THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR ADPAXIL (PACLITAXEL 260MG/43.4ML) INJECTION

Version number 1.0
21 August, 2023

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1. Introduction

ADPAXIL Injection is a generic medicine of Taxol 6 mg/ml concentrate for solution for infusion which has been registered in the UK by Bristol Myers Squibb ADPAXIL Injection contains Paclitaxel which is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerization. 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. ADPAXIL Injection is approved in Tanzania for use in adults only.

Product details

Registration number	TAN 23 HM 0240
Brand name	ADPAXIL
Generic name, strength, and form	Each mL contains Paclitaxel 6 mg
ATC classification	L01CD01 -plant alkaloids and other natural products, taxanes Antimicrotubule/ Antioneoplastic Agent/Taxanes.
Distribution category	POM
Country of origin	India
Associated product	ADPAXIL (100 mg/16.7 mL)
Marketing Authorization Holder	Beta Drugs Ltd Kharuni-Lodhimajra Road, Vill: Nandpur, Teh: Baddi,Distt:Solan, Himachal Pradesh, India
Local Technical Representative	Dawa Medicare Ltd P.O Box 16215 Dar Es Salaam

1.1 Assessment procedure

The application for registration of ADPAXIL was submitted on DD/MM/YYYY. The product underwent full assessment. Assessment was completed in 5 (five) rounds of evaluation and the product was registered on 01/06/2023.

1.2 Information for users

Visual description of the finished product	Clear colorless to slightly yellow viscous sterile, non-aqueous solution
Primary packing material	50 mL Clear Glass Vial USP Type I, containing Clear colorless to slightly yellow viscous sterile, non-aqueous solution, stoppered with 20 mm Bromo Butyl Rubber Plug and sealed with 20 mm Aluminium Flip off Seal having white colour.
Secondary packing materials	Printed carton box
Shelf-life and storage condition	24 months

	As packaged for sale: “Do not store above 30°C". Keep the vial in the outer carton, in order to protect from light. Reconstituted solution "Store at temperature between 2°C-8°C’’
Route of administration	Intravenous
Therapeutic indications	1. **Ovarian Cancer:** In first line chemotherapy of ovarian cancer, paclitaxel is indicated for the treatment of patients with advanced disease or a residual disease (> 1cm) after initial laparotomy, in combination with cisplatin. In second-line chemotherapy of ovarian cancer, paclitaxel is indicated in the treatment of metastatic carcinoma of the ovary after failure of standard platinum-based therapy. 2. **Breast cancer:** In the adjuvant setting, paclitaxel is indicated for the treatment of patients with node-positive breast carcinoma following anthracycline and cyclophosphamide (AC) therapy. Adjuvant treatment with paclitaxel should be regarded as an alternative to extended AC therapy. Paclitaxel is indicated for the initial treatment of locally advanced or metastatic breast cancer either in combination with an anthracycline in patients for whom anthracycline therapy is suitable, or in combination with trastuzumab, in patients who over-express human epidermal growth factor receptor 2 (HER-2) at a 3+ level as determined by immunohistochemistry and for whom an anthracycline is not suitable. As a single agent, treatment of metastatic carcinoma of the breast in patients who have failed to respond adequately to standard treatment with anthracyclines or in whom anthracycline therapy has not been appropriate. 3. **Advanced non-small cell lung cancer (NSCLC):** Paclitaxel, in combination with cisplatin, is indicated for the treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgical intervention and/or radiation therapy. 4. **AIDS-related Kaposi's sarcoma (KS):** Paclitaxel is indicated for the treatment of patients with advanced AIDS-related Kaposi's sarcoma who have failed prior liposomal anthracycline therapy. Limited efficacy data supports this indication; a summary

	of the relevant studies.

2. Labelling and product information

Summary of product characteristics
The SmPC included all the relevant information to ensure correct and safe use of the medicine by healthcare providers. The complete SmPC can be accessed here.

Package insert/leaflet
The package insert is confirmed to be derived from the SmPC and contains sufficient data for the end user. Since the product is POM, the package insert contains full prescribing information as per SmPC.

Container labels
The product label information is presented in English. Details in the secondary pack label include:

Brand name: ADPAXIL

Composition: Each mL contains Paclitaxel 6 mg

Pack size: 43.4 mL

Manufacturing details: batch number, manufacturing date, and expiry date

Storage conditions: As packaged for sale: “Do not store above 30°C". Keep the vial in the outer carton, in order to protect from light.

Reconstituted solution "Store at temperature between 2°C-8°C

Manufacturer address: physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: Not applicable

The details of the primary pack include:

Brand name and strength: ADPAXIL

Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: Beta Drugs Ltd

The content of the primary and secondary labels was aligned to the requirements of the Part V of the Compendium: Guidelines on Format and Content of Product Labels for Medicinal

products. The label contains sufficient information for proper identification of the medicine and post marketing follow up of the product.

Mock labels are appended as annex I.

3. Scientific discussion

Quality of Active Pharmaceutical Ingredients

Information on the quality of the API was submitted in form of DMF.

