TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR GLUMAC® (ARTEMETHER 20MG AND LUMEFANTRINE 120MG) TABLETS

Version number 01

March, 2022

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1. Introduction

Glumac is a generic medicine of Coartem. Glumac is an antimalarial medicine belonging to **P01BF01** antiparasitic products, insecticides and repellents, Antiprotozoal, Antimalarials Artemisinin and derivatives, combinations group. Glumac contains a fixed combination of 2 antimalarial active ingredients, artemether, an artemisinin derivative, and lumefantrine. Both components are blood schizontocides. Glumac is approved in Tanzania for use in adults, children and elderly.

1.1 Product details

Registration number	TAN 21 HM 0166
Brand name	Glumac
Generic name, strength and form	Artemether 20mg and Lumefantrine 120mg
ATC classification	**P01BF01 -** antiparasitic products, insecticides and repellents, Antiprotozoal, Antimalarials Artemisinin and derivatives, combinations
Distribution category	POM
Country of origin	China
Associated product	Not Applicable
Marketing Authorization Holder	Shanghai Fosun Pharmaceutical Development Co., Ltd. Room 350, No. 25 Kangshi road, Kangqiao town, Pudong New District (Kangqiao), Shanghai China.
Local Technical Representative	Tridem Pharma Tanzania Limited

1.2 Assessment procedure

The application for registration of Glumac was submitted on 26/07/2020. The product underwent abridged assessment. Assessment was completed in four rounds of evaluation. Glumac was registered on 29/03/2021.

1.3 Information for users

Visual description of the finished product	Yellow capsule-shaped tablet, debossed with a score line on one side
Primary packaging material	Polyvinyl Chloride (PVC)/ Polyvinyl Dichloride (PVDC) and Aluminum foil, heat-sealed
Secondary packaging materials	Carton box alongside with a package insert 640boxes/carton 20 blisters/box, 70boxes/carton
Shelf-life and storage condition	24 months Do not store above 30℃, store in the original package in order to protect from moisture
Route of administration	Oral
Therapeutic indications	Used for the treatment of acute uncomplicated

	malaria infections caused by a parasite called “Plasmodium falciparum”. This parasite is a tiny organism made-up of one cell that is found inside red blood cells.

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 prescription only medicine the package insert contains both full prescribing information as per SmPC and simplified information for patients.

Container labels
The product label information is presented in English. Details in the secondary pack label include:
Brand name: Glumac
Composition: Artemether 20 mg and Lumefantrine 120 mg and the following excipients:

1. Microcrystalline Cellulose PH102 (USP)
2. Polysorbate 80 (USP)
3. Hypromellose E6 (USP)
4. Croscarmellose sodium (USP)
5. Colloidal Silicon Dioxide (USP)
6. Talc (USP)
7. Magnesium Stearate (USP)
8. Purified water (removable) (Ph. Int. & Ch. P & USP & In-house)

Pack size: 1 x 6 tablets/blister and 2 x 6 tablets/blister

Manufacturing details: TMDA registration number

Storage conditions: Do not store above 30℃, store in the original package in order to protect from moisture

Manufacturer address: Guilin Pharmaceutical Co., Ltd, No. 43 Qilidian Road, China

Unique identifier: TMDA registration number
Special warnings/precautions or instructions for use: Not Applicable

The details of the primary pack include:
Brand name and strength: Glumac 20 mg/120 mg
Name of manufacturer: Guilin Pharmaceutical Co., 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

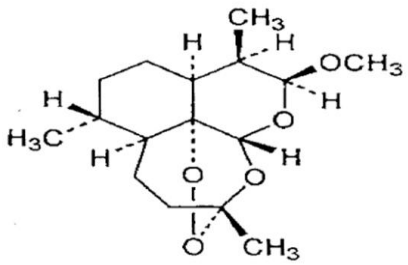
3. Scientific discussion

Quality of Active Pharmaceutical Ingredient(s)

1. Artemether

Information on quality of the API was submitted in form of proof of WHO prequalification and corresponding requirements as per Compendia.

General properties
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:



Critical physico-chemical properties of the API:
Artemether manufactured by Mangalam drugs and organics limited shows two crystal form A and B of which polymorph form was confirmed by manufacturer.

The API is practically insoluble in water thus, particle size is of critical concern, FPP manufacturer included test and limit for control of particles size has been included in the API specification

Manufacture
The API manufacturing site, Mangalam Drugs and Organics Ltd (Site 1: Unit-1, Plot No.187, 2nd Phase, G.I.D.C., Vapi Gujarat, 396195 and Site 2: Plant 2A, 2B and 2C, Unit 2 Plot No.: 1203, 3rd Phase, G.I.D.C, Gujarat 396195, India was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by Drugs Control Administration (DCA), Gujarat. 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 API specifications were set as per International Pharmacopeia standards, ICHQ3C and ICHQ3A. The parameters monitored during quality control are: description, melting point, specific rotation, identification, and sulphated ash, loss on drying, related substances, particle size distribution, residual solvents, assay and microbial limit. 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 colorless, virgin food grade, transparent LDPE bags, tied with plastic strip and second packing black LDPE bag in HDPE container and stored at or below 25℃ in well closed, light resistance containers.

