27 February 2025
EMA/97108/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Trabectedin Accord

International non-proprietary name: trabectedin

Procedure No. EMEA/H/C/006433/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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List of abbreviations

ADI – acceptable daily intake
Al / Alu – Aluminium
ALT – alanine aminotransferase
API – Active Pharmaceutical Ingredient
APS – aseptic process simulation
AR – Assessment Report
ASM – Active Substance Manufacturer
ASMF – Active Substance Master File
AST – aspartate aminotransferase
ASTM - American Society for Testing and Materials
AUC – area under the curve
DMF – Drug Master File = Active Substance Master File, ASMF
BCS – Biopharmaceutics Classification System
BE / BEQ – Bioequivalence
BET – bacterial endotoxin test
BSA – bovine serum albumin
BSE/TSE – Bovine Spongiform Encephalopathy / Transmissible Spongiform Encephalopathy
CAS – Chemical Abstracta Services
CCI – Container-closure integrity
CEP – Certificate of Suitability
CFR – Code of Federal Regulations
CFU – colony forming unit
CHMP - Committee for Human Medicine Products
CI – confidence interval
CIP – clean-in-place
C_{max} - maximum plasma Concentration
CMDh - Co-ordination Group for Mutual Recognition and Decentralised procedures - Human
CoA – Certificate of Analysis
COP – clean-out-of-place
CPP's - critical process parameters
CQA – Critical quality attribute
CRS – Chemical reference substances
CU – Content Uniformity
CV – Coefficient of variation
CV - Curriculum Vitae
DAD – diode-array detector
DNA – deoxyribonucleic acid
DPM – Drug Product Manufacturer
DSD – droplet-size distribution
EC – European Commission
ECG – electrocardiogram
EDQM – The European Directorate for the Quality of Medicines & HealthCare
EEA – European Economic Area
EI – Elemental Impurities
ELSD - evaporative light scattering detection
EMA / EMEA – European Medicines Agency
EPAR – European Public Assessment Report
ERA – Environmental Risk Assessment
ETFE - ethylenetetrafluoroethylene
EU - European Union
FCC – Food Chemical Codex
FDA – Food and Drug Administration
FPM – Finished Product Manufacturer
FRC - Functionality related characteristics
FTIR – Fourier-transform infrared spectroscopy
FTU – flip-tear-up
GC – Gas Chromatography
GC-MS - Gas chromatography–mass spectrometry
GCP - Good Clinical Practice
GLP - Good Laboratory Practice
GMP – Good Manufacturing Practice

HPLC – High Pressure Liquid Chromatography
HSM – High Shear Mixer
ICDD – International Centre for Diffraction Data
ICH – International Conference on Harmonisation
ICP-MS – Inductively coupled plasma mass spectrometry
INN – International Non-proprietary Name
IPC – In-Process Control
IR – Immediate-release (1), IR – Infrared spectroscopy (2)
IVR(A) – In Vitro Release (Assay)
JP – Japanese Pharmacopoeia
KF – Karl Fisher
LDPE – low density polyethylene
LOD – Loss of drying (1), Limit of Detection (2)
LOQ – Limit of Quantification
LoQ – List of Questions
LTL - Less-than-lifetime
MAA – Marketing Authorisation Application
MAH - Marketing Authorisation Holder
MDD – Maximum daily dose
MIA – Manufacturing / Importer Authorisation
MS – Mass spectroscopy
MVL - Multivesicular liposomes
N/A – not applicable
NaCl – sodium chloride
NLT – not less than
NMR – Nuclear magnetic resonance spectroscopy
NMT – not more than
OGD – Office of generic drugs
PBS – phosphate buffered saline
PDE – Permitted daily exposure
PE – polyethylene
PES – polyethersulfone
PGI / PGIs – potential genotoxic impurity(ies)
Ph. Eur. – European Pharmacopoeia
PK – pharmacokinetic
PI – Product Information
PLD – pegylated liposomal doxorubicin
PP – polypropylene
PPV – Packed Particle Volume
PSD – Particle Size Distribution
(e)PTFE – (expanded) polytetrafluoro-ethylene
PVC – polyvinyl chloride
PVDC – polyvinylidene chloride
QAR – Quality Assessment Report
QbD – Quality by Design
QC – Quality Control
QOS – Quality Overall Summary
QP – Qualified Person
q.s. – quantity sufficient
RH – Relative Humidity
RMP – reference medicinal product
RRF – Relative Response Factor
RRT – Relative Retention Time
RSD – Relative Standard Deviation
SAL – sterility assurance level
SD – standard deviation
SDS – sodium dodecyl sulfate
SGF – Simulated gastric fluid
SIP – sterilization-in-place (1), steam-in-place (2)
SLS – sodium lauryl sulphate
SmPC / SPC – Summary of Product Characteristics
SOP – steam-out-of-place
STS – soft tissue sarcoma
TAMC – Total Aerobic Microbial Count

