9 November 2023
EMA/535209/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Naveruclif

International non-proprietary name: paclitaxel

Procedure No. EMEA/H/C/006173/0000

Note

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

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List of abbreviations

AAS	Atomic Absorption Spectrometry
ANDA	Abbreviated New Drug Application (ANDA) is an application for a U.S. generic drug approval
AP	Applicant's Part (or Open Part) of a ASMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
CD	Circular Dichroism
CEP	Certificate of Suitability of the EP
CFU	Colony Forming Units
CMS	Concerned Member State
CoA	Certificate of Analysis
CRS	Chemical Reference Substance (official standard)
DLS	Dynamic Light Scattering
DoE	Design of experiments
DP	Decentralised (Application) Procedure
DPM	Drug Product Manufacturer
DSC	Differential Scanning Calorimetry
EDQM	European Directorate for the Quality of Medicines
EP	European Pharmacopoeia
FCR	Functional Related Characteristics
FPM	Finished Product Manufacturer
GC	Gas Chromatography
HCT	Hydrochlorothiazide
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
HSA	Human Serum Albumin
HT	Holding time
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
IR	Infrared
IU	International Units
KF	Karl Fischer titration
LDPE	Low Density Polyethylene
LOA	Letter of Access
LOD	Limit of Detection
LOQ	Limit of Quantitation
LoQ	List of Questions
LT	Less than
MA	Marketing Authorisation

MAH	Marketing Authorisation holder
MEB	Medicines Evaluation Board
MS	Mass Spectrometry
ND	Not detected
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
OOS	Out of Specifications
PDE	Permitted Daily Exposure
PE	Polyethylene
Ph.Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
PMF	Plasma Master File
PP	Polypropylene
PSD	Particle Size Distribution
PVC	Polyvinyl chloride
QOS	Quality Overall Summary
RH	Relative Humidity
RMS	Reference Member State
RP	Restricted Part (or Closed Part) of an ASMF
RRT	Relative retention time
RSD	Relative standard deviation
SOR	Specific Optical Rotation
SPC	Summary of Product Characteristics
TGA	Thermo-Gravimetric Analysis
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
XR(P)D	X-Ray (Powder) Diffraction
XRD	X-Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare S.L.U. submitted on 9 January 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Naveruclif, 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 15 September 2022.

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 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:

Naveruclif 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 (see section 4.4).

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

Naveruclif 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.

1.2. Legal basis, dossier content

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 literature based clinical and non-clinical overviews.

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: Bristol-Myers Squibb Pharma EEIG
- Date of authorisation: 14 January 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 dispersion for infusion
- Marketing authorisation holder: Bristol-Myers Squibb Pharma EEIG
- Date of authorisation: 14 January 2008
- Marketing authorisation granted by:
  - Union

Marketing authorisation number:

EU/1/07/428/001

EU/1/07/428/002

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. 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.

1.5. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Frantisek Drafi

The application was received by the EMA on	9 January 2023
The procedure started on	26 January 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 April 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	2 May 2023

The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 May 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	13 July 2023
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	21 August 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	31 August 2023
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	14 September 2023
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	10 October 2023
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	25 October 2023
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 Naveruclif on	9 November 2023
The CHMP adopted a report on similarity of Naveruclif with Onivyde pegylated liposomal, Lutathera, and SomaKit TOC on (Appendix on similarity)	9 November 2023

2. Scientific discussion

2.1. Introduction

This application for a marketing authorisation submitted via centralised procedure concerns a generic application according to article 10(1) of Directive 2001/83/EC for Naveruclif (paclitaxel) from Accord Healthcare S.L., Spain.

The reference medicinal product is Abraxane 5 mg/ml powder for dispersion for infusion (MAA No: EU/1/07/428/001-002, MAH: Bristol-Myers Squibb Pharma EEIG, Ireland) for which marketing authorisation was granted in the European Union on 14 January 2008 on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

Abraxane is a nanoparticle albumin-bound paclitaxel (also referred as nab-paclitaxel). 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). 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 applicant did not submit any bioequivalence study. Since paclitaxel albumin is recommended to be used after reconstitution with sodium chloride via intravenous route of administration, applicant has requested a biowaiver based on principles of ”Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **)”. The applicant justified the 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.

Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganisation of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or bundles of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis. Paclitaxel prevented cells from dividing by promoting the assembly of microtubules without inhibiting their disassembly.

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 generic has applied for all the indications of the reference product:

- Naveruclif 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 (see section 4.4).
- Naveruclif in combination with gemcitabine is indicated for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas.
- Naveruclif 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.

Relevant for the assessment is the Guideline on the Investigation of Bioequivalence, CPMP/EWP/QWP/ 1401/98 Rev. 1/ Corr **. Furthermore, the Reflection paper on the pharmaceutical development of intravenous medicinal products containing active substances solubilised in micellar systems

(EMA/CHMP/QWP/799402/2011) and the Reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development (EMA/CHMP/138502/2017) were considered as relevant too.

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.

Other ingredients are: Albumin (human) (containing sodium caprylate and N-acetyl-L-tryptophan).

The product is available in a glass vial with a bromobutyl rubber stopper and aluminium overseal as described in section 6.5 of the SmPC.

2.2.2. Active substance

2.2.2.1. General Information

The chemical name of paclitaxel is (2α,4α,5β,7β,10β,13α)-4,10-bis(acetyloxy)-13-{[(2*R*,3*S*)- 3-(benzoylamino)-2-hydroxy-3-phenylpropanoyl]oxy}-1,7-dihydroxy9-oxo-5,20-epoxytax-11-en-2-yl benzoate corresponding to the molecular formula $C_{47}H_{51}NO_{14}$. It has a molecular mass of 853.91 g/mol and the following structure:

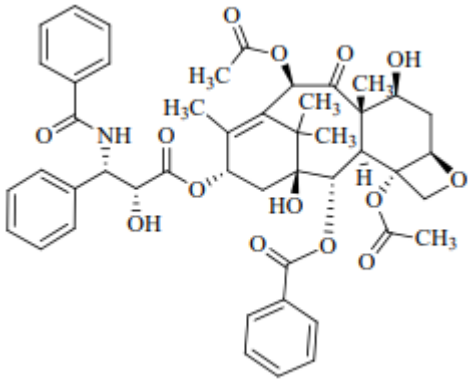

Figure 1: active substance structure

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.

The active substance is a white or almost white, crystalline powder. It is practically insoluble in water but freely soluble in methylene chloride. Paclitaxel exhibits stereoisomerism due to the presence of 11 chiral centres. Polymorphism has not been observed for paclitaxel.

2.2.2.2. Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

2.2.2.3. Specification(s)

The active substance specification includes tests for: description, solubility (Ph. Eur.), identification (IR, HPLC, SOR), water content (Ph. Eur.), appearance of solution (Ph. Eur.), assay (HPLC), related substances (HPLC), residual solvents (GC), bacterial endotoxins (Ph. Eur.), and microbiological quality (Ph. Eur.).

The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph. Additional specifications have been set for residual solvents in line with the CEP requirements and for bacterial endotoxins and microbiological quality in line with the intended use in a sterile product. The method for residual solvents is the same as assessed by the EDQM in granting the CEP. The tests for microbiological quality and bacterial endotoxins are conducted in line with the Ph. Eur. and suitably verified for the intended use. The analytical methods used have been adequately described and satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data of two commercial scale batches of the active substance as analysed by the proposed finished product manufacturer are provided. In addition to this batch analysis data, as analysed by the active substance manufacturer are provided. The results are within the specifications and consistent from batch to batch.

2.2.2.4. Stability

No re-test period is defined on the CEP granted by the EDQM. The applicant has presented stability data for the active substance in order to claim a re-test period. Stability data from three commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial container closure system for up to sixty months under long term conditions (25°C / 60% RH) and for up to six months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested*:* appearance, water content (Ph. Eur.), appearance of solution (Ph. Eur.), assay (HPLC), related substances (HPLC), and microbiological quality (Ph. Eur.). The analytical methods used were the same as for release and were stability indicating. All tested parameters were within the specifications without any notable trends.

Photostability testing following the ICH guideline Q1B was performed on one batch and the active substance is sensitive to light. The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable, at long-term and accelerated conditions all results remained within specification and no trends were observed. The stability results justify the proposed retest period and the applicant’s selected storage condition.

