Public Assessment Report

Scientific discussion

Bendamustine Hydrochloride Stada (Bendamustine hydrochloride)

DK/H/2413/001/DC

Date: 06-07-2015

This module reflects the scientific discussion for the approval of Bendamustine Hydrochloride Stada. The procedure was finalised at May 13, 2015. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States have granted a marketing authorisation for Bendamustine Hydrochloride Stada 2.5 mg/ml powder for concentrate for solution for infusion from Stada Arzneimittel AG.

The product is indicated for*:*

- First-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate.
- Indolent non-Hodgkin's lymphomas as monotherapy in patients, who have progressed during or within 6 months following treatment with rituximab or a rituximab containing regimen.
- Front line treatment of multiple myeloma (Durie-Salmon stage II with progress or stage III) in combination with prednisone for patients older than 65 years who are not eligible for autologous stem cell transplantation and who have clinical neuropathy at time of diagnosis precluding the use of thalidomide or bortezomib containing treatment.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the reference product Levact 2.5 mg/ml powder for concentrate for solution for infusion, which has been registered in Europe by Astellas Pharma GmbH, since 15 July 2010.

The marketing authorisation has been granted pursuant to Article 10.1 of Directive 2001/83/EC.

The reference product use to establishing the expiry of the data protection period is Ribomustin 25 mg/100 mg powder for solution for infusion from Astellas Pharma GmbH. Ribomustin was granted a marketing authorisation according to aquis 27 July 2005 in Germany.

II. QUALITY ASPECTS

II.1 Introduction

One vial contains 25 mg or 100 mg bendamustine hydrochloride, respectively.

The powder is a white to off-white freeze-dried powder.

The 25 mg strength is packed in Type I amber glass vial of 25 ml with bromobutyl rubber stopper and aluminium cap with flip-top and are supplied in packs of 5 and 20 vials.

The 100 mg strength is packed in Type I amber glass vial of 50 ml with bromobutyl rubber stopper and aluminium cap with flip-top and are supplied in packs of 5 and 20 vials.

Not all pack sizes may be marketed.

The excipients are: mannitol.

The powder for concentrate for solution for infusion has to be reconstituted with water for injection, diluted with sodium chloride 9 mg/ml (0.9%) solution for injection and then administered by intravenous infusion. Aseptic technique is to be used.

Compliance with Good Manufacturing Practice

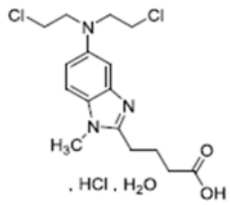
The RMS has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

II.2 Drug Substance

The active substance is not described in the European Pharmacopoeia. It is not optically active

International Non-proprietary Name (INN): Bendamustine hydrochloride monohydrate
Chemical name(s): 4–(5–(Bis(2–chloroethyl)amino)–1–methyl–1H–benzo[*d*]imidazol–2–yl)–butanoic acid hydrochloride monohydrate

Structure:



Molecular formula: $C_{16}H_{21}C_{12}N_3O_2$ HCl H_2O
Molecular mass: 412.7

There are no chiral centers and hence no chiral isomers.

Bendamustine hydrochloride is an White to off-white powder soluble in methanol and sparingly soluble in water and ethanol.

The documentation on the active substance bendamustine HCl is presented as an Active Substance Master File (ASMF). Both Applicant's and Restricted Part have been presented together with a suitable Letter of Access.

Manufacture, characterisation and testing of the drug substance according to the specification is described.

II.3 Medicinal Product

The finished product is freeze-dried powder as 25 mg strength in 25 ml glass vials and 100 mg strengths in 50 ml glass vials. The vials are for single use. Vials with strengths 25 mg/100 mg are reconstituted with water for injections to 2.5 mg/ml and are immediately further diluted with 0.9% NaCl solution to produce a final volume of about 500 ml.

The development of the product has been described, the choice of excipients is justified and their functions explained. The manufacturing process is adequately described, The manufacturing process has been described and justified by validation.