TFF – tangential flow filtration
TLC – Thin Liquid Chromatography
TYMC – Total Combined Yeasts/Moulds Count
ULN – upper limit of normal
USP/NF – United States Pharmacopoeia/National formulary
UV – Ultraviolet
WFI – water for injections
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 10 January 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Trabectedin Accord, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 14 September 2023.

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 in the Union on the basis of a complete dossier in accordance with Article 8(3).

The applicant applied for the following indications:

-Trabectedin Accord is indicated for the treatment of adult patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients.

-Trabectedin Accord in combination with pegylated liposomal doxorubicin (PLD) is indicated for the treatment of patients with relapsed platinum-sensitive ovarian cancer.

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 to demonstrate comparative pharmacokinetics and similar anti-tumour effects with the reference medicinal product Yondelis.

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: Yondelis 0.25 mg & 1 mg Powder for concentrate for solution for infusion Marketing authorisation holder: Pharma Mar, S.A., Spain
- Date of authorisation: 17-09-2007
- Marketing authorisation granted by: European Union
- Marketing authorisation number: EU/1/07/417/001-002

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

- Product name, strength, pharmaceutical form: Yondelis 0.25 mg & 1 mg Powder for concentrate for solution for infusion
- Marketing authorisation holder: Pharma Mar, S.A., Spain
- Date of authorisation: 17-09-2007

- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/07/417/001-002

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: Margareta Bego

The application was received by the EMA on	10 January 2024
The procedure started on	1 February 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	22 April 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	25 April 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	30 May 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	17 July 2024
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	26 August 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	5 September 2024
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	19 September 2024

The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	11 November 2024
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	27 November 2024
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 Trabectedin Accord on	27 February 2025
The CHMP adopted a report on similarity of Trabectedin Accord with Zejula on (Appendix on similarity)	27 February 2025

2. Scientific discussion

2.1. Introduction

The centralised procedure application for Trabectedin Accord 0.25 mg & 1 mg powder for concentrate for solution for infusion is submitted in accordance with Article 10(1) of Directive 2001/83/EC as a generic application and does not contain any non-clinical or clinical data.

The reference medicinal product is centrally authorised Yondelis 0.25 mg & 1 mg Powder for concentrate for solution for infusion (EU/1/07/417/001-002, Marketing authorisation holder: Pharma Mar, S.A. - Spain on 17.09.2007).

Trabectedin Accord contains the active substance Trabectedin. Trabectedin is an anti-neoplastic agent which binds to the minor groove of deoxyribonucleic acid (DNA), bending the helix to the major groove. This binding to DNA triggers a cascade of events affecting several transcription factors, DNA binding proteins, and DNA repair pathways, resulting in perturbation of the cell cycle.

The applied indications for Trabectedin Accord are as follows (same indications as for the reference product Yondelis):

- the treatment of adult patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients.
- the treatment of patients with relapsed platinum-sensitive ovarian cancer (in combination with pegylated liposomal doxorubicin (PLD)).

For the treatment of soft tissue sarcoma, the recommended dose is 1.5 mg/m^2 body surface area, administered as an intravenous infusion over 24 hours with a three-week interval between cycles.

For the treatment of ovarian cancer trabectedin is administered every three weeks as a 3-hour infusion at a dose of 1.1 mg/m^2, immediately after PLD 30 mg/m^2. To minimize the risk of PLD infusion reactions, the initial dose is administered at a rate no greater than 1 mg/minute. If no infusion reaction is observed, subsequent PLD infusions may be administered over a 1-hour period (see also PLD Summary of Product Characteristics [SmPC] for specific administration advice).

Relevant for the assessment are the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1).

