (n=20) intravenously in the tail vein with a bolus dose on study days 1, 5, and 9.

Immediately before dosing, reconstitution of test and reference products was done in accordance with the instructions of the SmPC of Abraxane in 0.9% sodium chloride for injection. Body weight determination and calliper measurement were performed frequently. The endpoint of the study for individual animals in groups 1-5 was a tumour volume of 1500 mm^3 or 59 days, whichever came first. All treated groups showed tumour growth delay as compared to vehicle group and a dose response was observed (Figure 4).

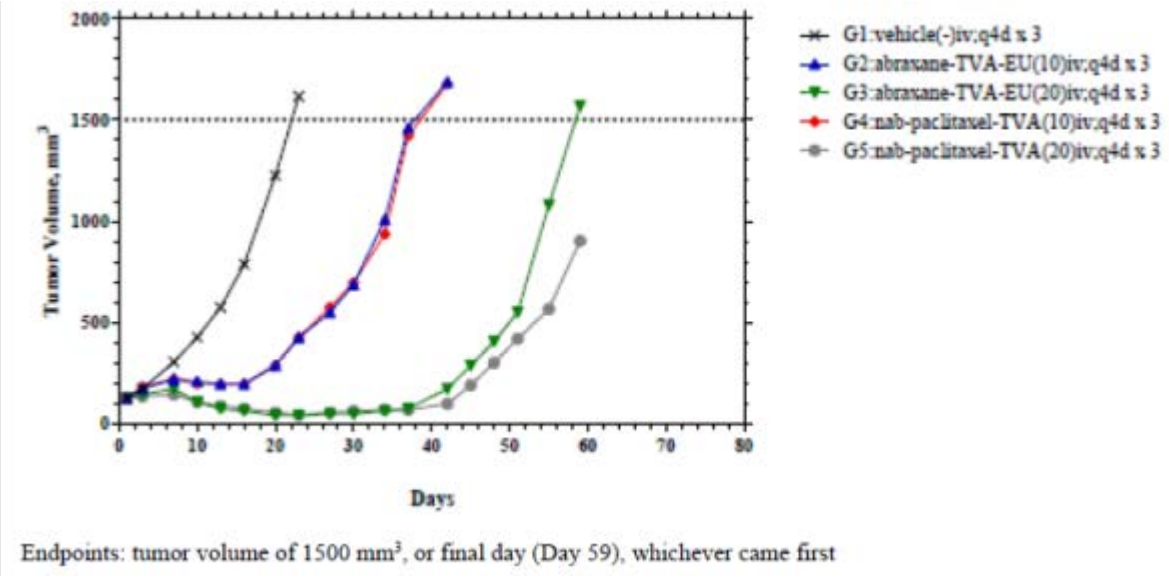

Figure 4: Median Tumor Volume in Study MDA-MB231-e461

The PK part of the study consisted of two groups (group 6 and 7; n=35) treated with Pazenir 5 mg/ml powder for dispersion for infusion or Abraxane. Group 8 (n=3) was not treated. Once tumours in Groups 6 and 7 reached an acceptable size range (approximately 500 mm^3), they were treated with Abraxane and Pazenir, respectively, at a dosage of 20 mg/kg i.v. once. The individual tumour volumes ranged from 172 to 1183 mm^3 with group mean tumour volumes ranging from 505 to 587 mm^3. Inadvertently the animals in the PK groups were dosed prematurely when group mean tumour volumes were between 128 and 129 mm^3. This error was corrected by obtaining replacement animals that had been injected previously with MDA-MB-231 cells for group 6+8 and group 7, respectively.

Animals treated with Abraxane and the non-treated animals were sampled 37 days post inoculation, whereas the animals treated with Pazenir 5 mg/ml powder for dispersion for infusion were sampled on 26 days post inoculation.

Terminal blood samples were collected via cardiac puncture while under isoflurane anaesthesia from five animals in each group at the following time points: 5 minutes, 15 minutes, 30 minutes, 1 hour, 3 hours, 8 hours and 24 hours post a single dose. Immediately following blood collection, tumour, heart and liver samples were collected. Group 8 had three non-treated animals that were sampled as previously described for Groups 6 and 7.

