COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Bendamustine HCl Amneal 100 mg/ml, concentrate for solution for infusion

(bendamustine hydrochloride)

NL/H/4291/001/DC

Date: 30 January 2020

This module reflects the scientific discussion for the approval of Bendamustine HCl Amneal 100 mg/ml, concentrate for solution for infusion. The procedure was finalised at 12 February 2019. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Bendamustine HCl Amneal 100 mg/ml, concentrate for solution for infusion, from Amneal Pharma Europe Limited.

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 hybrid application claiming essential similarity with the innovator product Ribomustin 25 mg/100 mg powder for solution for infusion which has been registered in Germany by Astellas Pharma GmbH since 26 July 2005 (original product). In the Netherlands, the reference product is Levact 2,5 mg/ml powder for concentrate for solution for infusion, which has been registered since 27 July 2010 in Germany through a decentralised procedure (DE/H/1250/001/DC). The Netherlands was added through a repeat-use procedure finalised on 15 June 2011.

The concerned member state (CMS) involved in this procedure was France.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application. The proposed formulation of the product differs from reference product Levact in the following:

- *Pharmaceutical Form* - Levact is a sterile, white, microcrystalline powder for concentrate for solution for infusion in vials whereas the proposed formulation is a sterile concentrate solution for infusion.
- *Composition* - the proposed formulation differs from Levact in qualitative and quantitative composition; i.e. there is a quantitative change to the active substance.

However, posology and method of administration of the proposed formulation are identical to that of the reference product. Consequently, the application is categorised as a hybrid application.

Similarity to medicinal products with orphan drug status

According to Article 8(1) of Regulation (EC) No 141/2000, where a marketing authorisation in respect of an orphan medicinal product is granted, the Union and the Member States shall not, for a period of 10 years, without prejudice to intellectual property law or any other provision of European Union law, accept another application for a marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, for the same therapeutic indication in respect of a similar medicinal product.

The MAH has submitted an assessment of molecular structural similarity addressing the potential similarity between Bendamustine HCl Amneal (bendamustine) and Imbruvica (ibrutinib), Gazyvaro (obinutuzumab), Arzerra (ofatumumab), Venclyxto (venetoclax), Revlimid (lenalidomide), Kyprolis (carfilzomib), Farydak (panobinostat), Imnovid (pomalidomide), Thalidomide Celgene (thalidomide), Ninlaro (ixazomib), Darzalex (daratumumab) and Mozobil (plerixafor).

The MAH has concluded that with regard to the similarity exercise the above mentioned products are not considered similar. Therefore, the MAH finds that with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for these products in the treatment of chronic lymphocytic leukaemia or multiple myeloma does not prevent a marketing authorisation for Bendamustine HCl Amneal.

II. QUALITY ASPECTS

II.1 Introduction

Bendamustine HCl Amneal is a clear colourless to yellow solution. The solution pH is in the range of 2.5 – 4.5 and the osmolality is between 230 and 330 mOsmol/kg.

The concentrate for solution for infusion is packed in Type I amber glass vials of 2 ml with chlorobutyl rubber stopper and an aluminium flip-off seal.

The excipients are: N,N-dimethylacetamide, sucrose, L-cysteine hydrochloride monohydrate (E920) and water for injection.

II.2 Drug Substance

The active substance is bendamustine hydrochloride monohydrate, an established active substance not described in the European Pharmacopoeia (Ph.Eur.). It is a white to off-white powder. The active substance is freely soluble in methanol, slightly soluble in ethanol and sparingly soluble in water. The aqueous solubility is pH dependent. Bendamustine does not exhibit any isomerism and is very hygroscopic. The manufacturing process produces a monohydrate polymorphic form.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The manufacturing process consists of six stages. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and is established in-house. The proposed drug specification of the ASMF holder contains tests for description, solubility, identification, pH, water content, residue on ignition, heavy metals, related substances, assay, hydrochloride content, residual solvents, bacterial endotoxins, and microbial limits. The proposed drug substance specification is acceptable. The specification of the MAH contains the same tests and limits as that of the ASMF holder, with additional tests for loss on drying and pathogens. Overall, analytical methods of the ASMF holder have been adequately described and validated. Batch analytical data demonstrating compliance with this specification have been provided for three production scale batches.

Stability of drug substance

Stability data on the active substance have been provided for three production scaled batches stored at 5°C (36 months) and 25°C/60% RH (6 months) in accordance with applicable European guidelines. No significant changes or specific trends are seen at both storage conditions. The provided stability data support the proposed re-test period of 36 months and storage conditions ´ Store in well closed light resistant container and preserve at temperature 5±3°C". Although protection from light does not appear to be necessary, no objection is made against the proposed storage conditions.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients in justified and their functions explained. Elements of quality by design were used for pharmaceutical development. The test product has a different dosage form, composition and concentration of the active substance than the reference product. Detailed instructions for use of the drug product have been provided, to avoid medication errors.

