14 December 2023
EMA/504544/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Mevlyq

International non-proprietary name: eribulin

Procedure No. EMEA/H/C/006134/0000

Note

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

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List of abbreviations

API: Active Pharmaceutical Ingredient

ASMF: Active Substance Master File = Drug Master File

BCS: Biopharmaceutics Classification System

CHMP: Committee for Medicinal Products for Human Use

CQA: Critical Quality Attribute

DIC: Disseminated Intravascular Coagulation

DSC: Differential Scanning Calorimetry

EEA: European Economic Area

EMA: European Medicines Agency

ERA: Environmental Risk Assessment

EU: European Union

EURD: European Union Reference Dates

GI: Gastro-intestinal

HPLC: High performance liquid chromatography

ICH: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

INN: International Non-proprietary Name

IR: Infrared

K_{ow}: Octanol-Water Partition Coefficient

MAH: Marketing Authorisation Holder

MS: Mass Spectrometry

NMR: Nuclear Magnetic Resonance

OECD: Organisation for Economic Co-operation and Development

Ph. Eur.: European Pharmacopoeia

PBT: Persistence, Bioaccumulation and Toxicity

PEC: Predicted Environmental Concentration

PRAC: Pharmacovigilance Risk Assessment Committee

QbD: Quality by design

QTPP: Quality target product profile

RH: Relative Humidity

RMP: Risk Management Plan

SmPC: Summary of Product Characteristics

TAMC: Total Aerobic Microbial Count

TYMC: Total Combined Yeasts/Moulds Count

USP: United States Pharmacopoeia

UV: Ultraviolet

XR(P)D: X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant YES Pharmaceutical Development Services GmbH submitted on 7 October 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Mevlyq, 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 19 May 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 indications:

Mevlyq is indicated for the treatment of adult patients with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease (see section 5.1). Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting unless patients were not suitable for these treatments.

Mevlyq is indicated for the treatment of adult patients with unresectable liposarcoma who have received prior anthracycline containing therapy (unless unsuitable) for advanced or metastatic disease (see section 5.1).

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 a justification for not conducting any bioequivalence study with the reference medicinal product Halaven instead of non-clinical and clinical.

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: Halaven 0.44 mg/ml solution for injection
- Marketing authorisation holder: Eisai GmbH
- Date of authorisation: 17-03-2011
- Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/11/678/001-002

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

- Product name, strength, pharmaceutical form: Halaven 0.44 mg/ml solution for injection
- Marketing authorisation holder: Eisai GmbH
- Date of authorisation: 17-03-2011

- Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/11/678/001-002

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 not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

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 were:

Rapporteur: Alar Irs Co-Rapporteur: N/A

The application was received by the EMA on	7 October 2022
The procedure started on	27 October 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	16 January 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	26 January 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	23 February 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	17 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 to be sent to the applicant on	14 September 2023

The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	13 November 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	29 November 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 Mevlyq on	14 December 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 Mevlyq (eribulin) from YES Pharmaceutical Development Services GmbH, Germany.

The reference medicinal product is Halaven 0.44 mg/ml solution for injection (MAA No: EU/1/11/678/001-002, MAH: Eisai GmbH, Germany) for which a marketing authorisation was granted in the European Union on 17 March 20111 on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

Eribulin mesylate is a microtubule dynamics inhibitor belonging to the halichondrin class of antineoplastic agents. Eribulin is a fully synthetic macrocyclic ketone analogue of the naturally occurring large polyether macrolide. It is a structurally simplified synthetic analogue of halichondrin B, a natural product isolated from the marine sponge *Halichondria okadai*.

Eribulin mesylate inhibits the growth phase of microtubules without affecting the shortening phase and sequesters tubulin into non-productive aggregates. Eribulin exerts its effects via a tubulin-based antimitotic mechanism leading to G2/M cell-cycle block, disruption of mitotic spindles, and, ultimately, apoptotic cell death after prolonged and irreversible mitotic blockage.

The applicant did not submit any bioequivalence study. Since eribulin solution for injection is recommended to be used via intravenous route of administration, the applicant has requested a biowaiver based on the principles of the "Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **)". The applicant justified the biowaiver on the basis of identical qualitative and quantitative composition, pharmaceutical form, route of administration and dose to be administered between Mevlyq and its chosen reference medicinal product Halaven.

The safety and efficacy profile of eribulin for the treatment of locally advanced or metastatic breast cancer and of unresectable liposarcoma has been demonstrated in several clinical trials for the reference medicinal product Halaven. In addition, there is a long-term post-marketing experience contributing to the knowledge of the clinical use of this active substance.

