TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR LAMITAR AM (ARTEMETHER 20 MG + LUMEFANTRINE 120 MG) FILM COATED TABLETS

Version number 01

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1. Introduction

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

1.1 Product details

Registration number	TAN 21 HM 0122
Brand name	Lamitar AM
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	India
Associated product	Not Applicable
Marketing Authorization Holder	**Ind-Swift Limited** Off. NH-21, Village Jawaharpur, Tehsil Derabassi, Distt. SAS Nagar (Mohali), Punjab 140507 **India.**
Local Technical Representative	**Planet Pharmaceutical Ltd** P.O. Box 38328, House No. 23, Plot No. 20, Kipata/Nyamwezi Street, Kariakoo, **Dar es salaam.**

1.2 Assessment procedure

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

1.3 Information for users

Visual description of the finished product	Yellow colored, round shaped, flat, bevelled edged uncoated tablets with one side plain and break line on other side
Primary packaging material	Alu-Alu Blister/8 tablets
Secondary packaging materials	Carton box alongside with a package insert
Shelf-life and storage condition	36 months Store below 30°C. 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 POM 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: Lamitar AM
Composition: Artemether 20 mg and Lumefantrine 120 mg and the following excipients:

1. Microcrystalline Cellulose
2. Croscarmellose Sodium
3. Hypromellose
4. Polysorbate 80
5. Colloidal Silicon Dioxide
6. Magnesium Stearate

Pack size:
Primary packaging

Alu-Alu Blister/8 tablets

Secondary packaging

Carton box alongside with a package insert

Manufacturing details: Space for printing batch number, manufacturing date, expiry date

Storage conditions: Store below 30°C. Protect from moisture.
Manufacturer address: Ind-Swift Limited, Off. NH-21, Village Jawaharpur,Tehsil Derabassi, Distt. SAS Nagar (Mohali), Punjab 140507, India

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

The details of the primary pack include:
Brand name and strength: Lamitar AM 20 mg/120 mg
Manufacturing details: batch number, manufacturing date, expiry date
Name of manufacturer: Ind-Swift Limited, Off. NH-21, Village Jawaharpur, Tehsil Derabassi, Distt. SAS Nagar (Mohali), Punjab 140507, India.

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

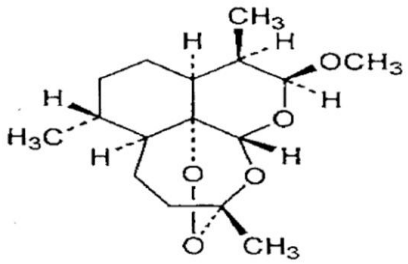
Quality of Active Pharmaceutical Ingredient(s)

1. Artemether

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

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

The structure of Artemether as provided in module 3 has been checked and confirmed to be in line with the structure available in international pharmacopoeia monograph. The molecule is a derivative of artemisinin containing a core structure of 1-oxacyloalkan-2-one. Upon theoretical examination of the structure of the molecule it was observed that, the molecule possesses 8 defined atom stereocenter count of which 7 stereogenic center were primarily present in the natural isolate “Artemisinin” and 1 was formed after synthetic conversion of carbonyl carbon of the parent molecule to ether bond. The presence of 8 chiral centers makes the molecule to occur in 256 possible stereoisomers with 1*R*, 4S, 5R, 8S, 9R, 10S, 12R, 13R absolute configuration and positive optical rotation. Since the molecule occurs as a set of stereoisomers to be sure that, manufacturer of API produce isomer with therapeutic value specific optical rotation and control of alpha-isomer were included in the API specifications.

Manufacture
The API manufacturing site, Vital Laboratories Pvt Ltd, Plant 1, Plot No 1416-21, 1507 1&2, 1601, GIDC Estate, Phase III, Vapi-396195, Gujarat, 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: descriptions, solubility, Identification by HPLC, related substances by HPLC, loss on drying, Assay, specific optical rotation, melting point, sulphated ash, foreign particles, aflotoxin and pesticides residuals. Compliance to these specifications were established via batch analysis data and stability studies.

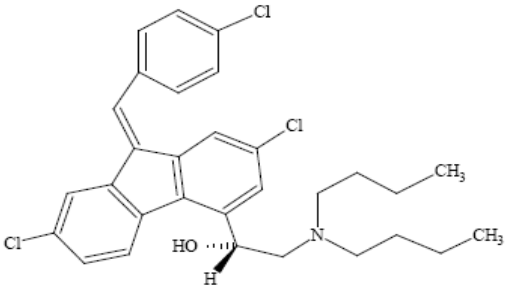
Stability and container closure system
The re-test period of Artemether API is 48 months when packed in Double Polyethylene bags enclosed in fiber drum container and stored at below 25℃ in well closed, light resistance containers.

2. Lumefantrine

Information on quality of the API was submitted in form of WHO Prequalification proof.

