25 April 2024
EMA/229035/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Eribulin Baxter

International non-proprietary name: eribulin

Procedure No. EMEA/H/C/006191/0000

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

AS: Active Substance

ASMF: Active Substance Master File = Drug Master File

CHMP: Committee for Medicinal Products for Human Use

DIC: Disseminated Intravascular Coagulation

EEA: European Economic Area

EMA: European Medicines Agency

ERA: Environmental Risk Assessment

EU: European Union

EURD: European Union Reference Dates

FP: Finished Product

GC: gas chromatography

GI: Gastro-intestinal

GMP: Good Manufacturing Practice

HPLC: High performance liquid chromatography

IC: ion chromatography

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

INN: International Nonproprietary Names

IR: Infrared

K_{ow}: Octanol-Water Partition Coefficient

MAH: Marketing Authorisation Holder

MDD: Maximum Daily Dose

MIA: Manufacturing and Importation Authorisation

NMR: Nuclear Magnetic Resonance

NMT: not more than

Ph. Eur.: European Pharmacopoeia

PBT: Persistence, Bioaccumulation and Toxicity

PEC: Predicted Environmental Concentration

PRAC: Pharmacovigilance Risk Assessment Committee

RH: Relative Humidity

RMP: Risk Management Plan

SmPC: Summary of Product Characteristics

USP: United States Pharmacopoeia

UV: Ultraviolet

XRPD: X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Baxter Holding B.V. submitted on 26 April 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Eribulin Baxter, 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 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:

Eribulin Baxter monotherapy is indicated for the treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least two chemotherapeutic regimens for advanced disease (see section 5.1). Prior therapy should have included an anthracycline and a taxane unless patients were not suitable for these treatments.

Eribulin Baxter 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	26 April 2023
The procedure started on	18 May 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	7 August 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	18 August 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 September 2023
The applicant submitted the responses to the CHMP consolidated List of	21 December 2023

Questions on	
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	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	8 February 2024
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	22 February 2024
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	25 March 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	10 April 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 Eribulin Baxter on	25 April 2024

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 Eribulin Baxter (eribulin) from Baxter Holding B.V., the Netherlands.

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 2011 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 biowaiver is considered justified on the basis of identical qualitative and quantitative composition, pharmaceutical form, route of administration and dose to be administered between Eribulin Baxter 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. Eribulin Baxter 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:

- Eribulin Baxter 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.
- Eribulin Baxter 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 solution for injection containing 0.44 mg/ml eribulin (equivalent to 0.5 mg/ml eribulin mesylate).

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

The product is available in 5 mL type I glass vial, with teflon-coated, butyl rubber stopper and flip-off aluminium over seal, containing 2 mL of solution as described in section 6.5 of the SmPC. The intended pack size is 1 vial.

2.2.2. Active substance

2.2.2.1. General Information

Eribulin (INN) is a synthetic macrocyclic ketone analogue of the naturally occurring large polyether macrolide, Halichondrin B, which was originally isolated from a marine sponge. Eribulin mesylate is the mesylate salt of this synthetic analogue.

The chemical name (IUPAC) is 2*R*,3*R*,3a*S*,7R,8a*S*,9*S*,10a*R*,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 monomethanesulfonate. It corresponds to the molecular formula: $C_{40}H_{59}NO_{11}\bullet CH_4O_3S$. It has a relative molecular mass of 826.0 g/mol (729.9 g/mol free base) and the following structure:

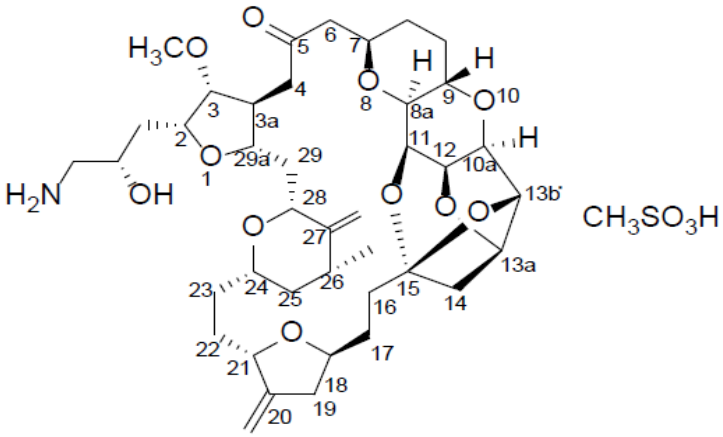

Figure 1: Active substance structure

The chemical structure of eribulin mesylate has been elucidated by IR, NMR, mass spectrum, UV and elemental analysis, as well as the absolute configuration study on derivatized eribulin carried out by means of single crystal X-ray crystallography.