The reference product Halaven is available in single dose presentations of 2 ml vials in pack sizes of 1 and 6 vials. Fezqizo is intended to be marketed as 2 ml single dose vial in pack size of 1 vial. The filled vials are placed into individual paperboard carton as secondary packaging.

This generic has applied for all the approved indications of the reference product Halaven:

- Mevlyq is indicated for the treatment of adult patients with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting unless patients were not suitable for these treatments.
- Mevlyq is also indicated for the treatment of adult patients with unresectable liposarcoma who have received prior anthracycline containing therapy (unless unsuitable) for advanced or metastatic disease.

The recommended dose of eribulin as the ready to use solution is 1.23 mg/m^2 which should be administered intravenously over 2 to 5 minutes on Days 1 and 8 of every 21-day cycle.

Relevant for the assessment is the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 rev.1/Corr **) as well as Questions & Answers: Positions on specific questions addressed to the Pharmacokinetics Working Party (EMEA/618604), Q6.3

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a solution for injection containing 0.44 mg/ml eribulin as active substance. The active substance is present as the salt form, eribulin mesilate.

Other ingredients are: ethanol anhydrous, water for injections, hydrochloric acid (for pH-adjustment), and sodium hydroxide (for pH-adjustment).

The product is available in a type I colourless glass vial with a teflon-coated, butyl rubber stopper and flip-off aluminium over seal as described in section 6.5 of the SmPC.

2.2.2. Active substance

2.2.2.1. General Information

The chemical name of eribulin is (2R, 3R, 3aS, 7R, 8aS, 9S, 10aR, 11S, 12R, 13aR, 13bS, 15S, 18S, 21S, 24S, 26R, 28R, 29aS)-2-[(2S)-3-amino-2-hydroxypropyl]-3-methoxy-26-methyl-20, 27-dimethylidenehexacosahydro-11, 15:18, 21:24, 28-triepoxy-7, 9-ethano-12, 15-methano-9H, 15H-furo[3,2-i]furo[2',3':5,6]pyrano[4,3-b][1,4]dioxacyclopentacosin-5(4H)-one corresponding to the molecular formula $C_{40}H_{59}NO_{11}$. It has a molecular mass of 729.9 g/mol as free base and a mass of 826 g/mol as the mesylate salt with the following structure:

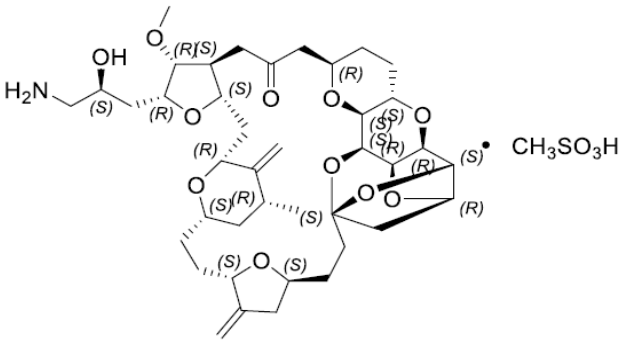

Figure 1: active substance structure

The chemical structure of eribulin was elucidated by a combination of MS, HREC (high resolution elemental composition), IR, UV, NMR, DSC, TGA. The solid state properties of the active substance were measured by XRPD.

The active substance is an amorphous powder. It is freely soluble in polar solvents including water and ethanol. The active substance is hygroscopic. Polymorphism is not observed and the active substance is dissolved during the preparation of the finished product.

Eribulin exhibits stereoisomerism due to the presence of 19 chiral centres. Of these chiral centres, 17 originate from the starting materials and 2 are introduced during the subsequent synthetic steps, only one pure stereoisomer is produced. The active substance enantiomeric purity is controlled routinely by specific optical rotation test in the active substance specification.

2.2.2.2. Manufacture, characterisation and process controls

The Active Substance Master File (ASMF) procedure is used. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and this was considered satisfactory. The active substance is manufactured at one site and sourced from one ASMF.

Eribulin is synthesized in 11 main steps using well defined starting materials with acceptable specifications. A major objection concerning information on the characterisation and control of starting materials as presented in the restricted part of the ASMF was raised during the procedure. This was resolved following the receipt of further information from the ASMF holder

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Reactions are conducted under a nitrogen atmosphere for reasons of stability.