The elimination half-life (t½) after IV administration of Abraxane or Pazenir was 0.62 and 0.66 hours respectively. It was noted that the 8-hour time point was excluded from the t½ calculation for both groups. The plasma AUC0-t was 8043 ng·h/mL for Abraxane and 9086 ng·h/mL for Pazenir, respectively.

Table 1: Pharmacokinetics of paclitaxel in plasma in a single dose i.v bolus study in tumor-bearing female mice administered Pazenir 5 mg/ml powder for dispersion for infusion or Abraxane at 20 mg/kg bw (Study MDA-MB231-e461)

Parameter	Abraxane®			Paclitaxel Albumin Teva 5 mg/ml Powder for Suspension for Infusion		
	Total paclitaxel	Unbound paclitaxel	Unbound paclitaxel % of total	Total paclitaxel	Unbound paclitaxel	Unbound paclitaxel % of total
C_0 (ng/mL)	10412	443.21	NA	25213	703.61	NA
C_{5min} (ng/mL)	8493	356.22	4.2	15679	543.40	3.5
AUC_{0-t} (ng ·h/mL)	8043	393	4.9	9086	424	4.7
CL (mL/min/kg)	39.0	NA	NA	36.6	NA	NA
V_z (L/kg)	2.1	NA	NA	2.1	NA	NA
$t_{½}$ (h)[a]	0.62	NA	NA	0.66	NA	NA
$AUC_{0-\infty}$ (ng ·h/mL)	8550	NA	NA	9110	NA	NA
% extrapolated	5.9	NA	NA	0.3	NA	NA

[a] 8-hour time point excluded from calculation
NA=not applicable

Table 2: Pharmacokinetics of total paclitaxel in tissues in a single dose i.v bolus study in tumor-bearing female mice administered Pazenir 5 mg/ml powder for dispersion for infusion or Abraxane at 20 mg/kg bw (Study MDA-MB231-e461)

Parameter	Abraxane®			Paclitaxel Albumin Teva 5 mg/ml Powder for Suspension for Infusion		
	Liver	Heart	Tumor	Liver	Heart	Tumor
C_{max} (ng/g)	124842	23320	3164	111612	31805	3930
t_{max} (h)	0.083	0.083	0.5	0.083	0.083	1
AUC_{0-t} (ng ·h/g)	193222	25761	56310	177863	26442	68309

2.3.2. Ecotoxicity/environmental risk assessment

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

2.3.3. Discussion on non-clinical aspects

The non-clinical development was limited to comparative studies of the pharmacokinetics and of the anti-tumour effects. Information on pharmacology, pharmacokinetics and toxicology of paclitaxel was derived from the literature. The non-clinical overview was based on up-to-date and adequate scientific literature and thorough literature search was done using a number of different databases/search tool. The following *in vivo* non-clinical studies were provided by the applicant: one PK study in non-tumour bearing rats with 40L scale

development batch in comparison with EU and US-sourced Abraxane (study 2215-003) and one PK/PD study in tumour bearing mice with a production scale development batch in comparison with EU-sourced Abraxane (study MDA-MB231-e461).

PK analyses in the rat model showed comparable AUC values, volume of distribution (Vz), and clearance (CL) for total paclitaxel between Pazenir and Abraxane (EU sourced). Generally, the EU-sourced Abraxane is considered the relevant comparator for this application. The test batches included in study 2215-003 were manufactured at different stages of scale-up ranging from early to mid-development. Various differences (e.g. a higher organic solvent content) between test batches and the "to be marketed product" were detected and their possible influence on PK is not entirely clear; e.g. literature suggests, that organic solvents play a significant role in nanoparticle formation (effect on the particle size and entrapment efficiency)[1]; thus, the relevance of this study for the overall bioequivalence approach is considered limited.

PK analysis showed that for total paclitaxel, AUC values, volume of distribution (Vz), and clearance (CL) were more or less comparable for all batches of Pazenir 5 mg/ml and of Abraxane (EU sourced). High variability in C0 was however observed (range from 570 ng/ml to 55 ng/ml), likely caused by differences in the exact times of sampling at the first post administration sampling time (i.e., 2 minutes post dose).

For unbound paclitaxel, the results of the PK analysis showed that AUC and t½ values were generally lower for Pazenir compared to the reference product EU Abraxane. These finding might partly be explained by a strong variability in C0 and varying mean values for LLQ.