The active substance (AS) is a white hygroscopic powder, freely soluble in water, methanol and ethanol.

Eribulin mesylate is a chiral compound having 19 asymmetric centres. The active substance stereoisomer is consistently manufactured and controlled.

The active substance eribulin mesylate is not a subject to a Ph. Eur. monograph.

2.2.2.1. Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF.

The AS is synthesized in 3 main steps using well-defined starting materials with acceptable specifications. The level of detail of the process description is considered sufficient.

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 are well discussed with regards to their origin and fate.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. It is further reported that the process parameters of the described synthetic route have been optimized to ensure that the manufacturing process effectively produces eribulin mesilate of the desired quality. Changes introduced have been presented in sufficient detail and have been justified.

The AS is packaged in 50 mL clear glass vial (neutral borosilicate glass, Type I) and a 20 mm rubber stopper (chlorinated butyl rubber coated with a tetrafluoroethylene-ethylene copolymer film). The active substance packaging material complies with EC Regulation 10/2011 as amended. A declaration certifying that the chlorobutyl rubber stoppers meet the requirements of the Ph. Eur. monograph 3.2.9 on rubber closures for containers has also been provided. The secondary packaging components consist of an aluminium-plastic composite cover used for sealing and a laminated aluminium bag.

2.2.2.2. Specification(s)

The AS specification includes tests for: appearance, identification (^{1}H NMR, HPLC), specific optical rotation (Ph. Eur.), related substances (HPLC), water content (Ph. Eur.), residual solvents (GC), sulphated ash (Ph. Eur.), assay (HPLC), content of methanesulfonic acid (IC), microbiological tests (Ph. Eur.) and bacterial endotoxins (Ph. Eur.).

The proposed AS specification is considered acceptable. The analytical methods employed in the control of the AS are considered satisfactorily described and validated. The reference standards used in the control of the active substance have been described in sufficient detail.

Batch analysis data for three commercial scale batches were presented and comply with the specification.

2.2.2.3. Stability

Stability data for three commercial scale batches of the AS packaged in the proposed container for 36 months under long-term conditions (-65 °C ± 5 °C) and 6 months under accelerated conditions (-20 °C ± 5 °C) according to ICH guidelines was presented.

The following parameters were tested*:* appearance, water content, optical rotation, identification by retention time, related substances, assay, bacterial endotoxin and microbial limit. The analytical methods used were the same as for release and were stability indicating.

A photostability study has not been performed in accordance with the ICH Q1B with respect to the UV exposure and hence no conclusion can be made regarding the photostability of the active substance. However, given that the AS is stored in a light-occlusive laminated aluminium outer bag, this has not been raised as an issue of concern.

In addition, transport stability study has been performed. Based on the presented results the AS is stable up to 30 days at 5±3 °C.

Based on the stability data available, the proposed re-test period and storage condition for eribulin mesylate AS is justified when packaged in the proposed container.

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and Pharmaceutical development

The finished product (FP) is a clear, colourless, sterile solution for intravenous administration that is essentially free from visible particles and packaged in a single-dose clear glass vial with a 13 mm Teflon stopper secured with aluminium-plastic composite cap. Each vial contains 1 mg of eribulin mesylate as a 0.5 mg/mL solution in ethanol: water (5:95). The FP physical description matches that of the originator product Halaven. The product is for single use.

The finished product has been developed to be a generic equivalent to the reference medicinal product Halaven 0.44 mg/mL solution for injection. Consequently, the objective was to prepare a solution for injection being essentially similar to the reference medicinal product.

The generic product has the same pharmaceutical form, the same qualitative and quantitative composition in terms of active substance and the same qualitative composition in terms of excipients as in the reference product Halaven.

All excipients are widely used for the manufacturing of pharmaceutical products being 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. The compatibility of the excipients with the active substance is proven by stability studies.

Regarding the presence of ethanol in the product, the relevant 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 in this medicine will not have any noticeable effects for the patients.

Formulation development aimed at the same qualitative and quantitative composition as the reference product Halaven solution for injection. The submitted documentation is considered sufficient in order to get an overview of performed development studies and drug specific quality aspects. Key physicochemical properties of AS, including solubility, hygroscopicity have been addressed and the impact of these characteristics for the pharmaceutical form and manufacturing process has been sufficiently discussed. The pH of the product has been also evaluated. The proposed pH range in the release and shelf-life specification is based on actual batch and stability data.

No overage is used in the manufacture of Eribulin Mesylate Injection.

Manufacturing process development has been properly discussed involving sufficient amount of data in order to have an overview of each phase. Several studies have been performed to optimise the manufacturing process of the FP. The performed investigations demonstrated that the process is robust for industrial manufacturing.