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 discussed with regards to their origin and characterised. The product is intended for the treatment of advanced cancer, therefore the limits described in ICH M7 are not relevant for potential genotoxic impurities and ICH Q3A limits can be applied.

The active substance is packaged in polytetrafluoroethylene (PTFE) bottle which complies with Ph. Eur. and EC 10/2011 as amended.

2.2.2.3. Specification(s)

The active substance specification includes tests for: appearance, identification (RS, HPLC), assay (HPLC), methanesulfonic acid content (Ion Chromatography), specific optical rotation (Ph. Eur.), impurities (HPLC), residual solvents (GC), water content (KF), endotoxins (Ph. Eur.), microbiological quality (Ph. Eur.) and residue on ignition (Ph. Eur.).

Limits for impurities have been set in line with ICH Q3A and no impurities are present above the relevant qualification threshold.

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 impurity testing has been presented.

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

2.2.2.4. Stability

Stability data from 3 production scale batches of active substance from the proposed manufacturer stored in a container closure system representative of that intended for the market for up to 36 months under long term conditions (< -65 ºC) and for up to 6 months under accelerated conditions (20 ºC ± 5 ºC) were provided. Photostability testing following the ICH guideline Q1B was performed on one batch. Results on stress conditions increased temperature, high humidity, acidic conditions, alkali conditions and under oxidation were also provided on one batch of active substance in both the solid phase and solution phase.

The following parameters were tested during the stability studies: appearance, assay (HPLC), impurities (HPLC), water content (KF), endotoxins (Ph. Eur.), and microbiological quality (Ph. Eur.). The analytical methods used were the same as for release and were stability indicating.

As a solid, the active substance is stable under high temperature, photolytic conditions, and room temperature conditions without significant degradation.

At long term and accelerated conditions during the stability studies the product remained within specification and no trends were observed. The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months with the chosen storage condition of the applicant as below 65 ºC in the proposed container protected from light.

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and Pharmaceutical development

The finished product is formulated as a clear colourless sterile solution for intravenous administration. Each vial contains 1 mg of eribulin mesylate as a 0.5 mg/mL solution in ethanol & water (equivalent to 0.88 mg eribulin as a 0.44 mg/ml solution).

The product was developed with reference to the originator Halaven, QbD principles were applied to develop a suitable generic product. The QTTP was defined as per the active substance properties and the reference product formulation. The following CQAs were identified; assay, pH, and degradation products. No bioequivalence studies were required as both the product in question and the reference product are parenteral solutions.

The active substance is very hygroscopic, and therefore manufacture and dispensing in a nitrogen humidity controlled environment was selected. The active substance is dissolved during the manufacture of the finished product and therefore solid-state characteristics of the active substance are not relevant for finished product performance. In solution the active substance is unstable at high temperatures, and following investigation into the feasibility of terminal sterilisation, aseptic filtration was chosen as the method of sterilisation. The order of addition of excipients for preparation of the solution was investigated, the order of addition has no impact on the formulation however for safe handling reasons ethanol is added first during processing.

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 excipients are qualitatively the same as the reference product.

The primary packaging is type I colourless glass vial, with teflon-coated, butyl rubber stopper and flip-off aluminium over seal. 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 consists of five main steps: preparation of the bulk solution, sterile filtration, aseptic filling, stoppering & sealing, and final packaging. The active substance is first dissolved in ethanol, following this the remaining excipients are added sequentially with various mixing steps to aid dissolution. The prepared solution undergoes sterile filtration via two sterilising filters and the resulting filtrate is filled into the vials which are then sealed. The vials then undergo secondary packaging. The process is considered to be a non-standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. Process validation data has been presented for three commercial scale batches, and is supported by media fill studies. 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 are adequate for this type of manufacturing process.

2.2.3.3. Product specification(s)

The finished product specifications include appropriate tests for this kind of dosage form appearance (Ph. Eur.), identification (MS, HPLC), assay (HPLC), degradation products (HPLC), uniformity of dosage units

(Ph. Eur.), pH (Ph. Eur.), extractable volume (Ph. Eur.), particulate matter (Ph. Eur.), sterility (Ph. Eur.), bacterial endotoxins (Ph. Eur.), container closure integrity (USP).

The specifications are considered acceptable, limits for degradation products have been set in line with ICH Q3B and considering available batch data. No impurities are present above the ICH qualification threshold.

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 and data presented from input materials 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 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 product is also within the scope of advanced cancer as described in ICH S9 and therefore standard limits as per ICH Q3 would apply for nitrosamine impurities.