Abraxane and Pazenir performed similarly in the MDA-MB-231 human breast carcinoma xenograft model. As compared to vehicle all treated groups showed tumour growth delay; a dose response was observed as well. Similar delay of tumour growth was observed after treatment with Abraxane and Pazenir, and numbers of partial and complete regressions and tumour-free survivors were comparable. Abraxane and Pazenir performed similarly in the MDA-MB-231 human breast carcinoma xenograft model.

The elimination half-life (t½) after IV administration of Abraxane or Pazenir was 0.62 and 0.66 hours respectively. It needs however to be mentioned, that the 8-hour time point was excluded from the t½ calculation for both groups. According to the Applicant, the reason was that in the Abraxane group the mean plasma concentration was higher at 8 hours post-dose than at 3 hours post-dose. This was inconsistent with the expected profile after IV administration. The underlying cause for this observation is unknown. The most likely explanation for this finding is however an unintended extravascular application, leading to delayed absorption and resulting in higher concentrations at later time points.

The plasma AUC0-t was 8043 ng·h/ml for Abraxane and 9086 ng·h/mL for Pazenir, respectively. The higher AUC0-t for Pazenir may be driven by the higher partial AUC0-5 min in this group. This can be explained by the higher C5min for Pazenir as the extrapolation to C0 relies heavily on the concentration at the 5-minute time point. Two animals in the nab-paclitaxel group had substantially higher plasma concentrations at the 5-minute time point had than did the other 3. This resulted in a higher mean concentration at 5 minutes post-dose (C5min) for nab-paclitaxel (C5min = 15679±11565 ng/ml) compared to Abraxane (C5min=8493±857 ng/ml). A source of this detected variability can be explained by the 5-minute collection time that was allowed to take place between 4 – 6 minutes, which may impact concentrations substantially due to the rapid decrease in concentrations occurring in that time period.

[1] Vineeth, P et al. (2014). Influence of organic solvents on nanoparticle formation and surfactants on release behaviour in-vitro using costunolide as model anticancer agent. International Journal of Pharmacy and Pharmaceutical Sciences. 6. 638-645.

Paclitaxel exposures (AUC0-t) in heart and liver tissue were comparable between the Abraxane and Pazenir groups. On the contrary, tumour exposure for Pazenir was higher than for Abraxane (AUC0-t: 68309 vs. 56310). Thus, the PK data on tumour tissue exposure apparently suggested a difference between both treatments. However, the differences in growth rates of the tumours, vascularization, etc. may be an underlying factor for the variability and the observed differences. Whether paclitaxel concentrations in tumour tissue represent an adequate and relevant endpoint for the comparability exercise is questionable. In this respect, the comparison of PK results in plasma and organ tissues (liver and heart) seems to be a more robust variable.

Overall, several methodological weaknesses have been identified in both *in vivo* non-clinical studies and the overall bioequivalence approach is based primarily on *in vitro* comparative characterization in simulated serum and human plasma, which is acceptable for the comparative exercise.

The justification for not submitting an ERA since it is considered that Pazenir is unlikely to result in a significant risk to the environment is acceptable.

2.3.4. Conclusion on the non-clinical aspects

The non-clinical overview is based on up-to-date and adequate scientific literature and is therefore considered adequate. Additional *in vivo* non-clinical studies were provided but their value in the assessment of similarity between Pazenir and Abraxane is considered limited due to methodological weaknesses.

The non-clinical aspects of the SmPC are in line with the SmPC of the reference product.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for a powder for dispersion for infusion containing paclitaxel formulated as albumin-bound paclitaxel.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of paclitaxel based on published literature. The SmPC is in line with the SmPC of the reference product.

Exemption

The applied indications, route of administration, dosage form and strength (100 mg) for Pazenir are the same as for Abraxane, except for the following:

- The indication “in combination with gemcitabine for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas” was excluded from the current applicant for patent reasons.

- The 250 mg strength, which is authorised for Abraxane, was not applied for in this MA procedure.

No clinical bioequivalence studies have been provided. The applicant applied for a waiver for bioequivalence studies/clinical studies on the basis of the qualitative and quantitative comparability with the reference product and based on its rapid dissociation after dilution.