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

The physicochemical properties of the Drug substance Lumefantrine were provided and it has been reported that the molecule occurs as a pale yellow to yellow crystalline powder that is practically insoluble in water, Soluble in Methylene dichloride, very slightly soluble in methanol

Manufacture
The API manufacturing site, Vital Laboratories Pvt Ltd, Plant 1, Plot No 1416-21, 1507 1&2, 1601, GIDC Estate, Phase III, Vapi-396195, Gujarat, India was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by Drugs Control Administration (DCA), Gujarat. Lumefatrine 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 and in line with the ICQ3A and ICHQ3C. The parameters monitored during quality control are; descriptions, solubility, Identification, related substance, loss on drying, Assay, water by KF and absorbance. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system
The re-test period of Lumefantrine API is 60 months when packed in Double Polyethylene bags enclosed in fiber drum container and stored at below 25℃ in well closed, light resistance containers.

Quality of the Finished Pharmaceutical Product

Formulation
Lamitar AM is a yellow colored, round shaped, flat, bevelled edged uncoated tablets with one side plain and break line on other side. Lamitar AM contains Artemether/Lumefantrine 20mg/120mg and other ingredients listed here after:

1. Microcrystalline Cellulose
2. Croscarmellose Sodium
3. Hypromellose
4. Polysorbate 80
5. Colloidal Silicon Dioxide
6. Magnesium Stearate

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 Ind-Swift Limited, Off. NH-21, Village Jawaharpur,Tehsil Derabassi, Distt. SAS Nagar (Mohali), Punjab 140507, India. The compliance of the site to TMDA GMP standards was confirmed through site inspection on 12/06/2017.

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 Diameter, Thickness, Average mass, Uniformity of Mass, friability, Resistance to crushing of tablets, Water Content (By Karl Fischer), Uniformity of Dosage Units by Content Uniformity (For Artemether), Uniformity of Dosage Units by Mass Variation (For Lumefantrine), Dissolution test 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 36 months when stored in Alu-Alu Blister as the primary

package and Carton box alongside with a package insert as the secondary package not store above 30℃, store in the original package in order to protect from moisture.

Safety and efficacy information

Safety and efficacy of Lamitar AM was established through bioequivalence trial.

BE report number OS/LUAR/01-13/05 was submitted.

Study title	A randomized, single dose, open label, bioequivalence study of the fixed dose combination (FDC) LAMITAR AM Tablets x4 (containing 20mg Artemether and 120mg Lumefantrine) of Ind-swift Lmited, India with the fixed dose combination (FDC) Coartem Tablets x4 (containing 20mg Artemether and 120mg Lumefantrine) manufactured by Norvatis Pharmaceuticals Corporation, New York USA for Norvatis Pharma AG, Basel, Switzerland in Normal Healthy Human Subjects under fasting condition	
Study design	The study design was an open label, two treatments, two-period, two sequences, single dose, crossover comparative bioequivalence study in healthy adult human male subjects under fasting conditions.	
Study site	Om Sai Clinical Research Pvt, Ltd. C.S.T. No. 379/1-6, Kamal Chowki Peth Bhag, Sangli-416416, Maharashtra, India.	
Study dates	Period I: 21/02/2013 to 12/04/2013	
Primary objective	To demonstrate the therapeutic equivalence of the test product; LAMITAR AM Tablets and the reference product; Coartem Tablets	
Secondary objective	To establish the pharmacokinetic parameters of the test product; LUMITAR AM	
Number of participants	48 normal health, adult, male human	
Monitored parameters	Cmax, Tmax, AUC and T1/2	
Investigational medicinal products	Test Product	Reference product
	Strength: 20 mg Artemether and 120 mg Lumefantrine Batch number: FG10113 Expiry date: Jan 2015	Strength: 20 mg Artemether and 120 mg Lumefantrine Batch number: F2392 Expiry date: June 2013
Analytical method	LC-MS/MS	
Statistical method	ANOVA by statistical package SAS® statistical software (Version 9.1 or a higher version.	

Efficacy results are summarized as follows:

For Artemether

Parameter	**Test**	**Reference**	**% Ratio of geometric means**	**90 % Confidence interval**	**DF**	**CV (%)**

AUC0-t (units)	605.289	591.019	101.058%	92.00-111.01	47	27-936
AUC0-inf (units)	614.930	601.019	100.85%	92.01-110.54	47	27.249
Cmax (units)	192.92	184.79	103.051%	94.08-112.87	47	27.046

For Lumefantrine

Parameter	**Test**	**Reference**	**% Ratio of geometric means**	**90 % Confidence interval**	**DF**	**CV (%)**
AUC0-t (units)	159.500	159.822	105.089%	94.33 – 117.07	47	32.310
AUC0-inf (units)						
Cmax (units)	5.06	4.79	108.643%	99.19-119.00	47	27.049

The acceptance limits of 80 – 125% are met by the AUC and Cmax values. Furthermore, the safety profile of the test product is similar to that of reference product. Therefore, LUMITAR AM (containing 20mg Artemether and 120mg Lumefantrine) is equivalent and interchangeable with COARTEM of Ind-swift Limited, India and reference product Coartem (containing 20mg Artemether and 120mg Lumefantrine) manufactured by Norvatis Pharmaceuticals Corporation, New York USA for Norvatis Pharma AG, Basel, Switzerland under acceptable in vivo experimental conditions.

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. LUMITAR AM 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