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 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 18 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, assay (HPLC), degradation products (HPLC), uniformity of dosage units (Ph. Eur.), pH (Ph. Eur.), particulate matter (Ph. Eur.), sterility (Ph. Eur.), bacterial endotoxins (Ph. Eur.), container closure integrity (USP). A decrease in the assay results was seen at the 9 month time-points during the long-term and intermediate conditions as compared to the initial and previous time-points. The results however remained within specification and this apparent decrease was determined to relate to analytical variability following the analysis of subsequent time-points of the same batches. During stability testing at long term and accelerated conditions the assay results generally decrease while impurity results increase, however the product remains within specification over the shelf life. The analytical procedures used are stability indicating.

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 the ICH Guideline on Photostability Testing of New Drug Substances and Products. The finished product is not photo-sensitive.

In-use stability studies were conducted on two commercial batches of the diluted and un-diluted finished product in line with the administration conditions described in the SmPC. Based on the available in-use study results, the product is chemically stable in a syringe when undiluted up to 4 hours at 25°C and 24 hours at 2-8°C. The diluted solutions are chemically stable for 72 hours at 2-8°C. All results were similar between the proposed finished product and reference product.

Based on available stability data, the proposed shelf-life of 24 months without specific storage conditions 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

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.

One quality major objection was raised during the procedure concerning the characterisation and control of the proposed starting materials as described in the restricted part of the ASMF. This was suitably resolved by the provision of the required additional information in the confidential restricted part of the ASMF.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

N/A

2.3. Non-clinical aspects

2.3.1. Introduction

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.

2.3.2. Ecotoxicity/environmental risk assessment

No new Environmental Risk Assessment (ERA) studies were submitted except the Phase I assessment. This has been justified by the applicant as the introduction of Mevlyq 0.44 mg/mL solution for infusion manufactured by YES Pharmaceutical Development Services GmbH is considered unlikely to result in any significant increase in the combined sales volumes for all eribulin mesylate containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar with previous results based on prevalence data in the EU member states – PECsw falls substantially below the action limit of 0.01 µg/L, i.e. Phase II testing is not required.

In the Table 1 below data from the ERA report has been provided: PBT screening results and Phase I assessment result.

Table 1: Summary of main study results

Substance (INN/Invented Name): eribulin mesylate			
CAS-number (if available): 441045-17-6			
PBT screening		***Result***	***Conclusion***
Bioaccumulation potential- log K_{ow}	OECD107 or …	2.31 (calculated value by Chemaxon)* * experimental value 2.25 provided in 2014 EPAR assessment report	Potential PBT: **No**
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.00014 µg/L	µg/L	> 0.01 threshold: No
Other concerns (e.g. chemical class)			No

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 an article 10(1) of Directive 2001/83/EC legal basis, 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, eribulin mesylate is a microtubule inhibitor used to treat metastatic breast cancer and metastatic or unresectable liposarcoma. Published values of log Kow of eribulin mesylate are 1.26 and 2.31. These values are < 4.5, which is a sound indicator that the API, which is administered intravenously as a water-based solution, is a highly hydrophilic compound with little or no potential for bioaccumulation in the environment. According to the guideline, PBT testing is not demanded for such compounds.

Eribulin mesylate is an anti-cancer drug administered in treatment cycles rather than a drug for continuous use. The PECsurface water for {(Invented) name} was calculated as 0.00013 µg/L for breast cancer and 0.0000068 µg/L for liposarcoma. Due to the very low dose and the noncontinuous usage of eribulin mesylate, the calculated PECsurface water value is low (0.00014 µg/L) and falls substantially below the Action Limit of 0.01 µg/L specified by the guideline. Phase II testing is therefore not required. There is therefore no relevant environmental risk associated with the clinical use of eribulin mesylate as described in the SmPC and the conduct of environmental studies as not necessary.

In conclusion, the data package submitted includes adequate justification for not providing a complete ERA and thus indicates that Mevlyq 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 eribulin are well known. As eribulin 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

This application concerns a generic application of a centrally authorised medicinal product according to Article 10 (1) of Directive 2001/83/EC. The reference product is Halaven, 0,44 mg/ml, solution for injection authorised in the European Union since 17 November 2011, with Eisai GmbH as marketing authorisation holder.

This generic medicinal product has been developed to be administered as an intravenous solution containing the same active substance in the same concentration as the chosen reference product Halaven.