Pazenir is not an aqueous intravenous solution but a “complex” formulation and as such, a bioequivalence study may be necessary, unless otherwise justified. According to the “Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **)”, the following requirements must be met in order to qualify for a

biowaiver in the case of “complex” formulations (where any excipient could interact with the drug substance or otherwise affect the disposition of the drug substance):

- the same excipients in very similar quantities or
- a justification that any difference in quantity does not affect the pharmacokinetics of the active substance.

Based on a rapid dissociation of the nanoparticles upon infusion, the situation shows resemblance to the situation of micellar parenteral drug products with rapid degradation of the micellar component. Hence, a bioequivalence study may be waived, if all prerequisites as outlined in the “*Reflection paper on the pharmaceutical development of intravenous medicinal products containing active substances solubilised in micellar systems, EMA/CHMP/QWP/799402/2011”* are fulfilled.

- the method and rate of administration should be the same as for the approved product;
- rapid disassembly of the micelles on dilution occurs and the drug product is not designed to control release or disposition;
- the excipients do not affect the disposition of the drug substance;
- the composition of the micelle infusion immediately before administration should be qualitatively and quantitatively the same as that currently approved, and satisfactory data should be provided to demonstrate similar physicochemical characteristics.

Pazenir has the same method and rate of administration, indication, dosage form and strength (100 mg) as Abraxane.

Regarding the qualitative and quantitative composition of the reference and the generic product, the concentration of Paclitaxel is the same and the concentration of the excipient albumin is similar. To further demonstrate comparability between the proposed product and the reference product Abraxane, the following physicochemical characteristics were compared (see quality assessment):

- The total paclitaxel and HSA content as well as paclitaxel/HSA molar ratios;
- average particle size and volume size distribution (by two different dynamic light scattering techniques);
- dissociation kinetics comparing three TEVA batches and two EU-reference batches (supported by further investigations of one CH-sourced reference batch and two TEVA batches with higher and lower paclitaxel: albumin ratio);
- encapsulated and non-encapsulated HSA in the reconstituted suspension using a specific dynamic light scattering technique indirectly representing the percentage of non-/encapsulated paclitaxel, which is bound to the non-/encapsulated HSA
- protein characterization and integrity studies to demonstrate that the albumin present in the Pazenir formulation is comparable with the albumin present in the reference product, and its integrity is not affected by the proposed manufacturing process;
- binding characteristics of paclitaxel to HSA using fluorescence spectroscopy and equilibrium dialysis (*in vitro* release kinetics of paclitaxel from paclitaxel-HSA complexes).

2.4.2. Pharmacokinetics

No new pharmacokinetic studies were presented (see clinical discussion).

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented (see clinical discussion).

2.4.4. Post marketing experience

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

2.4.5. Discussion on clinical aspects

The applicant has claimed a biowaiver on the basis that the relevant pharmaceutical properties of Pazenir are essentially similar to the reference product. The applicant received a scientific advice which related to multidisciplinary topics (i.e. pharmaceutical and clinical development) in relation to the suitability of the head-to-head *in vitro* physical and chemical characterisation studies to fulfil the requirements for eligibility for a biowaiver, based on the same route of administration (IV), comparability of the qualitative and quantitative composition as well as nature of the product (rapid dissociation upon *in vivo* dilution and binding to endogenous albumin). The applicant's justification was generally acceptable. The nanoparticle suspension is considered a "complex" parenteral, for which a clinical bioequivalence study may be necessary. However, a biowaiver could be justifiable, if the composition is qualitatively and quantitatively similar to Abraxane and the *in vitro* characteristics of the infusion suspension and the behaviour of the nanoparticles in blood/plasma following infusion can be sufficiently characterised by *in vitro* assays (e.g. showing very rapid dissociation of the paclitaxel-albumin nanoparticle during infusion, demonstration that the observed nanoparticles in the infusion suspension do not play a role from a PK perspective).

With regards to the qualitative and quantitative composition of the reference and the generic product, it is considered that the concentration of paclitaxel is the same and the concentration of the excipient albumin is similar. The possible impact of higher organic solvent content that was reported in one batch of Pazenir was also assessed. All important quality attributes (including dissociation kinetics) were shown to be similar between the Pazenir batch with a higher organic solvent content and Pazenir batches with normal organic solvent content and Abraxane batches. It is concluded that the qualitative composition of the Pazenir product compared to reference is the same and that the slight differences in quantitative composition are not expected to affect the biodistribution of paclitaxel (see also quality section).