Sterile filtration in combination with aseptic filling was selected as method for achieving sterility of the FP. The choice of the sterilisation methos has been justified.

The materials involved in the manufacturing process of the final product have been described in sufficient detail and their compatibility with the finished product adequately demonstrated.

The primary packaging is a single-dose 5 mL type I glass vial, with teflon-coated, butyl rubber stopper and flip-off aluminium over seal, containing 2 mL of solution. The primary packaging complies with Ph. Eur. The

suitability of the container-closure system has been confirmed by means of the stability studies carried out on the finished product in its container and based on the assessment of extractables and leachables. The filled vials are placed into individual paperboard carton as secondary packaging.

2.2.3.2. Manufacture of the product and process controls

Based on the EudraGMP database the manufacturing and release site has a valid MIA and sufficient evidence to prove that acceptable standards of GMP are in place has been provided.

The manufacturing process consists of six main steps: preparation of the bulk solution, sterile filtration, aseptic filling, stoppering, sealing and final packaging. The finished product is manufactured using combination of sterile filtration, pre sterilised containers and aseptic filling in line with the CHMP Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container (EMA/CHMP/CVMP/QWP/850374/2015). The process is considered to be a non-standard manufacturing process. The information provided on process hold times is adequately documented in the dossier. An overview of the production process was provided, including information about the used equipment, equipment sterilisation process and applied in-process control testing; this is satisfactory. The critical steps of the process, the critical process parameters and the applied in-process controls with their target values have been stated and are considered acceptable.

The batch formula was provided for the two proposed batch sizes. The proposed batch sizes are supported by the provided process validation and stability data on three production scale batches.

Validation of the manufacturing process has been completed on three commercial scale batches. The manufacturing process has been demonstrated to be robust and reproducible, consistently leading to a product complying with the acceptance criteria set, for the manufacturing site proposed in the application. Satisfactory filter validation data has been provided.

An acceptable scale up validation strategy has been set to validate the manufacturing process for the higher batch size. A final report will be issued before any commercial product release of product from the higher batch size.

Overall, it has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

2.2.3.3. Product specifications

The finished product release and shelf-life specifications include appropriate tests for the dosage form: appearance (visual), identification (UV, HPLC), pH (Ph. Eur.), appearance of solution (Ph. Eur.), visible and sub-visible particles (Ph. Eur.), extractable volume (Ph. Eur.), osmolality (Ph. Eur.), impurities (HPLC), assay for eribulin (HPLC), assay for ethanol (GC), Sterility (Ph. Eur.), bacterial endotoxins (Ph. Eur.), uniformity of dosage units (Ph. Eur.) and container closure integrity test (Ph. Eur.).

The degradation products indicated in the finished product specification are sufficiently controlled. The proposed shelf-life specification for one of them has been tightened in accordance with ICH Q3B following a Major Objection raised. The acceptance criteria for the other specified impurities remain within the recommended qualification threshold in line with the ICH Q3B guideline. This is acceptable.

The information on the specified impurities is considered acceptable taking into account the very low maximum daily dose (MDD), duration of treatment and the indication of the medicinal product. The limit for unspecified impurities is acceptable according to the ICH Q3B guideline.

The proposed limit for total impurities at release and during shelf life has been tightened based on the available data and is acceptable.

The pH acceptance range at release and during shelf-life is based on batch and stability results and is considered acceptable.

The residual solvents control strategy in the finished product is satisfactory. Ethanol anhydrous is controlled in line with Ph. Eur. The control of "residual solvents" is considered not necessary in the FP specification; this is acceptable.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach. The applicant has provided a satisfactory risk assessment report on elemental impurities in accordance with ICH Q3D guideline. Batch analysis data on three commercial batches using a quantitative inductively coupled plasma-mass spectrometry method has been provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on risk based approach, no further information is deemed necessary. Moreover, taking into account the elemental impurities risk assessment and the presented batch data, it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification.

Eribulin is intended for the treatment of an advanced cancer as defined in the scope of ICH S9. Furthermore, Eribulin was clastogenic in the *in vivo* rat micronucleus assay as indicated on the SmPC. Therefore, N-nitrosamine impurities should be controlled at limits for non-mutagenic impurities according to ICH Q3A(R2) and ICH Q3B(R2) guidelines. A risk evaluation concerning the 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 "European Medicines Regulatory Network approach for the implementation of the CHMP Opinion pursuant to Article 5(3) of Regulation (EC) Nº 726/2004 for nitrosamine impurities in human medicines (EMA/425645/2020). Also, the declarations by manufacturers of AS and excipients as well as suppliers of primary packaging components were provided. Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the related finished product. The conclusion in the risk assessment report is in line with the risk evaluation.

