TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR ARTEFAN 80/480 (ARTEMETHER 80 MG AND LUMEFANTRINE 480 MG) TABLETS

Version number 1.0
14 April, 2022

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1. Introduction

Artefan 80/480 is a generic medicine of innovator product Coartem® (Novartis Pharma, Switzerland). Artefan 80/480 contains a fixed combination of artemether and lumefantrine in the ratio of 1:6, which acts as an antimalarial against schizonts. Artemether is a semisynthetic chiral acetal derivative of artemisinin isolated from the plant Artemisia annua. Lumefantrine is a racemic mixture of a synthetic fluorene derivative. Like other antimalarials (quinine, mefloquine, halofantrine), lumefantrine belongs to the aryl-amino-alcohol family. Artefan 80/480 is approved in Tanzania for use in children who weigh between 25 kg to less than 35 kg.

1.1 Product details

Registration number	TAN 22 HM 0119
Brand name	Artefan 80/480
Generic name, strength and form	Each uncoated tablet containing 80 mg artemether and 480 mg lumefantrine
ATC classification	Artemisinin and derivatives, combinations (P01BF01)
Distribution category	POM
Country of origin	India
Associated product	Artefan 60/360, Artefan 20/120
Marketing Authorization Holder	Ajanta Pharma Limited, Ajanta House, Charkop, Kandivli (West), Mumbai - 400 067, India. E-Mail: info@ajantapharma.com
Local Technical Representative	Astra Pharma (T) Ltd Plot no-12, Vingunguti Industrial Area, Nyerere Road, opp: Pepsi tanzania Ltd, Dar es Salaam, Tanzania

1.2 Assessment procedure

The application for registration of Artefan 80/480 was submitted on 10 June, 2021. The product underwent abridged assessment. Assessment was completed in 2 (two) rounds of evaluation and the product was registered on 11 April, 2022.

1.3 Information for users

Visual description of the finished product	Yellow coloured, capsule shaped, biconvex, uncoated tablets
Primary packing material	ALU-PVC/PVdC Blister
Secondary packing materials	A printed carton box
Shelf-life and storage condition	36 months, Do not store above 30°C. Store in the original package in order to protect the product from light.
Route of administration	Oral

Therapeutic indications	Indicated for the treatment of uncomplicated malaria due to Plasmodium falciparum in children weighing 25 to less than 35 kg

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: Artefan 80/480

Composition: Each uncoated tablet containing 80 mg artemether and 480 mg lumefantrine

Pack size: 1 x 6 and 30 x 6

Manufacturing details: batch number, manufacturing date and expiry date

Storage conditions: Do not store above 30°C. Store in the original package in order to protect the product from light

Manufacturer address: physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use:

The details of the primary pack include:

Brand name and strength: Artefan 80/480

Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: Ajanta Pharma Limited

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 Ingredient(s)

Information on quality of the APIs was submitted in form of DMFs.

Artemether

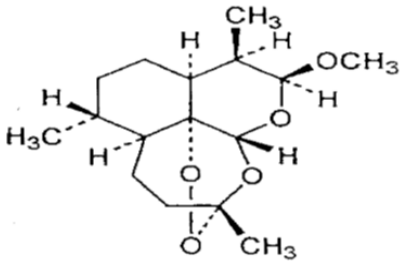
General Information

Artemether API is compendia in International Pharmacopeia.

Molecular formula: $C_{16}H_{26}O_5$

Chemical name:
(3R, 5aS, 6R, 8aS, 9R, 10S, 12R, 12aR)-Decahydro-10-methoxy-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2 benzodioxepin.

Structure:



General properties

Artemether is a white crystals or white crystalline powder. Artemether is practically insoluble in water; very soluble in dichloromethane and acetone; freely soluble in ethyl acetate and in dehydrated ethanol. Although Artemether is known to exhibit polymorphism based on literature data, the polymeric form produced by the proposed manufacturer is consistent.