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and Pharmaceutical development

The finished product is a powder for dispersion for infusion, containing 5 mg/ml paclitaxel bound to albumin as nanoparticles. Each glass vial contains 100 mg of paclitaxel as a white-yellow lyophilised cake. When reconstituted with sodium chloride solution it gives a white-milky white suspension.

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. The proposed product has the same active substance, dosage form, strength, and route of administration as the reference product.

The active substance is dissolved during the manufacture of the finished product, therefore the physical attributes of the active substance from the supplier are not critical in this context. Paclitaxel possess poor aqueous solubility and enhanced solubility is achieved through the use of excipients. The proposed formulation makes use of human serum albumin (HSA) to enhance the solubility. Amorphous nanoparticles of HSA bound with paclitaxel are manufactured, which improve dissolution characteristics and allow for the administration via infusion once the product has been suitably diluted with a sterile sodium chloride solution. This is in line with the reference product. 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.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. HSA is appropriately supported by a plasma master file. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The applicant has applied for a biowaiver for the proposed product, this is based on qualitative and quantitative comparability with the reference product, along with comparative analysis performed. Compositional comparability between the test and reference product was conducted and the products are compositionally similar in terms of the active substance and excipients.

In order to demonstrate essential similarity to the reference product, numerous different characterisation studies were carried out using different analytical methods to compare the proposed and reference formulations. This comparative analysis included analysis of the following parameters: drug association and free paclitaxel (HPLC/UV), mean particle size and PSD in simulated plasma and human plasma (DLS), particle surface charge in plasma (zeta potential), solid state analysis of paclitaxel (XRPD), oligomeric status in simulated and human plasma (SEC), albumin structural integrity (CD), bond analysis between albumin and paclitaxel (fluorescent spectroscopy). The comparative analysis of quality attributes compared three batches of the proposed product to three batches of the test product.

The applicant also conducted *in-vitro* release studies. Initially the *in-vitro* release studies available had not been performed in conditions considered to be suitably representative of *in-vivo* conditions. As this was critical to the biowaiver request, a major objection (MO) was raised and the applicant was requested to conduct *in-vitro* comparisons in human plasma or blood. In response, the applicant provided comparative release testing of the test and reference product in human plasma, it was accepted that the results demonstrated sufficiently similar characteristics and dissociation behaviour. The statistical analysis performed via one way analysis of variance (ANOVA) supported that the test and reference products exhibit comparable

behaviour and dissociate immediately in representative media. The biowaiver was accepted, refer also to the clinical section.

The manufacturing process development was critical in order to produce a product of essential similarity to the reference product. The chosen process is based on solubilisation of paclitaxel in solvents, and the separate solubilisation of albumin in water.

In order to optimise the process, various parameters were investigated including the concentrations of the relative solvents, mixing rates and times, pressure and temperature. The description of the manufacturing process development is suitably detailed. Overages of the active substance, excipients, and processing aids are included to compensate for losses during the manufacturing process. The overages are considered suitably justified and are reasonable in line with a manufacturing process of this type. Compatibility studies were conducted with the manufacturing equipment and process components.

The primary packaging is a glass vial with a bromobutyl rubber stopper. The material complies with Ph. Eur. requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.2.3.2. Manufacture of the product and process controls

The manufacturing process is considered to be non-standard and consists of eleven main steps: preparation of the aqueous phase with the excipients, preparation of the paclitaxel solution in organic solvents, preparation of the paclitaxel albumin mixture by combination of the two solutions, high pressure homogenisation, solvent evaporation, diafiltration, pre-filtration, sterilising filtration, filling, lyophilisation, and vial sealing. Critical equipment for the manufacturing process is defined and outlined in the dossier. Manufacturing times, process parameters and temperatures for the manufacturing steps are also described. With respect to sterile filtration, the integrity of the filter is tested both pre and post filtration and appropriate in-process controls have been set.