2. Lumefantrine

Information on quality of the API was submitted in form of proof of WHO prequalification and corresponding requirements as per Compendia.

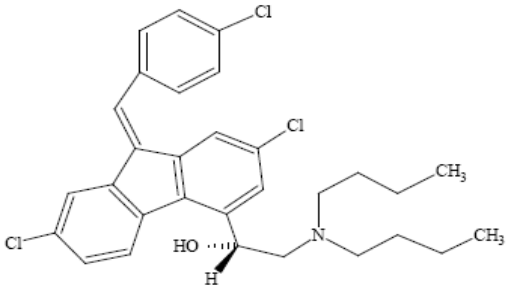
General properties

Artemether API is compendia in International Pharmacopeia

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 (Racemate)

Structure:



Critical physico-chemical properties of the API:

Artemether manufactured by Mangalam drugs and organics limited shows a single crystal form-I of which polymorph which was confirmed by manufacturer using pXRD studies.

Lumefantrine occurs as a yellow crystalline powder with a good solubility in chloroform, toluene, methylene dichloride, ethyl acetate and acetone. Lumefantrine is insoluble in water. The solubility profile of the API in various physiological pH was provided. The API is insoluble in water thus, particle size was of critical concern, FPP manufacturer included test and limit for control of particles size in the API specification.

Manufacture

The API manufacturing site, Mangalam Drugs and Organics Ltd (Site 1: Unit-1, Plot No.187, 2nd Phase, G.I.D.C., Vapi Gujarat, 396195 and Site 2: Plant 2A, 2B and 2C, Unit 2 Plot No.: 1203, 3rd Phase, G.I.D.C, Gujarat 396195, India was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by Drugs Control Administration (DCA), Gujarat.

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 API specifications were set as per International Pharmacopeia standards, ICHQ3C and ICHQ3A. The parameters monitored during quality control are: description, melting point, specific rotation, identification, and sulphated ash, loss on drying, related substances, particle

size distribution, residual solvents, assay and microbial limit. 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 two LDPE bags; Primary is white& secondary is black, followed by HDPE drum and stored at or below 30℃ in well closed, light resistance containers.

Quality of the Finished Pharmaceutical Product

Formulation
Glumac is yellow capsule-shaped tablet, debossed with a score line on one side packed in Polyvinyl Chloride (PVC)/ Polyvinyl Dichloride (PVDC) and Aluminum foil, heat-sealed. Glumac contains Artemether/Lumefantrine 80mg/480mg and other ingredients listed here after:

1. Microcrystalline Cellulose PH102 (USP)
2. Polysorbate 80 (USP)
3. Hypromellose E6 (USP)
4. Croscarmellose sodium (USP)
5. Colloidal Silicon Dioxide (USP)
6. Talc (USP)
7. Magnesium Stearate (USP)
8. Purified water (removable) (Ph. Int. & Ch. P & USP & In-house)

The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, Edition 9 in terms of function and quantities.

Manufacture
The finished product was manufactured at Guilin Pharmaceutical Co., Ltd of No. 43 Qilidian Road, Guilin Pharmaceutical, Co., Ltd, China. The compliance of the site to TMDA GMP standards was confirmed through site inspection on 04/06/2020.

Specifications
The FPP is International Pharmacopeia. The manufacturer controls the quality of the finished product as per International Ph/in-house and ICHQ6A requirements. The parameters monitored during quality control are: description, identification, and average tablet weight, friability, content uniformity, and dissolution, loss on drying, related substances, microbial limit and assay. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system
Stability studies were conducted on three batches of the finished product stored at 30±2°C/75± 5% RH for 6 months and 40±2°C/75±5% RH for 24 months. Based on the stability data presented, the approved shelf-life is 24 months when stored in PVC-PVDC- AL blister as the primary package and paper box as the secondary package not store above 30℃, store in the original package in order to protect from moisture.

Safety and efficacy information

The application underwent an abridged review therefore the data under this section were not assessed.

4. Benefit-Risk Assessment and Conclusion

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

5. Post-approval updates

Variation applications

NA

Feedback from pharmacovigilance, post marketing surveillance and enforcement activities

NA

Re-registration applications

NA

PART 5: CHANGE HISTORY

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

Annex I: Mock up label