Additional physicochemical characteristics were compared to support the biowaiver claim. Summarizing the results of the extensive set of *in vitro* experiments, slight differences exist in average paclitaxel:albumin ratio, nanoparticle size, nanoparticle size distribution and monomer/oligomer percentage of albumin between Pazenir and the reference product Abraxane. The relevance of these differences is discussed further below and PKWP input has been sought by the CHMP on the adequacy of the provided *in vitro* data and the biowaiver approach.

Dissociation kinetics

To prove rapid and complete dissociation of the nanoparticles, the *in vitro* dissociation behaviour was characterized in a variety of physiologically-relevant media using the specific dynamic light scattering (DLS) technique. The measurements conducted in human plasma are considered most predictive for the *in vivo* situation. Representativeness of this medium for the *in vivo* situation was sufficiently justified by the Applicant.

The average particle diameter and mass-percentage of the particles at different paclitaxel concentrations were compared in two EU-sourced Abraxane batches and one CH-sourced Abraxane batch (EU manufacture) three TEVA submission batches and two additionally produced batches with higher and lower albumin:paclitaxel ratios.

Demonstrating that the average particle diameter drops to the same average particle diameter of the blank human plasma (i.e. the same level as measured in blank plasma) may be accepted as confirmation that complete dissociation occurs. The investigated media can be accepted as representative for the in vivo situation in humans and the method seems sufficiently validated.

Statistical comparison (e.g. test versus reference, test versus test, test versus blank medium, reference versus blank medium and reference versus reference) was done for the parameter “time-point to reach plateau values” (i.e. complete dissociation), using the One-way Analysis of Variance (ANOVA). As also stated by the PKWP, variability within batch was higher than between batches, and variability in the determined parameters time to reach complete dissociation and the decay constant of the dissociation kinetics were overlapping. No statistical difference could be demonstrated between test and reference product for the selected parameters.

Overall, however, it is agreed that complete dissociation of the nanoparticles has been adequately shown in human plasma (and diluted human plasma) at a clinically relevant paclitaxel concentration. The Applicant adequately discussed the slight differences for the exact time-points, at which complete dissociation was achieved *in vitro*. Considering that nanoparticles are expected to dissociate even faster *in vivo* (bearing in mind the dilution effect upon (slow) intravenous infusion), no impact on the clinical aspects is to be expected.

Paclitaxel: albumin ratio

A further important consideration was the possible impact of the differing molar ratios between test and reference product.As also emphasised by the PKWP, drug binding characteristics and dissociation kinetic experiments indicated no apparent differences for the produced TEVA batches with high and low paclitaxel:albumin molar ratio compared to normal TEVA and Abraxane batches. This finding is in line with the *in vivo* PK data for the originator Abraxane, showing that the use of different paclitaxel: albumin molar ratios did not affect the exposure (in terms of dose-normalised AUCinf) of paclitaxel in patients (*EPAR Abraxane*). The differences in molar ratios are not expected to have any relevant clinical impact.

Monomer/oligomer status

A difference exists between reference and test product in the percentage of albumin monomers and oligomers of TEVA submission batches (i.e. freshly produced batches) compared to Abraxane reference batches (i.e. aged batches). The deviation from Abraxane oligomer status is slight.

Observed differences may be explained by differences in age of the batches at the time-point of testing and change of oligomer distribution over time (additional long term, intermediate and accelerated stability data have been presented). To support this statement, additional *in vitro* dissociation kinetics of the nanoparticles of one Teva submission batch , and one EU reference batch were conducted, both stored for 6 months under long-term and accelerated conditions, which showed the same trend of complete dissociation in human plasma, regardless of the differences in HSA monomer/oligomer content.

It is reassuring that batches under similar long term storage conditions are comparable in terms of monomer/oligomer status and dissociation kinetics. Furthermore, although recently produced Abraxane versus Teva batches were not compared, potential differences in oligomer status are not expected to have any clinically

relevant impact. In the worst case scenario, slight differences in paclitaxel uptake into tumour would be expected to be within the expected range of inter-individual variability of the patient population.