This marketing application (MAA) for Trabectedin Accord is based upon "essential similarity" to the reference medicinal product Yondelis in accordance with Article 10(1) of Directive 2001/83/EC (as amended by Directive 2004/27/EC). According to the dossier, Trabectedin accord has the same qualitative and quantitative composition and the same pharmaceutical form (Powder for concentrate for solution for infusion) as the reference product Yondelis.

No clinical data has been presented to characterise the pharmacodynamics and the pharmacokinetics of Trabectedin accord. Eligibility for biowaiver has been requested by the Applicant based on the known PD/PK profile of the reference product Yondelis.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a powder for concentrate for solution for infusion containing 0.25 mg and 1 mg of trabectedin as active substance.

Other ingredients are: sucrose, potassium dihydrogen phosphate, phosphoric acid, and potassium hydroxyde as listed in section 6.1 of the SmPC.

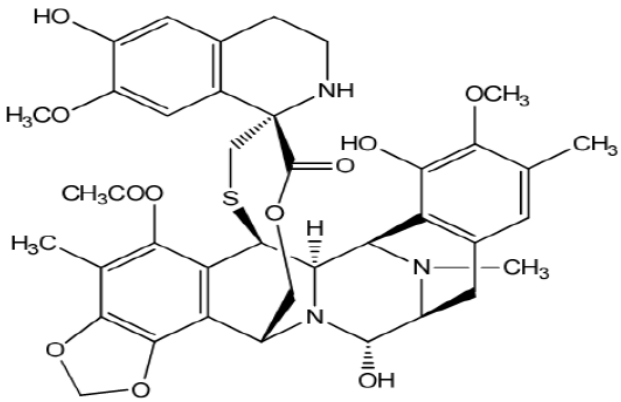
The product is available in type I glass vial with a bromobutyl rubber stopper with an aluminium flip-off seal with dark blue colour plastic disc as described in section 6.5 of the SmPC.

2.2.2. Active substance

2.2.2.1. General information

The chemical name of trabectedin is (1'R,6R,6aR,7R,13S,14S,16R)-5-(acetyloxy)-3',4',6,6a,7,13,14, 16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-spiro[6,16-(epithiopropanoxy methano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one corresponding to the molecular formula $C_{39}H_{43}N_3O_{11}S$. It has a relative molecular mass of 761.84 g/mol and the following structure:

Figure 1: active substance structure



The chemical structure of trabectedin was elucidated by a combination of the following methods: UV, FT-IR, ^{1}H NMR, ^{13}C NMR, DEPT, gCOSY, gHSQC, gHMBC, MS, thermal analysis (DSC and TGA) and

elemental analysis. The solid-state properties of the active substance were measured by XRD techniques.

Trabectedin is a white to off-white hygroscopic powder, soluble in 1.0% formic acidic and 0.1N HCl aqueous solution, insoluble in water. The solubility in aqueous solution is increased with acidic pH. The solubility of trabectedin was studied in several organic solvents where results range from slightly soluble in acetone, acetonitrile, and dichloromethane; to soluble in acetic acid, ethanol, methanol, N,N-dimethylformamide.

Trabectedin exhibits stereoisomerism due to the presence of seven chiral centres. Single crystal XRD technique has been used to confirm the crystal structure of trabectedin and its chirality. The enantiomeric purity is controlled routinely by specific optical rotation.

Polymorphism has been observed for trabectedin. XRPD studies were performed on validation batches. Since the active substance is completely dissolved during the manufacturing of the finished product, and given the finished product is administrated as a solution, specific physical properties of the active substance such as polymorphism and particle size are not considered relevant. Polymorphism is therefore not controlled on the active substance.

Trabectedin is not described in the European Pharmacopoeia.

2.2.2.2. Manufacture, characterisation and process controls

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

A QP declaration confirming the site's GMP compliance was provided. Trabectedin active substance used in the manufacture of the finished product is only supplied by this manufacturer and supported by an ASMF.

Trabectedin is synthesised in 8 main steps using three commercially available well defined starting materials with acceptable specifications.

The proposed route of synthesis is considered appropriate, and the manufacturing process description is provided in sufficient detail.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Adequate discussion on the origin and formation of absolute configuration of all seven chiral centres was provided.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

Information on the potential organic impurities present in trabectedin active substance have been adequately presented and adequate controls have been put in place. Organic impurities which are controlled on the active substance as specified impurities are process related impurities. Identified organic impurities have been listed with structures, names, origin as well as brief information on their control strategy and in general, the information presented on organic impurities in the active substance is considered satisfactory.