Major steps of the manufacturing process have been validated by the production of three commercial scale batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls such as mixing speeds, pH, conductivity measurements, temperature, appearance, particle size, homogenization pressure, vacuum applied, assay, transmembrane pressure, filter integrity and filling speed are adequate for this type of manufacturing process. The initially provided media fill results to support the proposed sterile filtration were not in line with the conditions to be applied to the product. Hence an MO was raised requesting the suitability of the media simulations to be justified. In the response the applicant submitted updated information and data outlining that media fill results are available from a worst case simulation and the MO was resolved.

2.2.3.3. Product specification(s)

The finished product release specifications include appropriate tests for this kind of dosage form including, description, identification (HPLC, IR), water content (KF), uniformity of dosage units by content uniformity (Ph. Eur.), reconstitution time (in-house), appearance of suspension (in-house), extractable volume (Ph. Eur.), pH (Ph. Eur.), assay (HPLC), related substances (HPLC), albumin content (HPLC), drug association & free drug content (HPLC), osmolarity (Ph. Eur.), caprylic acid (GC) and N-acetyl-DL-tryptophan (HPLC) content, particle size distribution & mean (laser light diffraction), zeta potential (in-house), bacterial endotoxins (Ph. Eur.),

sterility (Ph. Eur), sub-visible particles (Ph. Eur.), residual solvents (GC), polymorphic form (XRPD), oligomeric status (HPLC-SEC).

With respect to related substances, the limits for unspecified impurities are set in line with ICH Q3B requirements. Three specified impurities are included in the specifications and the limit set for an impurity exceeds the ICH Q3B qualification threshold (0.2%), however this impurity is considered suitably qualified at the proposed level based on the justification provided. The limits proposed for the residual solvents are in line with ICH Q3C requirements.

A number of characterisation parameters are included in the specifications. These are derived from the comparative analysis of the test and reference product discussed in the pharmaceutical development section and also take into account the batch analysis results of the test product. Initially the applicant proposed a number of wide ranges for some of these specification parameters, and these did not reflect the test product analysis or the comparative analysis exercise performed. As these aspects could reasonably impact product performance and the comparative link to the reference product a MO was raised regarding the ranges proposed. The applicant was requested to justify the limits for the parameters of drug association, free drug content, particle size distribution, zeta potential and oligomeric status. In particular the potential safety impact of wide limits for oligomeric status was highlighted as aggregates could lead to an immune response. This MO was resolved by the tightening of the relevant ranges and limits during the response in line with the request.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

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.

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

2.2.3.4. Stability of the product

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

Samples were tested for the same parameters discussed in the specification section. The analytical procedures used are stability indicating. All tested parameters of the product remained within the acceptance criteria throughout the duration of the studies. No significant trends were observed in the stability results under any of the storage conditions, at long term and accelerated conditions albumin levels tended to decrease slightly during shelf life but remained within specification. The levels of related substances also increased during stability but remained within specification.

With respect to ongoing stability studies, in accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

In addition, one batch was exposed to light as defined in ICH Q1B Guideline on Photostability Testing of New Drug Substances and Products. The finished product is unstable on exposure to light and significant degradation was evident.

In-use stability was performed on two commercial scale batches after reconstitution with 20 mL of 0.9 % sodium chloride as described in the product information. Stability data of the reconstituted suspension in the glass vials, PVC and non-PVC infusion bags (at 2 – 8°C for 24 hours, protected from light) followed by storage in PVC and non-PVC infusion bags (below 25°C for 4 hours unprotected from light) have been provided. Considering the results, chemical and physical in-use stability has been demonstrated for 24 hours at 2°C-8°C protected from light followed by 4 hours at 25°C unprotected from light, in glass vials as well as in infusion bags.

Based on available stability data, the proposed shelf-life of 24 months and store in the original package in order to protect from light as stated in the SmPC (section 6.3) are acceptable.

2.2.3.5. 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

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

During the procedure three MOs related to Quality were raised, these pertained to: i) the availability of data concerning *in-vitro* drug release testing at conditions sufficiently representative of the *in-vivo* environment; ii) the representativeness of the initially provided media fill study to support the aseptic process, and iii) the initial limits and ranges of some specification parameters proposed for control of the finished product. These issues were addressed by the provision of further information.

Updated characterisation data in human plasma was provided to address the *in-vitro* testing objection, on media fills it was clarified that the available media fill results do represent worst case conditions, and the relevant limits in the finished product specifications were suitably amended and tightened where relevant.