Free and bound paclitaxel fraction

The 'unencapsulated', protein unbound fraction of paclitaxel in plasma at various clinically relevant concentrations has not been compared for both products due to feasibility reasons (refer to the quality section). This point was also discussed by the PKWP, taking into consideration micellar formulations, for which this is considered an important factor for the demonstration of bioequivalence. The PKWP concluded that in the present case, considering that comparable dissociation kinetics have been demonstrated and, importantly, that the amount of HSA infused is low (<5% of serum albumin in blood) and that comparable binding affinity of paclitaxel-HSA has been shown for the TEVA and Abraxane products, it seems highly unlikely that the 'unencapsulated', protein unbound fraction of paclitaxel in plasma would be different at various clinically relevant concentrations.

PKWP responses to CHMP request for input regarding the possibility of a biowaiver for a generic Paclitaxel-Albumin nanoparticles

CHMP Question

1. Does the PKWP agree that the observed differences between the proposed generic formulation (Pazenir) and the reference product (Abraxane) in nanoparticle size, nanoparticle size distribution and molar ratio are not expected to impact on the PK as long as comparability of complete dissociation of the nanoparticles can be demonstrated?

PKWP answer:

Of note, the nanoparticle suspension of paclitaxel-albumin is considered by PKWP as a 'complex' parenteral. The PKWP also considers that a generic application with Abraxane as reference product is in principle possible because paclitaxel is the active substance, the concentration of paclitaxel is the same, concentration of the excipient albumin is similar and intravenous route of administration and dosing recommendations are the same for TEVA paclitaxel as for Abraxane.

Because of the rapid dissociation of the paclitaxel-albumin nanoparticles upon infusion, the situation shows resemblance to the situation of micellar parenteral drug products with rapid degradation of the micellar component. Hence, a bioequivalence study can be waived if all requisites as outlined in the Reflection (Reflection paper on the pharmaceutical development of intravenous medicinal products containing active substances solubilised in micellar systems, EMA/CHMP/QWP/799402/2011) are fulfilled.

The PKWP also considers that small differences in nanoparticle size, nanoparticle size distribution and molar ratio in the infusion solution can be accepted as long as comparability of complete dissociation of the nanoparticles in plasma can be demonstrated.

Argumentation:

The nanoparticle suspension of paclitaxel-albumin is considered a 'complex' parenteral, for which a bioequivalence study may need to be performed regardless of the intravenous route. The main objective of the paclitaxel nanoparticles is to overcome the poor solubility of paclitaxel in the infusion solution and not to control release or disposition in the bloodstream. During the marketing authorisation procedure of Abraxane, it was shown that the nanoparticles dissociate rapidly in the blood circulation into soluble individual albumin-paclitaxel complexes (Desai et al., 2008). The data presented by TEVA also show a rapid, complete dissociation of the nanoparticles when diluted in plasma.

As the nanoparticles dissociate very rapidly in the blood circulation into soluble individual albumin-paclitaxel complexes, the PKWP considers that the situation shows resemblance to the situation of micellar parenteral drug products with rapid degradation of the micellar component following intravenous infusion. (Reflection paper on the pharmaceutical development of intravenous medicinal products containing active substances solubilised in micellar systems EMA/CHMP/QWP/799402/2011).

Analogous to micellar parenteral drug products, a waiver of a bioequivalence study might be possible for a nanoparticle suspension of paclitaxel-albumin. The composition should be qualitative and quantitative very similar, the in vitro characteristics of the infusion suspension and the behaviour of the nanoparticles in blood/plasma following infusion should be sufficiently characterised by in vitro assays. This is in line with the CHMP's scientific advice in July 2015 (Procedure No: EMEA/H/SA/3120/1/2015/II).

Pazenir and Abraxane formulations have been characterised extensively by using different analytical methods: physico-chemical characterization and in vitro dissociation, protein characterization – structural integrity of HSA, and sameness and nature of bond between paclitaxel and HSA. It is understood that in general comparability has been sufficiently demonstrated but small differences in nanoparticle size, nanoparticle size distribution and molar ratio were observed.

