LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Paklitaxel albumin Reddy (paclitaxel)

SE/H/2608/01/DC - Public AR

This module reflects the scientific discussion for the approval of Paklitaxel albumin Reddy. The procedure was finalised at 2025-07-23. For information on changes after this date please refer to the module 'Steps taken after the finalisation of the initial procedure - Summary'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Paklitaxel albumin Reddy, 5 mg/ml, Powder for dispersion for infusion.

The active substance is paclitaxel, formulated as albumin bound nanoparticle. HSA is supported by a plasma master file. A comprehensive description of the indication and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1 About the product

Pharmacotherapeutic group: Antineoplastic agents, plant alkaloids and other natural products, taxanes, ATC Code: L01CD01

Mechanism of action
Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerisation. This stability results in the inhibition of the normal dynamic reorganisation of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or “bundles” of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

Paclitaxel contains human serum albumin-paclitaxel nanoparticles of approximately 130 nm in size, where the paclitaxel is present in a non-crystalline, amorphous state. Upon intravenous administration, the nanoparticles dissociate rapidly into soluble, albumin bound paclitaxel complexes of approximately 10 nm in size. Albumin is known to mediate endothelial caveolar transcytosis of plasma constituents, and in vitro studies demonstrated that the presence of albumin in paclitaxel enhances transport of paclitaxel across endothelial cells. It is hypothesised that this enhanced transendothelial caveolar transport is mediated by the gp-60 albumin receptor, and that there is enhanced accumulation of paclitaxel in the area of tumour due to the albumin-binding protein Secreted Protein Acidic Rich in Cysteine (SPARC).

Claimed indication
As 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.

II.2 General comments on the submitted dossier

The application for Paklitaxel albumin Reddy, 5 mg/ml, Powder for dispersion for infusion, is a Generic Art. 10(1) application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DE, ES, IT, RO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data

protection period is Abraxane, 5 mg/ml, Powder for dispersion for infusion authorised in the Union since 2008, with Bristol-Myers Squibb Pharma EEIG as marketing authorisation holder.

II.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.
For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

No clinical studies to support the application have been performed by the Applicant.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance
The structure of the drug substance has been adequately proven, and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described, and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

Drug Product
The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III.2 Non-clinical aspects

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of Paklitaxel albumin Reddy (paclitaxel) are well known. As paclitaxel is a widely used, well-known active substance, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
The applicant has included a Environmental Risk Assessment (ERA) evaluating the risks associated with the intended use of Paklitaxel albumin Reddy (paclitaxel).

In line with the new *Guideline on the environmental risk assessment of medicinal products for human use EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.** , the applicant has performed a Phase I ERA.

The log *K*ow was determined to be 3,69 (below 4.5) using the slow stirring method.

The PECSW, based on refined Fpen was less than 0.01 µg/L for all member states. The refined FPEN was determined using API consumption rather that prevalence data as suggested in the *Guideline on the environmental risk assessment of medicinal products for human use EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.**.

III.3 Clinical aspects

Pharmacokinetics
No bioequivalence study has been submitted for this application.

Discussion and overall conclusion
The Guideline on Investigation of Bioequivalence states that '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'. However, paclitaxel albumin is not an aqueous intravenous solution but a dispersion for infusion and as such, a bioequivalence study may be necessary, unless otherwise justified.

In the case of paclitaxel albumin, a waiver based on *in vitro* similarity might however be applicable if similarity in certain physicochemical characteristics is demonstrated, taking into consideration the rapid disassembly of the nanoparticles upon infusion in blood.

The proposed drug product contains the same active ingredient in the same concentration and quantity per unit as the currently approved product, Abraxane®. The proposed product also contains the same excipients in similar amounts as the reference product. The *in vitro* similarity of the proposed drug product and the reference product has also been evaluated. Since that *in vitro* similarity is shown, waiver for *in vivo* bioequivalence study is acceptable.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted, which is acceptable.

Pharmacovigilance system
Proposed MAH: Reddy Holding GmbH, betapharm Arzneimittel GmbH, Dr. Reddy's S.r.l., Dr. Reddys Laboratories Romania S.R.L., Reddy Pharma Iberia S.A.
The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System together with an annex listing all relevant subsidiaries. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

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 Paklitaxel albumin Reddy.

Part II Safety specification
The MAH has submitted the version 0.1 RMP dated 02-July-2024 and proposed the following summary safety concerns:

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• None
Missing information	• None

Having considered the data in the safety specification and that it is in line with the originator Abraxane, the assessor agrees and find the summary of safety concerns listed by the MAH appropriate.

Part III Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Part V Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.1 signed 02-July-2024 is considered acceptable.

The 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 RMS;
- 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)
Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

Common renewal date
The common renewal date will be 5 years after closure of the DCP.

IV. BENEFIT RISK ASSESSMENT

The quality of the generic product, Paklitaxel albumin Reddy, is found adequate. There are no objections to approval of Paklitaxel albumin Reddy, from a non-clinical and clinical point of view. The absence of bioequivalence studies is acceptable. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

N/A

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

N/A

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available in the MRI Product Index.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available in the MRI Product Index.

V.4.2 Assessment of User Testing

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to
Abraxane 5 mg/ml powder for dispersion for infusion, EMEA/H/C/000778 regarding content and
Icatibant 30 mg solution for injection in pre-filled syringe, DE/H/6796/001/DC and
Bortezomib 3,5 mg powder for solution for injection DE/H/4105/001/DC respectively for Reddy and betapharm regarding layout.
The bridging report submitted by the applicant has been found acceptable.

VI. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-