Since the to be administered solution (after dilution to 500 ml) is an aqueous intravenous solution with the same active substance in the same concentration as in the to be

administered reference product, no bioequivalence study is required. The to be administered solution for infusion (500 ml) prepared from the proposed product versus the reference product are therapeutically equivalent (efficacy and safety) and interchangeable. The pharmaceutical development of the product been adequately performed.

Manufacturing process

The manufacturing process has been validated according to relevant European guidelines. It consists of mixing and aseptic filtration. Process validation data on the product have been presented for three full-scale batches in accordance with the relevant European guidelines.

Control of excipients

The excipients are usual and comply with Ph. Eur. requirements. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, clarity of solution, colour of solution, water content, pH of the solution, osmolality, assay, related substances, extractable volume, particulate contamination, bacterial endotoxins, sterility and container closure integrity. Except for the related substances, the provided release and shelf-life limits are identical. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three full-scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three full-scale batches stored at 5±3°C (9 months) and 25°C/60% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the amber Ph. Eur. type I-glass vials. Photostability studies were performed in accordance with ICH recommendations and showed that the product is not stable when exposed to light. The proposed storage conditions “store in refrigerator (2 °C – 8 °C)” are acceptable and based on additional stability data, a shelf-life of 2 years is granted.

After dilution, the physicochemical stability of the diluted solution has been demonstrated for 3.5 hours at 25 °C/60%RH and 2 days at 2°C to 8°C in polyvinylchloride bags. From a microbiological point of view, the solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C unless dilution has taken place in controlled and validated aseptic conditions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Bendamustine HCl Amneal has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

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

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Levact which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Bendamustine hydrochloride is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Bendamustine HCl Amneal is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence "5.1.6 parenteral solutions", which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The concentrate for solution for infusion has to be diluted with sodium chloride 9 mg/ml (0.9%) solution for injection and then administered by intravenous infusion at the same concentration as reference product Levact. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

IV.3 Clinical safety

The proposed formulation of Bendamustine HCl Amneal, which is a concentrate for solution for infusion (100 mg/ml). The originator, Levact is a powder for concentrate for solution for infusion (2,5 mg/ml). The difference in strength of Bendamustine HCl Amneal to Levact and the other generics could lead to mediation errors; the required volume for Levact could be inadvertently interchanged for the volume of Bendamustine HCl Amneal, with an overdose (40x higher dose) of Bendamustine HCl Amneal as a consequence. However, the risk for this type of medication error is considered to be small, seeing that bendamustine is not used outside of a clinical setting and there are differences in the preparation procedures between Bendamustine HCl Amneal and Levact (and the other generics).
However, the clinical consequence of an interchanged vial of Bendamustine HCl Amneal with Levact (a 100 mg/ml vial mistakenly thought to contain 2,5 mg/ml), which will largely exceed the MTD of 280 mg/ml, is considered severe for individual patients. To mitigate this risk, the MAH proposes routine risk minimisation measures, including that the product should only be administered under the supervision of a physician qualified and experienced in the use of chemotherapeutic agents in section 4.2 of the SmPC, and the addition of a sentence that the concentration of the product differs from other bendamustine-containing products in section 6.6 of the SmPC. Detailed instructions for use are further included in section 6.6 of the SmPC:

- Instructions for dilution: the diluent, type of bag used for dilution, total volume and final concentrations.
- Preparation of the infusion solution: clear instructions for preparation of the infusion solution are provided. Tables with the total volumes of drug product required for a typical range of body surface areas of the patient population for each indication are included. The number of vials required to obtain these total volumes is included in these tables.

IV.4 Risk Management Plan

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 HCl Amneal.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	- Myelosuppression - Infections (including opportunistic infections of herpes zoster, cytomegalovirus, Pneumocystis jirovecii pneumonia) - Hepatitis B reactivation - Hepatic failure - Severe skin reactions - Cardiac disorders of cardiac failures, myocardial infarction, and atrial fibrillation - Tumour lysis syndrome - Renal failure - Anaphylaxis - Secondary malignancies of myelodysplastic syndrome and acute myeloid leukaemia
Important potential risks	- Medication errors
Missing information	- Exposure during pregnancy and lactation

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.5 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Levact. No new clinical studies were conducted. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Bendamustine hydrochloride ELC 2.5 mg/ml powder for concentrate for solution for infusion. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Bendamustine HCl Amneal 100 mg/ml, concentrate for solution for infusion has a proven chemical-pharmaceutical quality and is a hybrid form of Levact 2,5 mg/ml powder for concentrate for solution for infusion. Levact is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary. A biowaiver has been granted.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Bendamustine HCl Amneal with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 12 February 2019.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse