COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Bugvi 5 mg/ml, powder for dispersion for infusion
(paclitaxel)

NL/H/5505/001/DC

Date: 18 September 2024

This module reflects the scientific discussion for the approval of Bugvi 5 mg/ml, powder for dispersion for infusion. The procedure was finalised on 2 May 2024. 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
EMA	European Medicines Agency
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
RMS	Reference Member State
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 Bugvi 5 mg/ml, powder for dispersion for infusion, from Stada Arzneimittel AG.

The product is indicated for:

- monotherapy for the treatment of metastatic breast cancer in adult patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline containing therapy is not indicated
- in combination with gemcitabine for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas
- in combination with carboplatin for the first-line treatment of non-small cell lung cancer in adult patients who are not candidates for potentially curative surgery and/or radiation therapy

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Abraxane 5 mg/ml powder for dispersion for infusion, which has been registered in the EEA via a centralised procedure (license number EU/1/07/428) by Bristol-Myers Squibb Pharma EEIG since 11 January 2008.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Denmark, Finland, France, Germany, Hungary, Iceland, Luxembourg, Norway, Romania, Spain and Sweden.

Similarity assessment

According to Article 8(1) of Regulation (EC) No 141/2000, no marketing authorisation can be granted for a product similar to an orphan medicinal product for a period of ten years, when this concerns a similar medicinal product with the same therapeutic indication. A similarity assessment has been performed between Bugvi and Onyvide, which obtained orphan market exclusivity on 9 December 2011 in the United Kingdom and on 14 October 2016 in the EU, based on designation EU/3/11/933. The assessment took into account the therapeutic indications, mechanism of action and principal molecular structural features. The similarity assessment report was completed in April 2022 concluding the two products were not similar and that with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Onivyde in the treatment of pancreatic cancer, does not prevent the granting of the marketing authorisation of Bugvi.

II. QUALITY ASPECTS

II.1 Introduction

Bugvi is a white to yellow powder for dispersion for infusion. Each vial contains as active substance 100 mg of paclitaxel, formulated as albumin bound nanoparticles. After reconstitution, each mL of dispersion contains 5 mg of albumin bound paclitaxel. The reconstituted dispersion has a pH of 6-7.5 and an osmolality of 300-360 mOsm/kg.

The excipient is human albumin (containing sodium caprylate and N-acetyl-L-tryptophan).

The powder for dispersion for infusion is packed in a 50 mL type I glass vial with a stopper (bromobutyl rubber), with an aluminium flip-off seal.

II.2 Drug Substance

The active substance is paclitaxel, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The substance is a white to off-white powder or crystalline powder. A hydrated form (β-form) of crystalline paclitaxel has been reported. However, this hydrate is not expected to form since the final crystallisation is performed in a non-aqueous medium.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and CEP with additional requirements for bacterial endotoxins and microbial limit. The specification is acceptable. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

Stability of drug substance
The active substance is stable for four years when stored under the stated conditions. However, a re-test period of three years is stated on the CEP. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

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 composition of the product is based on the composition of the reference product. For the preliminary composition, various optimisation studies have been performed for optimisation of the organic phase, the aqueous phase, microbiological aspects, pH stability studies, and drug product release studies with varying human albumin contents. After performing the five formulation studies all initial risks were considered as low.

The proposed product contains more human serum albumin (HSA) than the reference product. The MAH that during the manufacturing process, the amount of paclitaxel bound to HSA changes slightly after sterile filtration due to the adsorption of paclitaxel. This variation is acceptable as drug release studies showed similar results.

Comprehensive *in vitro* release and characterisation studies were conducted to compare the proposed and reference products, following guidelines in the EMA's reflection paper on micellar systems (EMA/CHMP/QWP/799402/2011). The main objectives of the *in vitro* studies included:

- Physicochemical characterisation and *in vitro* dissociation (of paclitaxel nanoparticles)
- Protein characterisation and structural integrity
- Sameness and nature of bond between paclitaxel and HAS

Comparative studies were performed on multiple batches of both the proposed and reference products. Findings revealed:

- The releases from the test product and the reference product in 5% HSA and human plasma were similar. The release process of the nanoparticles is a very rapid release process.
- The proposed product has the same method and rate of administration, indication, dosage form and strength as those of reference medicinal product.
- Minor differences in albumin content did not affect the release behavior or biodistribution of paclitaxel.
- *In vitro* characterization studies demonstrated that the proposed product has comparable physicochemical properties and *in vitro* release behavior to the reference product, falling within the bioequivalence acceptance range.

