THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR ARTESIANE® 100 (ARTEMETHER 100MG/ML) SOLUTION FOR INJECTION

Version number 01, 06/01/2023

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1. Introduction

ARTESIANE® 100 is an antimalarial drug of the artemisinin family. The antimalarial activity of Artemether and its active metabolite dihydroartemisinin (DHA) has been attributed to endoperoxide moiety. The presence of the endoperoxide bridge (generating singlet oxygen and free radicals) appears to be essential for the antimalarial activity. ARTESIANE® 100 is approved in Tanzania for use in children and adult patients.

1.1 Product details

Registration number	TAN 22 HM 0137
Brand name	ARTESIANE® 100
Generic name, strength and form	Each ampoule (1 ml) contains 100 mg artemether
ATC classification	ATC code: P01BE02- Antimalarials, Artemisinin and derivatives, plain.
Distribution category	POM
Country of origin	India
Associated product	ARTESIANE® 80, ARTESIANE® 300, and ARTESIANE® 20
Marketing Authorization Holder	Dafra Pharma GmbH Muhlenberg 7, 4052 Basel Switzerland E-mail: regulatory@defra.be
Local Technical Representative	Harleys (T) Limited, P.O. Box 12589, Dar es Salaam. Email: tahir.muhammad@harleysltd.com

1.2 Assessment procedure

The application for registration of ARTESIANE® 100 was submitted on 23 November, 2020. The product underwent full assessment. Assessment was completed in 2 (two) rounds of evaluation and the product was registered on 20/08/2021.

1.3 Information for users

Visual description of the finished product	Clear, colourless to slightly yellow oily solution
Primary packing material	Ph. Eur. Type I glass ampoule
Secondary packing materials	A printed carton box
Shelf-life and storage condition	36 months, Store below 30º C, in the original packaging protect from light
Route of administration	Intramuscular injection
Therapeutic indications	Artesiane is indicated for the treatment of malaria in children and in adults caused by all species of Plasmodium, including severe malaria caused by multiple drug resistant strains of Plasmodium falciparum.

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: ARTESIANE® 100

Composition: Each ampoule (1 ml) contains 100 mg Artemether, fractionated coconut oil

Pack size: 5 Ampoules

Manufacturing details: batch number, manufacturing date and expiry date

Storage conditions: Store below 30º C, in the original packaging protect from light.

Manufacturer address: physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: Strictly follow the prescribed doses.

The details of the primary pack include:

Brand name and strength: ARTESIANE® 100 (Artemether 100 mg/mL)

Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: Anfarm Hella S.A

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 API was submitted in form of WHO Prequalification proof.

Site No. 1: Mangalam Drugs and Organics Ltd. Unit-2

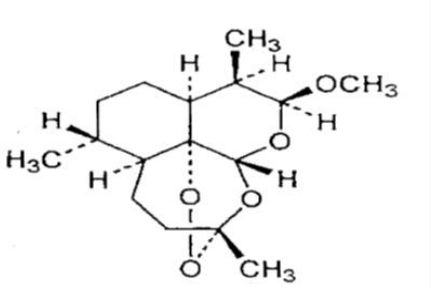
General Information

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. Nonetheless, the active is present in the drug product dissolved in fractionated coconut oil, hence the polymorphic form and particle size distribution are not considered as critical quality aspects.

Manufacture

Artemether API manufacturer is Mangalam Drugs and Organics Ltd., Block 2A, 2B and 2C; Unit-2, Plot No. 1203, 3rd Phase, GIDC, Vapi, 396 195, Gujarat, India.The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by Food and Drug Control Administration, Gujarat, India. 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: Appearance, solubility, identification (by IR, TLC, and colour tests), specific rotation, melting range, loss on drying, sulphated ash, related substances (HPLC), assay (HPLC), particle size, residual solvents (GC), bacterial endotoxins, and bioburden. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system
The re-test period of Artemether API is 24 months when packed in tied double PE bags inner white -outer black, placed in HDPE drum with storage condition 'Do not store above 25°C'.