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. Data has been presented as part of the PMF to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of albumin-bound paclitaxel are well known. As albumin-bound paclitaxel is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Non-clinical overview based on literature review is, thus, appropriate.

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 has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

The Fpen of 0.001% was used to calculate the PECsw.

Table 1. Summary of main study results

Substance (INN/Invented Name): paclitaxel			
CAS-number (if available): 33069-62-4			
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.001%	µg/L	> 0.01 threshold (N)

2.3.3. Discussion on non-clinical aspects

The non-clinical overview based on literature review is appropriate. The non-clinical section of the SmPC is acceptable.

The applicant did not present additional non-clinical data in the non-clinical overview (Module 2.4). As this application is based on the auspices of Article 10, the Applicant is not required to provide the results of preclinical tests and clinical trials as long as the generic medicinal product has the same qualitative and quantitative composition in terms of active substance and the same pharmaceutical form as the reference medicinal product.

In terms of ERA, data on the use of paclitaxel provided by the applicant indicated an overall decrease in use in the corresponding member states. Of note, this could be due to the COVID-19 pandemic years (2020, 2021 and 2022), which might have caused decrease in overall diagnosis and treatment of oncologic diseases. Nevertheless, the list of countries submitted by the applicant omits the following EU member states: CY, EE, LU, MT, and NL, as well as EEA member states such as IS and LI. The applicant considers that use data in these countries are not available in the data package taken from IQVIA/IMS health data, which is acceptable. All consumption data cover the period for the last 4 years (between 2020 to 2023).

The applicant also presented an ERA Phase I assessment, where the PECsw was determined based on the refined Fpen value based on consumption data. This approach is considered to be less relevant since market research data are generally not accepted for the refinement of Fpen as they take into account competitive products and therefore do not assume treatment of 100% of the patients in the relevant diseases. The Fpen of 0.001% was used to calculate the PECsw value for paclitaxel in Naveruclif because all other amended Fpen values derived from consumption data from those countries were lower than this value. The PECsw has been calculated to be 0.00234 µg/L which is below the action limit for further ERA studies. These data are considered supportive.

In conclusion, the data package submitted includes adequate justification for not providing a complete ERA and thus indicates that Naveruclif is likely to pose a minor risk to the environment when used as recommended as well as during storage and disposal.

2.3.4. Conclusion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of albumin-bound paclitaxel are well known. As albumin-bound paclitaxel is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Non-clinical overview based on literature review is, thus, appropriate.

2.4. Clinical aspects

2.4.1. Introduction

The medicinal product applied for, is a generic of the EU reference product, Abraxane 5 mg/mL powder for dispersion for infusion (MAH: Bristol-Myers Squibb Pharma EEIG, Ireland) as defined in Article 10(1) of Directive 2001/83/EC as amended, which is or has been authorized for not less than 10 years in the member state or in the community. The applicant's product Paclitaxel powder for dispersion for infusion, 5 mg/mL, 20

mL is of the same indication, strength and route of administration as that of the EU reference product, Abraxane 5 mg/mL powder for dispersion for infusion (MAH: Bristol-Myers Squibb Pharma EEIG, Ireland).

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.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

Exemption

The product the Applicant is applying for the grant of marketing authorization is the generic equivalent to Abraxane 5 mg/mL powder for dispersion for infusion having the same qualitative and quantitative composition in terms of active substance(s) and also is of the same pharmaceutical form as the comparator product. Indications, route of administration, dosage form and strength (100 mg) are the same as for Abraxane. The strength of 250 mg, additionally licensed for Abraxane, was not applied for in this MA procedure. The applicant is thus applying for a bio-waiver request only.

Composition comparison

The qualitative and quantitative compositions of the applicant's product against the reference product were provided.

In vitro drug release

The *in vitro* release of paclitaxel after reconstitution from the drug products (test and reference) were carried out. The applicant has submitted the drug release profiles for the test and reference products at 37 °C ± 0.5 °C as requested on day 120. The following three batches of test products were compared with the reference product batches for dissolution profiles.

Test product: Paclitaxel 5 mg/mL Powder for Dispersion for Infusion 100 mg/vial (Batch nos.: P2202121, P2202149, P2201847; Manufactured by Intas Pharmaceuticals Ltd.).