Discussion on the control and origin of inorganic reagents used in the manufacturing process of active substance has been provided along with the summary of the risk assessment concerning potential

presence of elemental impurities in the active substance. Based on risk assessment, no further control of elemental impurities is deemed required on the active substance.

Trabectedin is a genotoxic active substance both in vitro and in vivo while the indication of the finished product is for the treatment of adult patients with advanced forms of cancer. The evaluation of potential genotoxic impurities is therefore not applicable as per ICH M7 guideline.

Most solvents used in the manufacturing process are controlled in the active substance specification and are found in trabectedin active substance batches within the proposed limits. Benzene could be a possible contaminant in solvents used prior to the final step of the process. Since its absence in three active substance batches is demonstrated (below 30% of ICH limit), no further control of benzene in the active substance is needed.

2.2.2.3. Specification(s)

The active substance specification includes tests for description (Ph. Eur.); solubility (Ph. Eur.); identification (IR, HPLC), weight loss (TGA); specific optical rotation (In-House); related substance (HPLC); assay (HPLC); residual solvents (GC); bacterial endotoxin (Ph. Eur.); elemental impurities (ICP-MS).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The limit for weight loss is based on batch results and stability data provided. Limits set for residual solvents are in line with ICH Q3C.

Considering the set limits for total sum of specified cations, omission of the sulphated ash testing is acceptable.

The analytical methods used have been adequately described and non-compendial methods 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 data on three validation batches produced within the active substance manufacturing batch size range are provided. The results are within the specifications and consistent from batch to batch.

2.2.2.4. Stability

Stability data from three validation batches of trabectedin manufactured by the proposed manufacturer stored in the intended commercial package for up to 48 months under long term conditions (-20±5°C) and for one validation batch of trabectedin for up to 6 months under accelerated conditions (5±3°C) were provided in accordance with ICH guidelines.Photostability testing following the ICH guideline Q1B was performed. Results on stress conditions under elevated temperature, 75% RH, water hydrolysis, acid hydrolysis, base hydrolysis, and oxidation were also provided.

All tested parameters remained within the specifications at all time-points up to 48 months at long-term conditions and also up to 6 months in accelerated conditions.

The stability results justify the proposed retest period and storage conditions.

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and pharmaceutical development

The finished product is a white to off-white lyophilised powder for concentrate for solution for infusion containing 0.25 mg or 1 mg of the active substance trabectedin. The lyophilised powder must be reconstituted with either 5 mL (0.25 mg strength) or 20 mL (1 mg strength) of water for injection to obtain a solution with a concentration of 0.05 mg/mL in active substance and then be further diluted with an appropriate solution for infusion (0.9% sodium chloride or 5% glucose) prior to administration.

The finished product was developed as a generic equivalent to the reference medicinal product Yondelis. Consequently, the formulation development of the finished product is based on the composition of the reference product Yondelis 0.25 mg and 1 mg Powder for Concentrate for Solution for Infusion. The active substance, excipients, dosage form, strengths and route of administration are the same as that of the reference medicinal product.

All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards. 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 formulation used during clinical studies is the same as that intended for marketing. The initial development trials began with a strength 1 mg, using a bulk solution of the product with a Trabectedin concentration of 0.25 mg/ml. Based on the conducted trials, the order of addition of raw materials and the lyophilisation cycle have been established.

The pharmaceutical development of the finished product contains Quality by Design (QbD) elements.

The formulation and manufacturing development have been evaluated through the use of risk assessment and design of experiment. An initial risk assessment was performed to understand the impact of material attributes, unit operations, process parameters and packing components on the finished product's CQAs. A design of experiment (DoE) was conducted in order to investigate the critical process parameters, and the compatibility with contact materials (stainless steel, tubings and filters) used during the manufacturing process. An overview of the manufacturing development and optimisation of the manufacturing process was provided to reduce the risks identified, and the manufacturing process was optimized with trabectedin 1 mg Powder for Concentrate for Solution for Infusion regarding the fill volume and lyophilization cycle.

Adequate justification for the selection of the sterilisation method was provided in accordance with the decision tree for sterilisation choices for dry powder products from the Guideline on sterilisation of medicinal products, active substances, excipients, and primary containers.
Comparative impurity profiles of one batch of the reference medicinal product Yondelis and three batches of the finished product for both strengths are provided. The level of impurities is similar between the reference and the finished product.