Artemether is a BCS low soluble API in the BCS classification system. Appropriate limits have been included in the active substance specifications to monitor the particle size and size distribution.

Manufacture

Artemether API manufacturer is Mangalam Drugs and Organics Limited, Unit 1, Plot No 187, 2nd Phase GIDC, Vapi, Gujarat, 396195, India, and Mangalam Drugs and Organics Limited, Unit 2, Plot No 1203, 3rd Phase GIDC, Vapi, Valsad, Gujarat, 396195, India.The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by Gujarat Food and Drug Control Administration. Artemether 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 Artemether is compendia, specifications were set as per International Pharmacopeia standards and ICH guidelines. The parameters monitored during quality control are: Description, solubility, identification, specific rotation, melting range, loss on drying, sulphated ash, related substances, assay, particle size, and residual solvents. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The shelf-life period of Artemether API is 24 months when packed in LDPE bag, followed by a black LDPE bag. These are further placed in a HDPE drum with storage condition 'Store below 25°C in well closed, light resistant containers.

Lumefantrine:

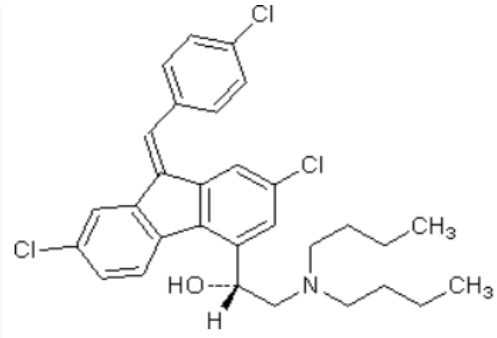
General Information

Lumefantrine API is compendia in International Pharmacopeia, BP and Ph. Eur.

Molecular formula: $C_{30}H_{32}Cl_3NO$

Chemical name:
(1RS)-2-(dibutylamino)-1-{(9Z)-2,7-dichloro-9-[(4-chlorophenyl) methylidene]-9H-fluoren-4-yl} ethanol

Structure:



General properties

Lumefantrine is a yellow crystalline powder. Lumefantrine is practically insoluble in water, freely soluble in ethyl acetate, slightly soluble in ethanol, soluble in Ethanol. Although Lumefantrine is known to exhibit polymorphism based on literature data, the polymeric form produced by the proposed manufacturers is consistent. Lumefantrine is critically insoluble (of BCS low solubility across the physiological pH range), hence particle size distribution (PSD) is considered critical parameter and form part of the FPP manufacturer's API specification.

Manufacture

Lumefantrine API manufacturers are Mangalam Drugs and Organics Limited, Unit 1, Plot No 187, 2nd Phase GIDC, Vapi, Gujarat, 396195, India, and Mangalam Drugs and Organics Limited, Unit 2, Plot No 1203, 3rd Phase GIDC, Vapi, Valsad, Gujarat, 396195, India.The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by Gujarat Food and Drug Control Administration. Lumefantrine 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 Lumefantrine is compendia, specifications were set as per International Pharmacopeia standards and ICH guidelines. The parameters monitored during quality control are: Description, solubility, identification, melting range, residue on ignition, heavy metal, loss on drying, related substances, assay, particle size, and residual solvents. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The shelf-life period of Lumefantrine API is 60 months when packed in transparent low density polyethylene (LDPE) bag followed by black low density polyethylene (LDPE) bag. It is then placed in HDPE drums with storage condition 'Store below 30°C in well closed, light resistant containers'.

Quality of the Finished Pharmaceutical Product

Formulation

Artefan 80/480 is a yellow coloured, capsule shaped, biconvex, uncoated tablets

Artefan 80/480 contains the API Artemether and Lumefantrine and other ingredients listed here after: microcrystalline cellulose, crospovidone, sodium lauryl sulfate, colloidal silicon dioxide, purified talc and magnesium stearate. 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 Ajanta Pharma Limited, Plot No. Z-103/A, Dahej SEZ Part II, Ajanta Pharma Limited, District Bharuch, Gujarat State, 392130, India. The compliance of the sites to TMDA GMP standards was confirmed through site inspection on 11 August, 2017.

Specifications

The FPP is compendia in International Ph. The manufacturer controls the quality of the finished product as per in-house standards and ICH requirements. The parameters monitored during quality control are: description, identification of the APIs (HPLC and TLC), average and uniformity of weight, resistance to crush, water content, uniformity of content, dissolution, related substances, assay (HPLC) and microbiological purity. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on a 1(one) batch 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 with updated post-acceptance stability protocol and stability commitment to place the first production-scale batch of the FPP produced at the new site, into the long-term stability program. Based on the stability data presented, the approved shelf-life is 36 months when stored in ALU-PVC/PVdC Blister with storage conditions 'Do not store above 30°C. Store in the original package in order to protect the product from light'.

Safety and efficacy information

The current application was intended for an additional manufacturing and batch control testing site for Artefan 80/480 tablets to meet market demands, as this application meet all conditions stipulated in the TMDA guidelines on variations on registered medicinal products hence there is no requirement for a bioequivalence study.

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. Artefan 80/480 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

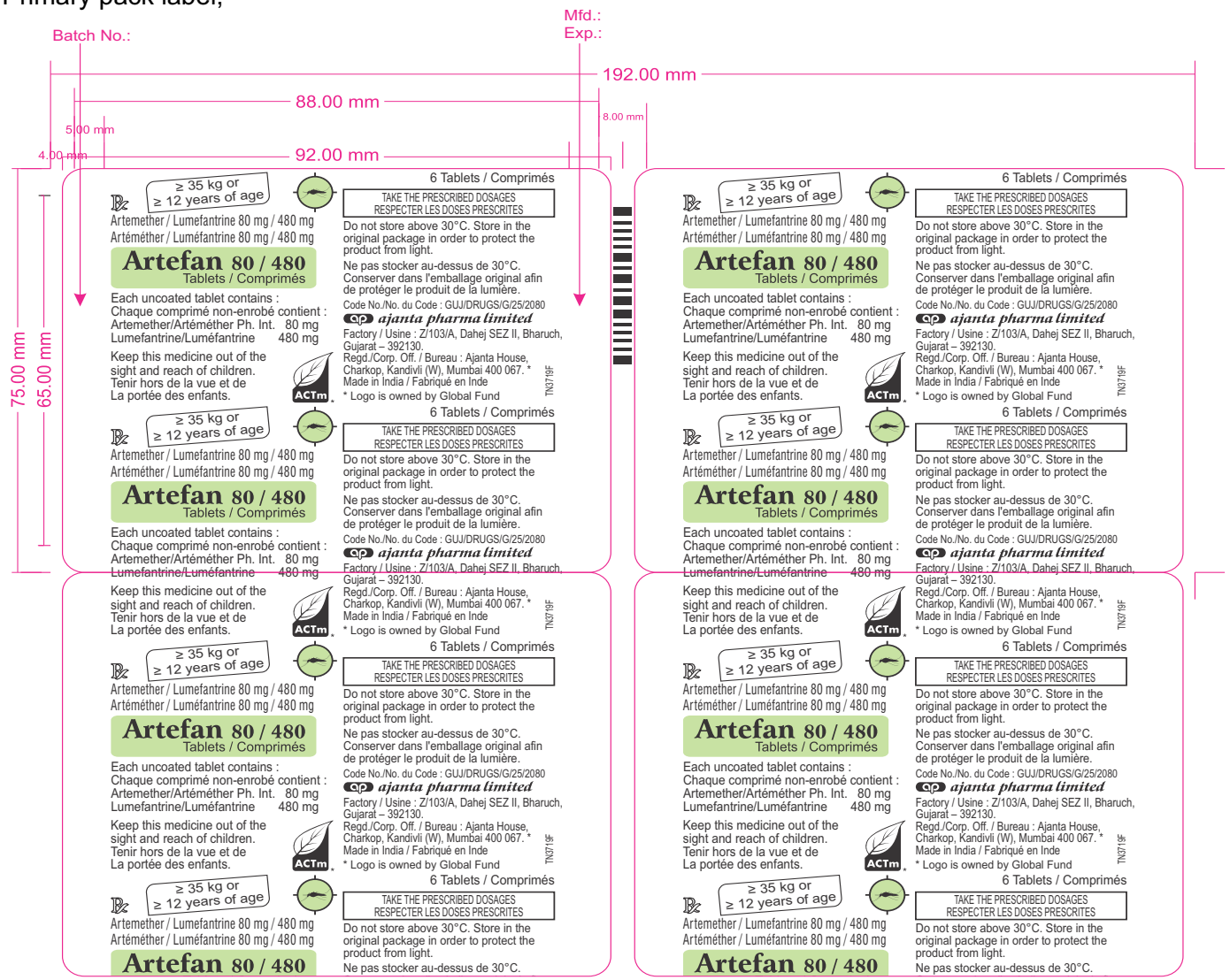
NA

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;

8 901111 050040

Artefan 80 / 480

TN4645C

Actual Size : 285 x 97 x 80 mm

Pharma Code : 100000 Standard

Direction for Travel

Date	: 14.12.2021
Artist	: Ganesh
Product	: Artefan 80/480
Actual Size	: 285 x 97 x 80 mm
