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Public Assessment Report

Scientific discussion

Bortezomib Teva 1 mg and 3.5 mg powder for solution for injection
Bortezomib

HR/H/0102/001-002/DC

This module reflects the scientific discussion for the approval of Bortezomib Teva 1 mg and 3.5 mg powder for solution for injection. The procedure was finalised at June 29th 2015 (day 210). For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Bortezomib Teva 1 mg and 3.5 mg powder for solution for injection, from Teva/Pliva.

The product is indicated in the treatment of:

- adult patients with progressive multiple myeloma who have received at least 1 prior therapy and who have already undergone or are unsuitable for haematopoietic stem cell transplantation (as monotherapy or in combination with pegylated liposomal doxorubicin or dexamethasone)
- adult patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with haematopoietic stem cell transplantation (in combination with melphalan and prednisone)
- adult patients with previously untreated multiple myeloma who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation (in combination with dexamethasone, or with dexamethasone and thalidomide)
- adult patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation (in combination with rituximab, cyclophosphamide, doxorubicin and prednisone).

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

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC with Velcade 1 mg and 3.5 mg powder for solution for injection, Janssen-Cilag International NV as the reference product, authorised in the EU since 2004 through centralised procedure.

II. QUALITY ASPECTS

II.1 Introduction

The powder for solution for injection is a white to off-white cake or powder.

The powder for solution for infusion is packed in type I clear glass 5 ml-vial (1 mg) and 10 ml-vial (3.5 mg) with a bromobutyl rubber stopper and aluminium cap fitted with a flip-off disc containing 1 mg or 3.5 mg bortezomib respectively.

Each pack contains 1 single-use vial.

The excipient is Mannitol (E421).

Compliance with Good Manufacturing Practice (GMP)
The RMS has been assured that acceptable standards of GMP 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.

II.2 Drug Substance

The active substance is bortezomib. The Active Substance Master File (ASMF) procedure is used for the active substance.

The starting materials have been adequately defined and are acceptable. The manufacture of the active substance is adequately described.
The control tests and provided specifications for drug substance are adequately drawn up.
Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. The proposed retest period is accepted.

II.3 Medicinal Product

The development of the product has been described, the choice of excipients is justified and their functions explained. Choice of excipients has been based on the excipients present in the reference product and the physicochemical characteristics of the reference product. Manufacturing process is well described with in-process parameters which are adequate for this product.
The specification for the finished drug product at release and during the shelf-life is acceptable as well as used analytical methods. All analytical methods are properly validated.
Provided stability results justify the proposed shelf life of 24 month without any temperature storage restriction. Storage conditions after reconstitution (8 hours at 25°C) are adequately supported by provided data.

III. NON-CLINICAL ASPECTS

The documentation does not contain non-clinical data. This is acceptable for generic applications, because the pharmacological and toxicological properties of bortezomib are well known and no new preclinical data are available.
The applicant provided a non-clinical overview which is adequate.

III.1 Environmental risk assessment (ERA)

Since Bortezomib Teva 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

The documentation does not contain clinical data. This is acceptable for generic applications, because the clinical properties of bortezomib are well known and no new clinical data are available.
The applicant provided a clinical overview.
No bioequivalence studies have been performed which is acceptable as the product is a powder for solution for injection.

IV.1 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 Bortezomib Teva.

- Summary table of safety concerns as approved in RMP

Table 1. Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Heart failure • Hepatotoxicity • Acute hypersensitivity reaction • Tumour lysis syndrome • Peripheral motor neuropathy (including paralysis) • Autonomic neuropathy • Acute diffuse infiltrative pulmonary disease • Pericardial disease • Pulmonary hypertension • Herpes zoster infection • Posterior reversible encephalopathy syndrome • Optic neuropathy and different degrees of visual impairment (up to blindness) • Thrombocytopenia and thrombocytopenia with associated bleeding • Neutropenia and neutropenia with associated infection
Important potential risks	• Progressive multifocal leukoencephalopathy • Ventricular rhythm abnormalities • Guillain-Barré syndrome • Other central nervous system disorders • Medication/dispensing errors
Missing information	• Safety in patients with cardiac impairment or with NYHA Class III or IV impairment • Safety in patients with ECOG>2 • Second primary malignancies with BtzTD induction therapy

Additional risk minimisation measures:

In line with the reference product, additional risk minimisation measures are necessary for the safe and effective use of the product regarding the safety concern medication / dispensing errors (potential risk for medication error with the 2 different routes of administration with different reconstituted concentrations).
The MAH shall ensure that all healthcare professionals, involved in the prescribing, dispensing, handling or administration of Bortezomib Teva, are provided with educational material.

V. USER CONSULTATION

The package leaflet for 3.5 mg strength has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.
The results 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.
A user consultation with target patient groups on the package leaflet for 1 mg strength has been performed on the basis of a bridging report making reference to Bortezomib Teva 3.5 mg powder for solution for injection. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Bortezomib Teva 1 mg and 3.5 mg powder for solution for injection has a proven chemical-pharmaceutical quality and is a generic form of Velcade. Bortezomib is a well-known active substance with an established favourable efficacy and safety profile.

An adequately justified waiver for not conducting a bioequivalence study has been presented.

The marketing authorisation holder has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

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

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 Bortezomib Teva with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 29th June 2015.