Reference product: Abraxane 5 mg/mL; (Batch nos.: 1L088C, 1H079E, 1H079D; MAH: Bristol Myers Squibb)

The release of paclitaxel was analysed by HPLC after periodic time intervals (1, 2, 4, 6, 10, 12 hrs.). Greater than 90% release was observed in 12 hours in both the test and the reference batches. The similarity factor for all three batches were found to be above 50. The methodological comparison to a complementary particular Ph.Eur. experimental dissolution method and analytical method validation of *in vitro* drug release were provided.

Table 2. Results of the drug release profiles

Test product				Reference product
Batch no.	P2202121	P2202149	P2201847	1L088C
Time (in hours)				
1	29	31	29	30
2	55	58	54	54
4	76	80	76	77
6	89	89	87	84
10	94	94	95	91
12	95	95	96	93
f2	78	73	79	

Comparative dissolution profiles test product Vs reference product (batch no. 1H079E)

Test product				Reference product
Batch no.	P2202121	P2202149	P2201847	1H079E
Time (in hours)				
1	29	31	29	33
2	55	58	54	58
4	76	80	76	78
6	89	89	87	88
10	94	94	95	93
12	95	95	96	95
f2	80	89	77	

Comparative dissolution profiles test product Vs reference product (batch no. 1H079D)

Test product				Reference product
Batch no.	P2202121	P2202149	P2201847	1H079D
Time (in hours)				
1	29	31	29	28
2	55	58	54	55
4	76	80	76	80
6	89	89	87	87
10	94	94	95	93
12	95	95	96	95
f2	83	83	83	

Dissolution profiles have been carried out on three batches of test products and compared against the reference product batches. The similarity factor for all three batches were found to be above 50.

The applicant has justified the suitability of USP Apparatus 3. The methodological comparison to a complementary particular Ph.Eur. experimental dissolution method was provided as well as the analytical method validation of *in vitro* drug release method in human plasma.

Nature of bonding

The interaction of paclitaxel with human serum albumin (HSA) were studied by employing fluorescent spectroscopy. This approach is based on the attenuation in intrinsic fluorescence (quenching) when paclitaxel binds to HAS. Such binding is considered mostly hydrophobic and reversible in nature. The results showed a comparable quenching of fluorescence between the test and the Reference product indicating that paclitaxel

in both formulations binds with HAS.

Paclitaxel-bound human serum albumin nanoparticles are expected to rapidly dissociate into soluble form upon intravenous administration. As expected, when diluted into 5% human serum albumin (simulated human plasma), nanoparticles of Abraxane or test product, rapidly disintegrated into individual albumin-paclitaxel complex as confirmed with Dynamic Light Scattering (DLS). The rapid onset of the disintegration in plasma/blood indicates that the nanoparticles exert limited impact on the *in vivo* disposition of paclitaxel. The rapid disintegration of Abraxane nanoparticles was also shown earlier in pig plasma and whole blood (Desai et al. Cancer Res (2008) 68 (9_Supplement): 5624).

Dissociation kinetics in human plasma and simulated plasma (5% HSA)

The applicant performed the *in vitro* dissociation study in human plasma and 5% HSA by measuring mean particle size using the dynamic light scattering technique mentioned in the literature. The summary of the dissociation study is part of the quality assessment. The applicant submitted the comparison of decay constant of the dissociation kinetics between the test and reference product with statistical analyses for the particular decay constant (K, 1/min) parameter and 95% CI using the One-way Analysis of Variance (ANOVA). No significant differences between reference medicinal product (Abraxane) and proposed generic product (Naveruclif) was observed.

2.4.1.1. Post marketing experience

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

2.4.2. Discussion on clinical aspects

The applicant submitted a marketing authorisation application for a generic version of paclitaxel formulated as albumin bound nanoparticles, powder for dispersion for infusion.

The submitted Clinical Overview is sufficient, as it contains a good review of published clinical safety and efficacy data.