General Information

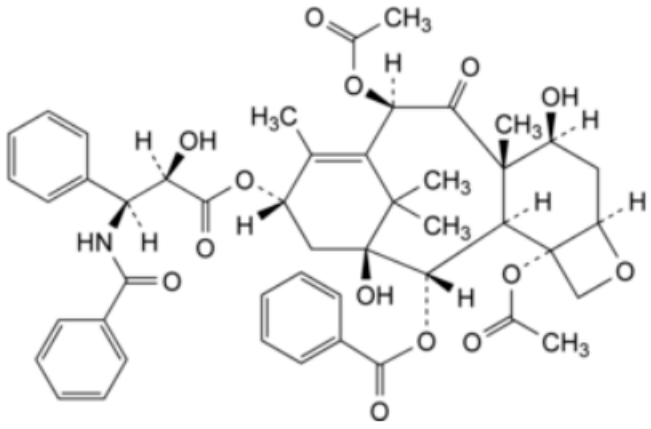
Paclitaxel API is compendia in USP, Ph.Eur., and BP.

Molecular formula: $C_{47}H_{51}NO_{14}$

Chemical name:

Benzenepropanoic acid, β-(benzoylamino)- α-hydroxy-, 6,12b- bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano- 1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester, [2aR-[2aα ,4β ,4aβ ,6β ,9α (αR*, βS*),11α,12α ,12aα ,12bα]]-.(2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-1,2a,3,4,4a,6,9,10,11,12,12a,12b-Dodecahydro-4,6,9,11,12,12b-hexahydroxy-4a,8,13,13-tetramethyl-7,11-methano-5H-cyclodeca[3,4]-benz[1,2-b]oxet-5-one6,12b-diacetate,12-benzoate, 9-ester with(2R,3S)-N-benzoyl-3-phenylisoserine.

Structure:



General properties

The active substance is a white to off white powder, which is freely soluble in methanol, soluble in alcohol and acetonitrile and sparingly soluble in water. No polymorphic forms are described in literature, and also XRD and DSC difractograms of the material show absence of polymorphism. The molecule contains four chiral centers. The active is present in the drug product dissolved in water, hence the polymorphic form and particle size distribution are not considered as critical quality aspects.

Manufacture

Paclitaxel API manufacturer is Jiangsu Yew Pharmaceutical Co., Ltd, Hongdou Industrial District, Donggang Town, Wuxi, Jiangsu, China 214199. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by the China Food and Drug Administration. Paclitaxel API is manufactured by chemical synthesis using conventional techniques. Sufficient controls of quality of materials and in-process checks were employed throughout the manufacturing process.

Specifications

The API specifications were set as per USP standards and ICHQ3A. The parameters monitored during quality control are: appearance, appearance of solution, identification by IR and HPLC, heavy metals, residue on ignition, bacterial endotoxins, microbial enumeration, water content, residual solvents, and assay. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Paclitaxel API is 36 months when packed in LDPE bag with storage condition ‘Store below 25 °C’.

Quality of the Finished Pharmaceutical Product

Formulation

ADPAXIL is a clear colorless to slightly yellow viscous sterile, non-aqueous solution

ADPAXIL contains the Paclitaxel and other ingredients listed here after: polyoxyl 35 castor oil, anhydrous citric acid, and dehydrated alcohol. The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, 8th Edition in terms of function and quantities.

Manufacture

The finished product manufacturer is Beta Drugs Ltd, Kharuni-Lodhimajra Road, Vill: Nandpur, The: Baddi, Distt: Solan, Himachal Pradesh, India. The compliance of the sites to TMDA GMP standards was confirmed through site inspection on 14-15/12/2018.

Specifications

The FPP is compendia. The manufacturer controls the quality of the finished product as per USP standards and ICH requirements. The parameters monitored during quality control are: description, identification, pH, average fill volume, particulate matter, light absorption, clarity of solution, related substances, ethanol content, limit of degradation product, assay, bacterial endotoxins, and sterility. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on 3(three) batches of the finished product stored at 30 ± 2°C & RH: 75 ± 5% RH for 24 months and 40± 2°C & RH: 75% ± 5% RH for 6 months. Based on the stability data presented, the approved shelf-life is 24 months when stored in 50 mL Clear Glass Vial USP Type I, containing Clear colorless to slightly yellow viscous sterile, non-aqueous solution, stoppered with 20 mm Bromo Butyl Rubber Plug and sealed with 20 mm Aluminium Flip off Seal having white colour with storage condition ‘Do not store above 30°C". Keep the vial in the outer carton, in order to protect from light’

After reconstitution, the Paclitaxel injection is demonstrated through in-use stability study physically and chemically stable for 24 hours when store at temperature between 2°C-8°C.

Safety and efficacy information

ADPAXIL Injection is a parenteral formulation and therefore fulfils the exemption mentioned in the part III: guidelines on therapeutic equivalence requirements, which states that a bioequivalence study is not required if the solutions for injection that contain the same active ingredients and excipients in the same concentrations as currently registered products and which are administered by the same route(s). The quantitative composition of ADPAXIL Injection is entirely the same as the reference products in the market. 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
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4. Benefit-Risk Assessment and Conclusion

On basis of the data submitted, the current state of knowledge and compliance to Good Manufacturing Practice, the benefit of the product outweighs the risks associated with its use when used in accordance to the summary of product characteristics. ADPAXIL is recommended for registration.