No bioequivalence study was required since the generic finished product qualifies for a bio waiver. During the procedure, a Major Objection was raised on an overfill that was applied prior to lyophilisation on vials target fill volumes to achieve withdrawal volume. As supporting data for the justification of the overfill, assay results on three different fill volumes after reconstitution and withdrawing the whole vial content were compared to the theoretical assay. A difference in assay was observed. With the applied overfill, a more concentrated solution after reconstitution than declared in the SmPC was obtained on one hand; and on the other hand, considering the assay determination on the whole vial content, higher assay results were obtained which led to assay release/shelf-life specification outside the 95-105% range. As a result, the applied overfill was considered an overage.

In line with ICH Q8(R2) guideline, any overage in the manufacture of the finished product should be justified considering the safety and efficacy of the product. Based on the provided data, it could not be concluded that the overfill/overage was necessary. Consequently, the proposed upper limits for the assay at release and shelf-life specifications were not justified. The Applicant was therefore requested to omit the overfill. In response, the overfill was omitted and the Major Objection was resolved.

The primary packaging is Type I glass vial with a bromobutyl rubber stopper covered with an aluminium flip-off seal. Basic information about container closure system for the medicinal product is provided. The rubber stoppers comply with the requirements outlined in the Ph. Eur. monograph 3.2.9, and the glass vials comply with the requirements outlined in the Ph. Eur. monograph 3.2.1. 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 finished product is released at Accord Healthcare Polska Sp.z.o.o., Poland; Pharmadox Healthcare Ltd., Malta; or Accord Healthcare Single Member S.A., Greece, for which evidence of GMP compliance was provided.

The manufacturing process consists of three main steps: compounding, filling, and packing.

The compounding step consists of the preparation of the bulk solution and includes the following steps: dispensing, WFI collection, addition of the excipients, pH adjustment, addition of the active substance, final volume adjustment, and primary sterilising filtration.

The filling operations start with a secondary sterilising filtration of the bulk solution, then the sterile and depyrogenated vials are filled aseptically to the target fill volumes and half-stoppered in view of lyophilisation.

After lyophilisation, the vials are sealed and packed.

The process is considered to be a non-standard manufacturing process since it includes aseptic processing and lyophilisation steps.

The in-process controls are adequate for this type of manufacturing process and pharmaceutical form

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The aseptic and sterilisation processes were adequately validated.

2.2.3.3. Product specification(s)

The finished product specifications include appropriate tests for this type of dosage form: appearance before and after reconstitution; identification (HPLC, UV); pH on reconstituted solution (Ph. Eur.); Reconstitution time; **water determination (Ph. Eur.)**; **assay (HPLC)**; organic impurities (HPLC); uniformity of dosage units (Ph. Eur.); **extractible volume (Ph. Eur.)**; sterility (Ph. Eur.); color absorbance at 420 nm (UV); transmittance at 650 nm (Ph. Eur.); clarity and particulate matter of the constituted solution; bacterial endotoxins (Ph. Eur.); foreign and particulate matter (Ph. Eur.). The specification parameters for which acceptance criteria differ between the 0.25 mg and 1 mg strengths are highlighted in bold.

During the procedure, a Major Objection was raised in relation to the applied overfill that led to assay limits proposed outside of the 95.0% - 105% range. As the applied overfill/overage was not considered justified, the Applicant was requested to omit the overfill and tighten the limits of the assay according

to the range 95.0–105.0% of EU Directive 2001/83/EC. The Applicant tightened the assay limits, and the Major Objection was resolved.

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. 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. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls. 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. Batch analysis results are provided for 3 commercial batches of the finished product for each strength, manufactured using 3 different batches of the active substance, hence 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 validation batches of each dosage strength of the finished product stored for up to 18 months for the 0.25 mg strength and 36 months for the 1 mg strength under long-term conditions 5°C ± 2°C; and stored for up to 6 months for both strengths under accelerated conditions 25°C ± 2°C / 60 % ± 5 % 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. Under long-term and accelerated conditions, stability data were provided for upright and inverted position of the vials.

Samples were tested for appearance, identification, pH, reconstitution time, water determination, assay, organic impurities, extractible volume, sterility, color absorbance at 420 nm, transmittance at 650 nm, constituted solution, bacterial endotoxins, and foreign and particulate matter. The analytical procedures used are stability indicating.