Based on the data provided and the fulfilment of all regulatory guidelines, a bioequivalence study can be waived for the proposed product.

Overall, the pharmaceutical development of the product has been considered acceptable.

Manufacturing process

The product is processed with lyophilisation step by aseptic processing, so the manufacturing process is considered as non-standard. The manufacturing process has been described in sufficient detail. Human albumin is added in two steps.
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 human albumin has a marketing authorisation in the EU and is linked to a certified Plasma Master File (PMF). The PMF dossier and certificate have been provided, as well as a compilation of the manufacturing flow chart, the finished product specifications, summary of stability data including the approved shelf-life, virus risk assessment, and the qualitative and quantitative composition. These specifications are acceptable.

Microbiological attributes

A justification for the applied sterilisation method (sterile filtration, pre-sterilisation for containers and aseptic processing) and non-possibility of terminal sterilisation is given. The concise information on the container closure system, microbiological attributes, and compatibility is considered 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 methods of particle size (mean and distribution), water content, sterility and bacterial endotoxins. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches from the production site(s) have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three submission batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months) and one production scale batch stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable European guidelines demonstrating the stability of the product for three years. A photostability study was conducted on one batch and a significant change and atypical trend for related substances testing were observed in the immediate pack when exposed to photostability storage condition. However, there is no significant change or trend for all testing were observed in the secondary pack. On basis of the data submitted, a shelf life was granted of three years. The labelled storage condition for unopened vials is: “Keep the vial in the outer carton in order to protect from light”.

In-use stability data have been provided demonstrating that the product remains stable for up to 24 hours, following first reconstitution, when stored in a refrigerator (2°C-8°C), in the vial when kept in the outer carton to protect it from light or in the intravenous drip protected from light. This may be followed by storage in the infusion bag for 4 hours below 25°C.

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

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Abraxane which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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 Pharmacokinetics

Biowaiver

A biowaiver was requested for Bugvi 5 mg/ml, powder for dispersion for infusion as the composition is qualitatively and quantitatively similar to the reference product, Abraxane 5 mg/ml, lyophilisate for suspension for injection. The *in vitro* characteristics of the infusion suspension and the behaviour of the nanoparticles in blood/plasma following infusion have been sufficiently characterised through *in vitro* assays. These studies demonstrate a very rapid dissociation of the paclitaxel-albumin nanoparticle during infusion and showed that the observed nanoparticles in the infusion suspension do not impact pharmacokinetics. *In vitro*

comparison, as outlined in the Reflection paper on the pharmaceutical development of intravenous medicinal products containing active substances solubilised in micellar systems, (EMA/CHMP/QWP/799402/2011) is considered fulfilled. Therefore, a biowaiver for the bioequivalence study has been adequately justified accepted. The current product can be used instead of its reference product.

IV.2 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 Bugvi.

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

Important identified risks	None
Important potential risks	None
Missing information	None

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

IV.3 Discussion on the clinical aspects

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

V. USER CONSULTATION

The package leaflet (PL) 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 PL was English.
The test consisted of two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
The results show that the PL 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Bugvi 5 mg/ml, powder for dispersion for infusion has a proven chemical-pharmaceutical quality and is a generic form of Abraxane 5 mg/ml, lyophilisate for suspension for injection.

Abraxane is a well-known medicinal product with an established favourable efficacy and safety profile.

Therapeutic equivalence with the reference product has been shown by the comparison of qualitative and quantitative composition and the results of *in vitro* studies on the relevant quality attributes. 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 Bugvi with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 2 May 2024.

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
NL/H/5505/001 /IA/001	Replacement or addition of a site where batch control/testing takes place	No	7 August 2024	Approved	-