5. Post-approval updates

Variation applications

Reference number	Date submitted	Change requested	Recommendation	Granting date

Feedback from pharmacovigilance, post marketing surveillance and enforcement activities

Type of feedback	Impact	Response

Re-registration applications

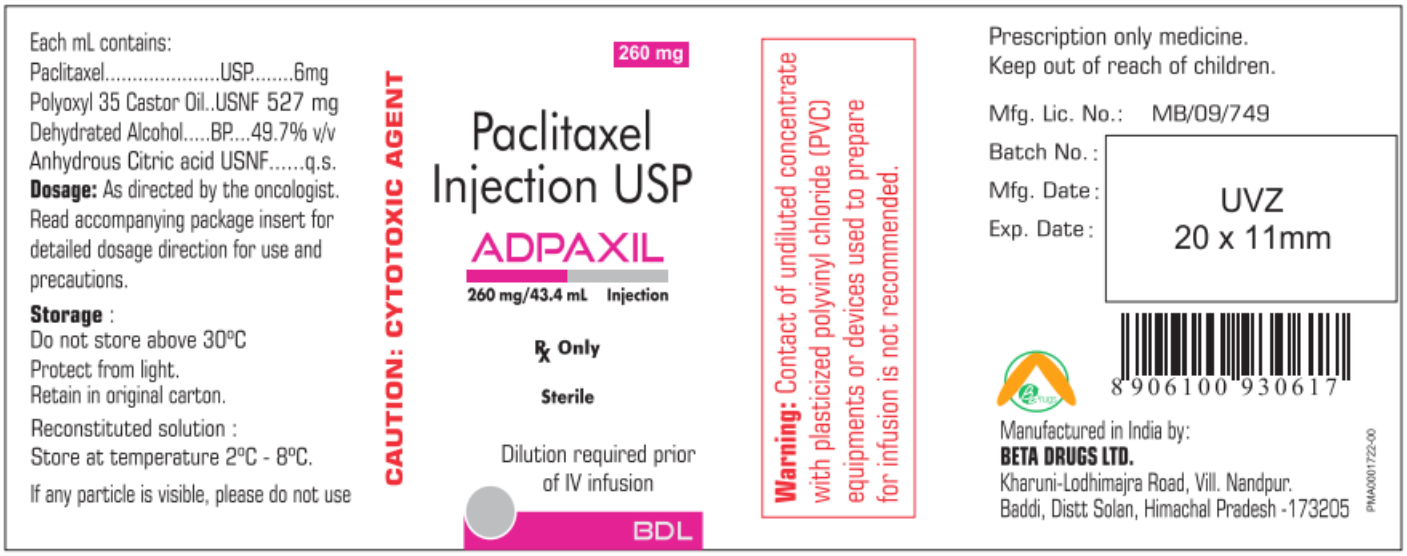
Application for renewal of registration was submitted on <DDMMYYYY>. The application was finalized in <number> rounds of evaluation. The product was confirmed to still be compliant to the standards of quality, safety and efficacy, hence registration was renewed on <DDMMYYYY>.

PART 5: CHANGE HISTORY

Version number	**Date**	**Description of update**	**Section(s) Modified**	**Approval date**

Annex I: Mock up labels;

Primary pack label;



Secondary pack label:

53 x 53 x 86mm

260 mg

Paclitaxel Injection USP

ADPAXIL

260 mg/43.4 mL Injection

℞ Only

Sterile

Dilution required prior of IV infusion

BDL

Each mL contains:
Paclitaxel.....USP.....6mg
Polyoxyl 35 Castor Oil...USNF 527 mg
Dehydrated Alcohol.....BP....49.7% v/v
Anhydrous Citric acid USNF.....q.s.

Dosage: As directed by the oncologist. Read accompanying package insert for detailed dosage direction for use and precautions.

Storage :
Do not store above 30°C
Protect from light.
Retain in original carton.

Reconstituted solution :
Store at temperature 2°C - 8°C.
If any particle is visible, please do not use

CAUTION: CYTOTOXIC AGENT

Warning: Contact of undiluted concentrate with plasticized polyvinyl chloride (PVC) equipments or devices used to prepare for infusion is not recommended.

260 mg

Paclitaxel Injection USP

ADPAXIL

260 mg/43.4 mL Injection

℞ Only

Sterile

Dilution required prior of IV infusion

BDL

Prescription only medicine.
Keep out of reach of children.

Mfg. Lic. No.: MB/09/749

Batch No. :

Mfg. Date :

Exp. Date :

8 906100 930617

Manufactured in India by:
BETA DRUGS LTD.
Kharuni-Lodhimajra Road, Vill. Nandpur,
Baddi, Distt Solan, Himachal Pradesh -173205

Effective date: 03/10/2022