Reason for waiving a bioequivalence study, is that the main function of the paclitaxel nanoparticles is to overcome the poor solubility of paclitaxel in the infusion solution and not to control release or disposition in the bloodstream. Hence, the critical step is the dissociation kinetics of the nanoparticles following infusion. Following dissociation, the paclitaxel molecules can still attach to the dissociated albumin or re-complex with abundantly available circulating albumin. The amount of albumin in the nanoparticles is only a few percent of the endogenous amount of albumin in blood, and therefore the added amount of albumin from the nanoparticle will not contribute significantly to the paclitaxel albumin binding in blood. Therefore, small differences in nanoparticle size, nanoparticle size distribution and molar ratio in the infusion solution can be accepted as long as comparability of dissociation of the nanoparticles can be demonstrated.

In this respect the additional data of two batches of Abraxane for the EU and CH market, and two TEVA batches with a high and low paclitaxel:albumin ratio submitted at 2nd D180 responses are important data to support the comparability between Pazenir and Abraxane. HSA binding and dissociation kinetic experiments confirmed that there was no apparent differences for the batches with high and low paclitaxel:albumin molar ratio compared to normal TEVA and Abraxane batches. This is in agreement with the in vivo PK data for Abraxane, which showed the use of different albumin: paclitaxel mass ratios did not affect the exposure of paclitaxel in patients. Data from 2 new Abraxane batches were provided: one batch from the EU market and one batch for CH market as no 2 different batches for EU market could be obtained by the applicant. The batch for CH market is manufactured within Europe. Overall, the data set of reference and test products seems now sufficient to draw a conclusion on comparability.

2. Is the provided data sufficient to conclude on "similar" dissociation kinetics of Pazenir and the reference product? If not, what additional comparative PK data would be needed?

PKWP answer:

The comparative dissociation kinetics should be conducted with a sufficient number of test and reference batches to evaluate if there is a similar variability in dissociation kinetics between test and reference products. Comparability should be supported by statistical analyses or the results of the test product should be within the variability observed for the reference product (analogous to comparability assessment of quality attributes of biosimilars).

This has been addressed in the response to the 2nd D180 LOQ: 2 additional batches of Abraxane one for EU market and one for CH market were submitted, providing information on inter- and intra-batch variability of the various dissociation parameters. Variability within batch was higher than between batches, and variability in the determined parameters time to reach to plateau values and the decay constant of the dissociation kinetics were overlapping. Statistical comparison between the batches (e.g. test versus reference, test versus test, test versus blank medium, reference versus blank medium and reference versus reference) was done using the One-way Analysis of Variance (ANOVA). No statistical difference could be demonstrated between test and reference product for the selected parameters. It is noted that the objective of the statistical analysis is to demonstrate that there is no statistical difference between the batches rather than demonstration of comparability. Conduct of statistical analysis for demonstration of comparability for quality attributes is an ongoing discussion (Draft reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development, EMA/CHMP/138502/2017), and the PKWP considers it is out of their scope to evaluate if appropriate statistical methodology has been applied to demonstrate comparable dissociation kinetics.

For micellar formulations, an important assay to waive a bioequivalence study is demonstration of comparable free fraction of the active substance in plasma at various clinical relevant concentrations to support comparable disposition in vivo. It seems from the D180 report that determination of the 'unencapsulated', protein unbound fraction of paclitaxel in plasma at various clinical relevant concentrations has not been compared for both products. On the other hand, comparable dissociation of the nanoparticles has been demonstrated at various paclitaxel concentrations in plasma. As it has been demonstrated that at clinical relevant concentrations the nanoparticles are fully dissociated, the amount of HSA infused is <5% of serum albumin in blood, and comparable binding affinity of paclitaxel-HSA has been shown for TEVA and Abraxane, PKWP considers it highly unlikely that the 'unencapsulated', protein unbound fraction of paclitaxel in plasma at various clinical relevant concentrations would be different.

In summary, PKWP considers the submitted data are sufficient to conclude that any observed differences between the proposed generic formulation (Pazenir) and the reference product (Abraxane) in nanoparticle size, nanoparticle size distribution and molar ratio are not expected to impact on PK and as such no additional comparative PK data are needed.