All tested parameters on all batches remained within the specification During the procedure, a Major Objection was raised on the stability of the finished product. The Applicant proposed to extrapolate the shelf-life of the 0.25 mg strength based on early available long-term stability data. However, in line with ICH Q1E, given the OOS results under accelerated conditions, no extrapolation of the shelf-life can be accepted. The Applicant was requested to justify the shelf-life solely based on real-time stability data. The applicant submitted a new justification based on real-time stability data, thus solving the Major Objection.

In addition, one batch of the 1 mg strength of the finished product was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results indicated that the finished product is photostable.

Based on available stability data, the proposed shelf-life of 24 months for the 1 mg strength, and 18 months for the 0.25 mg strength, when the unopened vials of the finished products are stored in a refrigerator (2ºC-8ºC) as stated in the SmPC section 6.3 are acceptable.

2.2.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

During the procedure, three Major Objections were raised on pharmaceutical development, and on the control and stability of the finished product. The Major Objections pertained to an applied overfill/overage that was not appropriately justified (1) leading to assay limits on the finished product outside the 95% - 105% range (2), and a non-acceptable extrapolation of shelf-life (3). Further details on the Major Objections raised can be found in relevant sections of this assessment report. As the Applicant did not adequately address the Major Objections on the overfill (1) and assay limits (2) after D180, a second List of Outstanding Issue was adopted by the CHMP and the CHMP Opinion was delayed. The Major Objections were ultimately resolved after the Applicant provided satisfactory responses to the second List of Outstanding Issue. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. 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. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of trabectedin are well known. As trabectedin is a widely used, well-known active substance, the applicant has not provided additional studies,

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on scientific literature. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed.

2.3.2. Ecotoxicity/environmental risk assessment

The Applicant submitted a justification that marketing authorization of the proposed product will not lead to any increased environmental risk since it is a generic. The justification was updated with consumption data for trabectedin in Europe. Submitted data show that consumption of the trabectedin increased through last 4 years. The Applicant was asked to perform Phase I environmental risk assessment for trabectedin in accordance with the respective EMA guideline. The Applicant refined Fpen based on published epidemiological data and the treatment regimen for each of the two indications. The total $PEC_{SURFACE\ WATER}$ is below the action limit for Phase II assessment. The study report confirms that the log KOW value of trabectedin is below the action limit for further PBT assessment.

Summary of main study results

Substance (INN/Invented Name): trabectedin			
CAS-number (if available): 114899-77-3			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log P_{ow}	OECD107	2.41	Potential PBT: N
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (prevalence)	Default: Refined:	0.013 μg/L 0.00001 μg/L	> 0.01 threshold N

2.3.3. Discussion on non-clinical aspects

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology which is based on up-to-date and relevant scientific literature is adequate.

As this is a generic application and trabectedin is a well-known substance, the applicant has not provided additional studies and further studies are not required. The non-clinical overview based on scientific literature review is therefore appropriate. Pharmacological and toxicological properties of trabectedin are well-documented in the non-clinical overview through 32 references up to year 2023. An assessment of impurities present in the drug substance and drug product was provided based on which it is concluded that there are no impurities of mutagenic nor genotoxic potential.

ERA

The predicted environmental concentration of trabectedin in surface water has been calculated with refined Fpen values for each indication, resulting in a total $PEC_{SURFACE\ WATER}$ value of 0.00001094 µg/L, which is below the action limit for Phase II assessment.

2.3.4. Conclusion on the non-clinical aspects

Non-clinical sections of the proposed SmPC are in line with the currently approved version of the reference product Yondelis. There are no objections to approval of Trabectedin Accord from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

The medicinal product applied for, is a generic of the EU reference product, Yondelis 0.25 mg & 1 mg powder for concentrate for solution for infusion. Trabectedin accord, 0.25 mg & 1 mg powder for concentrate for solution for infusion, is of the same indication, strength and route of administration as that of the EU reference product.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of trabectedin based on published literature.

The SmPC is in line with the SmPC of the reference product.

Exemption

The medicinal product applied for is a generic version of the EU reference product supplied as a powder for concentrate for solution for infusion.