The analytical methods have been sufficiently described. The validation data provided for in house methods are in line with the requirements of the ICH Q2 guideline. The suitability of the sterility test for the product has been sufficiently confirmed. Forced degradation studies under several stress conditions have been provided. The product is susceptible to degrade under heat and acidic conditions. The stability indicative nature of the assay and impurities method has been satisfactorily demonstrated.

The information provided on the used reference standards and container closure system is considered sufficient.

Batch analyses results have been provided for three production scale batches of FP. Batch analysis results are within the specification, 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

18 months real time stability data under long-term (25 °C ± 2 °C/60% RH ± 5% RH) and intermediate (30 °C ± 2 °C/ 65% RH ± 5% RH) conditions and 6 months data at accelerated conditions (40 °C ± 2 °C/ 75% RH ± 5% RH) were presented on three production scale batches packaged in the intended commercial container closure system. The stability studies were carried out at ICH conditions.

Samples were tested as per the shelf-life specification. The analytical procedures used are stability indicating.

An increase in impurities level can be seen along the stability studies at all storage conditions. However, all tested samples comply with the established requirements and impurities levels remained within the acceptance criteria under long-term and intermediate conditions only. Therefore, the proposed storage condition to be stored below 30 °C, is supported.

A significant assay change from its initial value was observed under long-term and accelerated conditions for one batch. However upon further investigation it has been adequately clarified that the initial assay value (T0) had been erroneously reported higher than it actually was. Thus the actual assay decrease was lower than calculated initially and the concern was resolved. Also, a statistical analysis was carried out and data provided to corroborate this conclusion; this is aceptable.

A photostability study was conducted on one commercial scale batch per ICH Q1B. Based on the photostability testing results, the medicinal product is stated to be not sensitive to light in the clear glass vials. This is also in line with the reference product.

A freeze-thaw study has been performed and the data shows that the product is stable after temperature excursions that may be encountered during shipment and/or storage.

Three undiluted commercial scale batches of the FP (6 months old and 12 months old) have been subjected for the in-use compatibility studies with administration syringes. The results demonstrate the chemical and physical in-use stability of the undiluted solution in a syringe for 4 hours at 15-25 °C and ambient light and 24 hours at 2 °C -8 °C. as indicated in the SmPC section 6.3

Three commercial scale batches of the FP (6 months old) were initially subjected for the in-use compatibility studies diluted with 0.9% Sodium Chloride Injection. Additionally, in-use study data obtained after 12 months long-term storage with the same three product batches have been provided. the dilution concentrations were according to those in SmPC section 4.2. The provided data demonstrate the chemical and physical in-use stability of the diluted solution for 24 hours at room temperature (20 °C ± 5 °C and ambient light) and 72 hours at 2 °C - 8 °C as described in SmPC section 6.3.

Separate in-use specification have been established for diluted and undiluted product and are in accordance with actual results.

The compliance of the product expiry date calculation with the Note for Guidance on Start of the Shelf-life of the Finished Dosage Form (CPMP/QWP/072/96) is confirmed.

Based on available stability data, the proposed shelf-life of 2 years when stored below 30 °C as stated in the SmPC (section 6.3 and 6.4) is 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

Eribulin Baxter has been developed as a generic of Halaven 0.44 mg/mL solution for injection.

The applicant's and restricted parts of ASMF for eribulin mesylate are considered acceptable. The data from the finished product manufacturer concerning the AS is acceptable. Information on development, manufacture and control of the active substance and finished product have been presented in a satisfactory manner. Pharmaceutical comparability between the test and reference products has been demonstrated. The Major Objection raised during the procedure regarding the limit of one impurity has been resolved by tightening the specification limit as requested. The results of tests carried out indicate satisfactory 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 the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendations for future quality development

None.

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 Environmental Risk Assessment studies were submitted. This was justified by the applicant as the introduction of Eribulin Baxter 0.44 mg/mL solution for infusion manufactured by Baxter Holding B.V. is considered unlikely to result in any significant increase in the combined sales volumes for all eribulin 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 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}	Literature and modelling data	2,25-3,88 average 2,91	Potential PBT – NO
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	$8,2 \times 10^{-7}$	µg/L	> 0.01 threshold NO (Y/N)
Other concerns (e.g. chemical class)	-	-	NO (Y/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 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 Halaven 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 Eribulin Baxter 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.

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 as well as in the generic product. 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 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 Eribulin Baxter 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:

- Eribulin Baxter 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.
- Eribulin Baxter 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 analyses 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.

In general, the applicant did demonstrate the equivalence between the test (Eribulin Baxter) 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 2 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 0.2 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

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

3. Benefit-risk balance

This application concerns a generic version of 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 (Eribulin Baxter) 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 Eribulin Baxter is favourable in the following indications:

> *Eribulin Baxter 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.

Eribulin Baxter 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.