Site No. 2: IPCA Laboratories Ltd

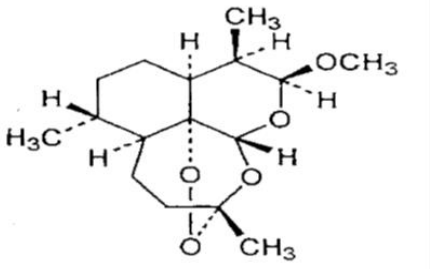
General Information

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. Nonetheless, the active is present in the drug product dissolved in fractionated coconut oil, hence the polymorphic form and particle size distribution are not considered as critical quality aspects.

Manufacture

Artemether API manufacturer is Ipca Laboratories Limited. Block - IBD XII, Sejavta, District Ratlam (Madhya Pradesh), Pin: 457 002, India.The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by Office of the controller Food and

Drugs Administration- Madhya Pradesh. 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 (by IR and TLC), specific rotation, melting range, loss on drying, sulphated ash, heavy metals, related substances (HPLC), assay (HPLC), residual solvents (GC), bacterial endotoxins, and bioburden. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system
The re-test period of Artemether API is 36 months when packed in clear LDPE bag (Nitrogen purging) with storage condition 'Do not store above 25°C'.

Quality of the Finished Pharmaceutical Product

Formulation

ARTESIANE® 100 is a clear, colourless to slightly yellow oily solution.

ARTESIANE® 100 contains the API Artemether and other ingredients listed here after: Fractionated coconut oil and Nitrogen 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 Anfarm Hellas S.A., 61st km. Nat. Rd. Athens, Lamia, Schimatari Viotias, 32009, Greece. Current the compliance of the site to TMDA GMP standards was not confirmed but the applicant has already applied for inspection and is on waiting list for inspection.

Specifications

The FPP is compendia in International Ph. The manufacturer controls the quality of the finished product as per International Ph. and in-house standards and ICH requirements. The parameters monitored during quality control are: Appearance, Colour, Identification, Particulate contamination ((visible and sub-visible), Extractable volume, Related substances, Assay, Bacterial endotoxins, Sterility. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on a 3 (three) batches of the finished product stored at 30 ± 2°C & RH: 65 ± 5% RH for 36 months and 40± 2°C & RH: 75% ± 5% RH for 6 months. Based on the stability data presented, the approved shelf-life is 36 months when stored in type I glass ampoule with storage condition 'Store below 30º C, in the original packaging protect from light'.

Safety and efficacy information

The applicant submitted one published ethically supportable comparative pharmacokinetic study was performed in 2004 between Artesiane® 80 (Dafra Pharma, Artemether in miglyol oil (fractionated coconut oil)) against Paluether ® 80 (Sanofi, Artemether in arachis oil) (Penali; L.K., 2004). The study was performed on 23 patients, suffering from non-complicated malaria. The plasma levels of Artemether and its principal metabolite dihydroartemisinin were determined by LC-MS. Summarizing, in this trial no differences were observed between the two formulations.

According to Part III of the compendium: Guidelines on Therapeutic Equivalence Requirements, bioequivalence studies are generally not required if the test product is to be administered parenterally (e.g. intravenously, subcutaneously or intramuscularly) as a parenteral oily solution containing the same active substance as the currently registered product, but, in this case, the use of the same oily vehicle is essential. Both products, generic product Artesiane® 100 and the innovator product Paluether ® 80 of the same active substance, Artemether, but different oily vehicle, however from above study it was found although the carrier oil in which the Artemether is dissolved for both products is different, miglyol oil (fractionated coconut oil)), arachis oil, no difference in plasma levels of Artemether were detected. Therefore, it is concluded that there is no difference between the Artesiane® 100 and Paluether ® 80. A bioequivalence study is not required.

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. ARTESIANE® 100 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;

Effective date: 03/10/2022