Ref artwork	: TN3727C
Colour	: Pantone 3415 C, Pantone 7486 C, Pantone 355 C, Pantone 390 C, Pantone 2748 C, Pantone 185 C, Black
Country	: Kenya & Uganda

≥ 35 kg or
≥ 12 years of age

ACTm*

℞

Artemether / Lumefantrine 80 mg / 480 mg Tablets

Artéméther / Luméfantrine 80 mg / 480 mg Comprimés

Artefan 80 / 480

30 X 6 Tablets / Comprimés

ajanta

COMPOSITION :
Each uncoated tablet contains :

Artemether Ph. Int.	80 mg
Lumefantrine	480 mg

DOSAGE, INDICATION, ADMINISTRATION, CONTRAINDICATION :
Refer to enclosed Patient information leaflet.

Do not store above 30°C. Store in the original package in order to protect the product from light.

CAUTION : KEEP THIS MEDICINE OUT OF THE SIGHT AND REACH OF CHILDREN.

READ THE LEAFLET CAREFULLY BEFORE USE.

FORMULE :
Chaque comprimé non-enrobé contient :

Artéméther Ph. Int.	80 mg
Luméfantrine	480 mg

POSOLOGIE, INDICATION, MODE D'EMPLOI, CONTRE-INDICATION :
Se reporter à la notice jointe

Ne pas stocker au-dessus de 30°C. Conserver dans l'emballage original afin de protéger le produit de la lumière.

PRECAUTION : TENIR HORS DE LA VUE ET DE LA PORTÉE DES ENFANTS.

VEUILLEZ LIRE LES INDICATIONS SOIGNEUSEMENT AVANT L'UTILISATION.

≥ 35 kg or
≥ 12 years of age

ACTm*

℞

Artemether / Lumefantrine 80 mg / 480 mg Tablets

Artéméther / Luméfantrine 80 mg / 480 mg Comprimés

Artefan 80 / 480

30 X 6 Tablets / Comprimés

ajanta

Code No./No. du Code :
GUJ/DRUGS/G/25/2080
Tanzania :

TAKE THE PRESCRIBED DOSAGES
RESPECTER LES DOSES PRESCRITES

PRESCRIPTION USE ONLY
UNIQUEMENT SUR ORDONNANCE

ajanta pharma limited
Factory / Usine : Z/103/A, Dahej SEZ II, Bharuch, Gujarat-392130.
Regd./Corp. Off. / Bureau: Ajanta House, Charkop,Kandivli (W), Mumbai 400 067. *
Made in India / Fabriqué en Inde

*Logo is owned by Global Fund

OPZ Area
50 x 34 mm