The applied product also contains the same excipients in similar amounts as the reference product, based on the characterisation studies with the reference product performed by the Applicant. For this type of product, no bioequivalence studies are required according to the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1). Ethanol as an excipient is in the composition of the reference product at the almost identical concentration as in the generic product (based on the comparative measurements of the reference product by the Applicant). The warning has been included in the product information. In line with the Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use', the small amount of alcohol (approximately 2.8 mg/kg per dose considering 70 kg patient) in this medicine will not have any noticeable effects for the patients.

The clinical overview on the clinical pharmacology, efficacy and safety has been provided and is adequate. There are no new clinical efficacy or safety data provided. The clinical sections of the SmPC of Mevlyq are in accordance with the reference product Halaven. No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted, which is considered acceptable.

This generic has applied for all the approved indications of the reference product Halaven:

- Mevlyq is indicated for the treatment of adult patients with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting unless patients were not suitable for these treatments.
- Mevlyq is also indicated for the treatment of adult patients with unresectable liposarcoma who have received prior anthracycline containing therapy (unless unsuitable) for advanced or metastatic disease.

No new or additional indications are claimed by the Applicant. No further clinical studies have been conducted by the Applicant.

No formal scientific advice by the CHMP was given for this medicinal product.

Exemption

Relevant for the assessment is the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 rev.1/Corr **) as well as Questions & Answers: Positions on specific questions addressed to the Pharmacokinetics Working Party (EMEA/618604), Q6.3.

No bioequivalence study or other biopharmaceutic studies have been performed by the Applicant to support this generic application. Based on the comparative characterisations studies and investigations as performed by the Applicant during the drug product development, these studies are not considered necessary based on the following:

- The qualitative composition of the reference product and of the proposed generic medicinal product is identical as well as the salt form of the API
- The pH of the solution and the physicochemical properties are the same
- Both medicinal products are intended for parenteral administration, the dose and the route of administration are the same with no difference in indications and to the patient population.

Please kindly refer to section 2.2.3. Finished medicinal product for further information on the development of this generic medicinal product.

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 eribulin mesylate solution for injection.

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

This generic medicinal product has been developed to be administered as an intravenous solution containing the same active substance in the same concentration as the chosen reference product, Halaven solution for injection. The applied product also contains the same excipients in similar amounts as the chosen reference product, based on the characterisation studies with the reference product performed by the Applicant.

Based on Appendix II of the current Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1), bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product. However, if any excipients interact with the drug substance (e.g. complex formation), or otherwise affect the disposition of the drug substance, a bioequivalence study is required unless both products contain the same excipients in very similar quantity and it can be adequately justified that any difference in quantity does not affect the pharmacokinetics of the active substance.

In general, the applicant did demonstrate the equivalence between the test (Mevlyq) and the reference medicinal product (Halaven).

2.4.3. Conclusions on clinical aspects

The application contains an adequate review of published clinical data. The indications applied for are the same as for the chosen reference medicinal product Halaven, as well as the method of administration, posology, patient population and pharmaceutical form. The absence of bioequivalence studies is considered acceptable.

2.5. Risk Management Plan

2.5.1. Safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Tachycardia • Disseminated intravascular coagulation (DIC)
Important potential risks	• Adverse Pregnancy Outcomes • Male infertility • Gastrointestinal (GI) perforation
Missing information	• None

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 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

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

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 Halaven 0.44 mg/ml solution for injection. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of eribulin mesylate solution for injection. The reference product Halaven is authorised in the following indications:

> *HALAVEN is indicated for the treatment of adult patients with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease (see section 5.1). Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting unless patients were not suitable for these treatments.*
>
> *HALAVEN is indicated for the treatment of adult patients with unresectable liposarcoma who have received prior anthracycline containing therapy (unless unsuitable) for advanced or metastatic disease (see section 5.1).*

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 new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

No bioequivalence study was conducted due to the route of administration (intravenous route) and the pharmaceutical form (solution for injection). The applicant demonstrated the bridge between the test (Mevlyq) and reference medicinal product (Halaven) based on the same qualitative and quantitative composition in active substance, same pH of the solution and same physicochemical properties, same route of administration, same pharmaceutical form.

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

Outcome

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

> *Mevlyq is indicated for the treatment of adult patients with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease (see section 5.1). Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting unless patients were not suitable for these treatments.*
>
> *Mevlyq is indicated for the treatment of adult patients with unresectable liposarcoma who have received prior anthracycline containing therapy (unless unsuitable) for advanced or metastatic disease (see section 5.1).*

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.