The applicant claims essential similarity of the proposed product with Yondelis based on the following:

- The qualitative and quantitative composition of Trabectedin Accord in terms of active substance is identical to the reference product Yondelis.
- Both products are to be administered as an aqueous intravenous solution, i.e. the pharmaceutical form is the same (powder for concentrate for solution for infusion).

Both products have a similar analytical profile in terms of appearance, pH, assay, reconstitution time, water content and organic impurities.

2.4.2. Discussion on clinical aspects

The clinical overview on the clinical pharmacology, efficacy and safety based on literature is adequate. The report references a total of 41 publications from 1991 up to 2020. Information regarding pharmacodynamic and pharmacokinetic properties of trabectedin are well described and in accordance with the SmPC of the reference product Yondelis.

Trabectedin Accord has the same method and rate of administration, indications, dosage form and strengths as Yondelis. The SmPC is in line with the SmPC of the reference product. This is agreed.

Exemption

The medicinal product applied for is a generic version of the EU reference product supplied as a powder for concentrate for solution for infusion.

The applicant claims essential similarity of the proposed product with Yondelis.

According to the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr **, Appendix II) bioequivalence studies are not required for parenteral solutions. Instead, the conclusion on similarity with the reference medicinal product is only based on pharmaceutical equivalence. Therefore, the rationale for biowaiver application based on the pharmaceutical form is acceptable.

2.4.3. Conclusions on clinical aspects

Since the concerned generic medicinal product Trabectedin Accord 0.25 mg and 1 mg powder for concentrate for solution for infusion is essentially similar to the reference medicinal product Yondelis 0.25 mg and 1 mg powder for concentrate for solution for infusion, i.e. same qualitative and quantitative composition, same pharmaceutical form and route of administration, the request for a waiver for bioequivalence studies/clinical studies on the basis of the qualitative and quantitative comparability with the reference product is sufficiently justified. Trabectedin Accord is considered bioequivalent to Yondelis.

2.5. Risk Management Plan

2.5.1. Safety concerns

Important identified risks	• Injection site reactions
Important potential risks	• Acute Myeloid Leukaemia/ Myelodysplasia (AML/ MDS) • Cardiac Dysfunction • Pancreatitis, Lipase and/or Amylase increased
Missing information	• None

Safety concerns are in line with the reference product.

2.5.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.5.3. Risk minimisation measures

In line with the reference medicinal product, routine risk minimisation measures are considered sufficient to mitigate the safety concerns of trabectedin accord.

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 1.1 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 Yondelis 0.25 mg & 1 mg Powder for Concentrate for Solution for Infusion and zoledronic acid accord 4 mg/5 ml concentrate for solution for infusion.

Bridging report was prepared in accordance with CMDh guideline "Consultation with Target Patient Groups: meeting the requirements of Article 59(3) without the need for a full test - Recommendations for bridging".

The applicant has demonstrated that the Parent PIL 1 (YONDELIS 0.25 mg & 1 mg Powder for Concentrate for Solution for Infusion) and Daughter PIL are sufficiently similar regarding content. The applicant also demonstrated sufficient similarity with regards to design, layout and format with Parent PIL 2 (Zoledronic Acid Accord 4 mg/5 ml concentrate for solution for infusion).

The bridging report has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of trabectedin powder for concentrate for solution for infusion. The reference medicinal product Yondelis 0.25 mg and 1 mg powder for concentrate for solution for infusion is indicated:

- as monotherapy for the treatment of adult patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients.

- in combination with pegylated liposomal doxorubicin (PLD) for the treatment of patients with relapsed platinum-sensitive ovarian cancer.

No non-clinical studies have been provided for this application, but an adequate summary of the available non-clinical information based on literature review for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance, the clinical overview on these clinical aspects based on information from published literature is considered sufficient.

Since the proposed product is to be administered as an aqueous intravenous solution, no bioequivalence study has been submitted. Instead, in line with the respective European requirements a biowaiver has been requested and adequately justified as both products have the same qualitative and quantitative composition in terms of active substance, same excipients, pharmaceutical form and route of administration.

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

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

The overall benefit /risk balance of Trabectedin Accord is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Trabectedin Accord is not similar to Zejula within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix 5.1.

Outcome

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

- Trabectedin Accord is indicated for the treatment of adult patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients.

- Trabectedin Accord in combination with pegylated liposomal doxorubicin (PLD) is indicated for the treatment of patients with relapsed platinum-sensitive ovarian cancer.

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.