In conclusion, taking the below points into consideration,

- The main function of the paclitaxel nanoparticles is to overcome the poor solubility of paclitaxel in the infusion solution (and not to control release or disposition in the bloodstream).
- Similarly rapid complete dissociation of the nanoparticles was shown for two EU reference, one CH reference and three generic batches (as well as two batches with lower and upper paclitaxel: albumin ratios of 6:1 and 10.3:1).
- Protein characterisation, structural integrity of HSA and drug binding characteristics were shown to be similar between test and reference batches.
- Weak hydrophobic bonds are present between paclitaxel and HSA.
- Endogenous albumin is abundantly available *in vivo* and the added amount of albumin from the albumin-paclitaxel complexes is not expected to contribute significantly to the paclitaxel albumin binding in blood. It is therefore expected that paclitaxel is transferred to endogenous albumin *in vivo* in a similar way for the reference as well as the generic product.

it is concluded that the slight differences in nanoparticle size, nanoparticle size distribution and molar ratios as well as in HSA polymer content (as seen in the freshly produced TEVA batches as compared to older EU reference batches) between the proposed generic formulation and the reference product Abraxane are not expected to have an impact on the pharmacokinetics. Based on the same argumentation, no differences in free paclitaxel between the products are expected *in vivo*.

Overall, it is concluded that the prerequisites for the biowaiver approach have been met.

Safety aspects

In terms of safety aspects, a concern was raised on potential risk of medication errors associated with the initially proposed product name due to the existence of generics of other formulation of paclitaxel. The name of the product has been changed and the SmPC section 4.4 reflects that Pazenir is an albumin-bound nanoparticle formulation of paclitaxel, which may have substantially different pharmacological properties compared to other formulations of paclitaxel and that it should not be substituted for or administered with other paclitaxel formulations. This was considered adequate to minimise this risk of medication errors.

2.4.6. Conclusions on clinical aspects

The Pazenir nanoparticle dispersion is considered a complex parenteral. A generic application with Abraxane as the reference product is in principle acceptable, as paclitaxel is the active substance, the concentration of Paclitaxel is the same, the concentration of the excipient albumin is similar and intravenous route of administration and dosing recommendations are the same for TEVA paclitaxel and Abraxane.

The biowaiver approach is considered acceptable. Based on the provided *in vitro* comparability data the bioequivalence between the proposed Pazenir formulation and the reference product Abraxane at the clinical level can be concluded.

2.5. Risk management plan

Safety Specification

There are no important identified or potential risks or missing information.

The applicant aligned the safety specification with the latest approved safety specification of the reference product.

The CHMP considers that the safety specification in line with the reference product is appropriate.

Pharmacovigilance plan

Routine pharmacovigilance activities are considered sufficient to monitor the benefit-risk profile of the product and detect any safety concerns. This is in line with the reference product.

The PRAC, having considered the data submitted, is of the opinion that routine pharmacovigilance plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Routine risk minimisation measures are considered sufficient for all safety concerns of the product.

Conclusion

The RMP version 1.2 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

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

This application concerns a generic version of paclitaxel formulated as albumin-bound paclitaxel and presented as a powder for dispersion for infusion. The reference product is Abraxane 5 mg/ml powder for suspension for infusion. The applied indications are in monotherapy for the treatment of metastatic breast cancer and in combination with carboplatin for the first-line treatment of non-small cell lung cancer (see SmPC section 4.1).

The applicant provided an adequate summary of the available nonclinical literature. In addition, nonclinical studies have been provided for this application and are considered acceptable. Although the findings of different paclitaxel exposures in the tumour between the Abraxane and Pazenir groups in the mouse study were inconclusive, the distribution of paclitaxel to healthy tissue (heart and liver) appeared more robust and supportive for the clinical conclusion of a biowaiver.

The applicant did not submit clinical studies (pharmacokinetics and pharmacodynamics as well as the efficacy and safety studies). The applicant provided a clinical overview with clinical information from published literature and this was considered adequate. Furthermore, exemption from the need to conduct a bioequivalence study was considered adequately substantiated.

Based on the quality, non-clinical and clinical data submitted, the benefit/risk balance of Pazenir is considered positive.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

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

- Pazenir monotherapy is indicated for the treatment of metastatic breast cancer in adult patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline containing therapy is not indicated.

- Pazenir in combination with carboplatin is indicated for the first-line treatment of non-small cell lung cancer in adult patients who are not candidates for potentially curative surgery and/or radiation therapy.

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 restricted 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.