Based on Appendix II of the current Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1), a bioequivalent study is not required if certain requirements are 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): test product should have the same excipients in very similar quantities as a reference medicinal product or a justification that any difference in quantity does not affect the pharmacokinetics of the active substance should be submitted. This issue is further discussed in the Reflection paper on the pharmaceutical development of intravenous medicinal products containing active substances solubilised in micellar systems (EMA/CHMP/QWP/799402/2011). The requirements (for Module 2/5) were fulfilled by means of statistical analysis of the dissociation kinetics.

The physicochemical data as well as the qualitative and quantitative analysis have demonstrated the sameness between the test and reference products. In particular, based on the similar *in vitro* release profile, it is very likely that the test product will have comparable *in vivo* performance to that of EU reference product, Abraxane. Further, all other physicochemical attributes such as description, pH, and osmolality were also comparable between the test and the reference product.

A comprehensive comparison of some of the essential physicochemical attributes, such as: 1. Composition comparison, 2. Related substances, 3. Percent drug association and free drug, 4. Particle size distribution, 5. Oligomeric status, 6. Polymeric identification, 7. In vitro drug release, 8. Residual solvents, 9. Nature of bond between paclitaxel and HSA was presented in the application. Furthermore, the comparative *in vitro* release study of the Test vs the Reference product is also provided in the quality section.

The comparability of physicochemical characterization of proposed and reference drug, to support biowaiver request were presented.

In addition, the *in vitro* dissociation kinetics study to compare mean particle diameter obtained at specified paclitaxel concentration of tested and reference product has been provided in human plasma and simulated plasma, since measurement conducted in plasma are most predictive for the *in vivo* behaviour. The dissociation kinetics, as a key parameter was satisfactory presented. The data indicate absence of any difference for in vitro dissolution at multiple time points between test product and reference product. The dissociation rate constant "kd" describes the stability of the complex, i.e. the fraction of complexes that decays per second. Therefore, the statistical comparison was performed for the particular decay constant (K, 1/min) parameter and 95% CI, using the One-way Analysis of Variance (ANOVA) by the applicant. The statistical analysis of the PSD parameters did not show significant differences in the mean values between reference medicinal product (Abraxane) and proposed generic product (Naveruclif).

In general, the applicant did demonstrate the equivalence between the test (Naveruclif) and the reference medicinal product (Abraxane). The submitted *in vitro* data are currently considered sufficiently justified from the pharmacokinetic point of view.

2.4.3. Conclusions on clinical aspects

The submitted statistical analysis of the PSD parameters did not show significant differences between the test (Naveruclif) and the reference medicinal product (Abraxane), and thus, the *in vitro* data supports the biowaiver request. Therefore, the proposed generic medicinal product Naveruclif is considered bioequivalent to Abraxane.

2.5. Risk Management Plan

2.5.1. Safety concerns

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.

2.5.2. 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.

2.5.3. Risk minimisation measures

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

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 2.2 is acceptable.

2.6. Pharmacovigilance

2.6.1. 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.

2.6.2. 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 Abraxane 5 mg/ml powder for dispersion for infusion and Levetiracetam Accord 50/500/750/1000 mg film-coated tablets. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of albumin-bound paclitaxel, 5 mg/ml powder for dispersion for infusion. The reference product Abraxane 5 mg/mL powder for dispersion for infusion is indicated:

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,

in combination with gemcitabine for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas,

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.

With regard to quality, the dossier is generally well presented and all processes regarding the finished

product appear to be well controlled. The physico-chemical comparability between reference and proposed drug product was demonstrated in 0.9% NaCl solution and in human plasma. The application for Paclitaxel powder for dispersion for infusion 5 mg/mL, 20 mL is considered approvable.

No non-clinical studies have been provided for this application but an adequate summary of the available non-clinical information for the active substance was presented and considered sufficient.

From a clinical perspective, this application does not contain any 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 is considered sufficient.

The bioequivalence study was not performed due to the *i.v*. formulation of the product.

The applicant demonstrated the bridge between the test (Naveruclif) and reference medicinal product (Abraxane) from the pharmacokinetic perspective.

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

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. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Naveruclif is not similar to Onivyde pegylated liposomal, Lutathera and SomaKit TOC within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix

Outcome

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

Naveruclif 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 (see section 4.4).

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

Naveruclif 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 marketing authorisation holder (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.