The drug product specifications cover appropriate parameters for this dosage form. The analytical procedures have been adequately described and validated. Batch analysis has been performed on three batches. The batch analysis results show that the finished products meet the specifications proposed.

Shelf-life/storage conditions of the unopened product: 2 years/ Keep the vial in the outer carton in order to protect from light.
After reconstitution: The powder should be reconstituted immediately after opening of the vial. The reconstituted concentrate should be diluted immediately with 0.9% sodium chloride solution. After reconstitution and dilution, chemical and physical stability has been demonstrated for 3.5 hours at 25ºC/60% RH and 2 days at 2ºC to 8ºC in polyethylene bags. From a microbiological point of view, the solution should be used immediately.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This product is a generic formulation of Levact, powder for concentrate for solution for infusion, which is available on the European market.
Since pharmacodynamic, pharmacokinetic and toxicological properties of bendamustine hydrochloride are well-known the applicant has not provided additional studies and further studies are not required.
Overview based on literature review is, thus, appropriate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

According to "Guideline on the Enviromental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00, 01 June 2006), an ERA dossier for a generic product may not contain specific data, provided the ERA report includes an appropriate and sound justification for the absence, taking into consideration a possible significant increase of enviromental exposure to the drug substance.

Since Bendamustine Hydrochloride Stada is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

Bendamustine hydrochloride is a well-known active substance with established efficacy and tolerability. This generic application does not contain new clinical data. This is acceptable for those generic applications for which bioequivalence studies are not required, and because the clinical properties for bendamustine hydrochloride are well-known. Overview based on literature review is, thus, appropriate.

IV.2 Risk Management Plan & pharmacovigilance sytem

RMP

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Bendamustine Hydrochloride Stada .

The following summary list of safety concerns, with no additional pharmacovigilance or risk minimisation measures has been approved:

Summary of safety concerns	
Important identified risks	• Anaphylaxis • Cardiac disorders • Extravasation • Hepatic failure • Infection (including pneumonia and sepsis) • Myelosuppression • Severe skin reactions • Tumour lysis syndrome
Important potential risks	• Renal toxicity • Secondary tumours (including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukaemia and bronchial carcinoma)
Missing information	• Effect on different races • Use in paediatric patients • Use in patients with severe hepatic impairment (severe bilirubin > 3.0 mg/dl)

Summary of safety concerns	
	• Use in patients with severe renal impairment • Use in pregnant and breastfeeding women

Summary of Pharmacovigilance System Master File (PSMF)
The applicant has provided a summary of PSMF in which proof is provided that the applicant has at his disposal a qualified person responsible for pharmacovigilance.
Information about the Member States in which the qualified person resides and carries out his/her tasks and the contact details of the qualified person is also included.
A statement signed by the applicant to the effect that the applicant has the necessary means to fulfill the tasks and responsibilities listed in Title IX of Directive 2001/83/EC as amended has been provided together with a reference to the location where the pharmacovigilance system master file for the medicinal product is kept.

V. PRODUCT INFORMATION

SmPC and Package leaflet
The content of the SmPC and package leaflet approved during the decentralised procedure is in accordance with that accepted for the reference product.

User consultation
A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Levact, DE/H/1250/001/DC. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Bendamustine Hydrochloride Stada 2.5 mg/ml powder for concentrate for solution for infusion have a proven chemical-pharmaceutical quality and is a generic form of Levact.
Levact is a well-known medicinal product with an established favourable efficacy and safety profile.

The SmPC, package leaflet and labelling are in the agreed templates and are in agreement with the texts for Levact.

Agreement between Member States was reached during a written procedure. There was no discussion in the CMD(h). The Concerned Member States, on the basis of the data submitted, considered that essential similarity has been demonstrated for Bendamustine Hydrochloride Stada with the reference product, and have therefore granted a marketing authorisation.
The decentralised procedure was finalised on May 13, 2015.

Bendamustine hydrochloride is a well known active substance which has been marketed for many years throughout the EU. No routine PSURs have to be submitted for this product as it is application based on Article 10(1) of Directive 2001/83/EU as amended, and otherwise is not specified in the EURD list.

The date for the first renewal will be: May 13, 2020.