TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR LARIACT 20 MG/120 MG (ARTMETHER 20 MG AND LUMEFANTRINE 120 MG) TABLETS

Version number 1.0
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1. Introduction

Lariact 20 mg/120 mg is a generic medicine of innovator product Coartem® (Novartis Pharma, Switzerland). Lariact 20 mg/120 mg 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. Lariact 20 mg/120 mg is approved in Tanzania for use in adults, children and infants of 5 kg and above.

1.1 Product details

Registration number	TAN 22 HM 0080
Brand name	Lariact 20 mg/ 120 mg
Generic name, strength and form	Each tablet containing 20 mg artemether and 120 mg lumefantrine
ATC classification	Artemisinin and derivatives, combinations (P01BF01)
Distribution category	POM
Country of origin	India
Associated product	Lariact Dispersible, Lariact Forte, Lariact DS, Lariact 180 mg/1080 mg
Marketing Authorization Holder	Abacus Pharma (A) Limited Plot No. 18C, Nyerere Road PO Box 12294, Dar es Salaam.
Local Technical Representative	N/A

1.2 Assessment procedure

The application for registration of Lariact 20 mg/ 120 mg was submitted on 30 December, 2016. The product underwent full assessment. Assessment was completed in 7 (seven) 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, circular, uncoated flat, bevelled edges tablet, having break line on one side and another side plain
Primary packing material	ALU-PVC/PVdC Blister
Secondary packing materials	A printed carton box
Shelf-life and storage condition	24 months, Store in dry place below 30^{o}C, protect from light
Route of administration	Oral
Therapeutic indications	Indicated for the treatment of acute uncomplicated Plasmodium falciparum malaria in adult, children and infants of 5 kg and above. Consideration should be given to official guidance regarding the appropriate use of antimalarial agents.

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: Lariact 20 mg/ 120 mg

Composition: Each tablet containing 20 mg artemether and 120 mg lumefantrine

Pack size: 1 x 6's,1 x 12's, 1 x 18's, 1 x 24's tablets

Manufacturing details: batch number, manufacturing date and expiry date

Storage conditions: Store in dry place below 30^{o}C, protect 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: Lariact 20 mg/120 mg

Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: S Kant Healthcare 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

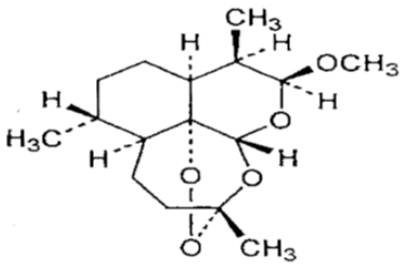
General Information

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 S kant Healthcare Limited, 1802-1805, G.I.D.C. PHASEIII, Vapi -396195, Gujarat, India and Calyx Chemicals & Pharmaceuticals Ltd Plot No-102/91/90, MIDC Industrial Area, Tarapur, Boisar, Maharashtra, 401 506 India.The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by Gujarat Food and Drug Control Administration and Maharashtra Food and Drug 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, bulk density, tap density, particle size, and residual solvents. 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 double polyethylene bag properly sealed with strip and labelled and further kept in HDPE container with storage condition 'Do not store above 30°C. Protect from light and moisture'.

Lumefantrine:

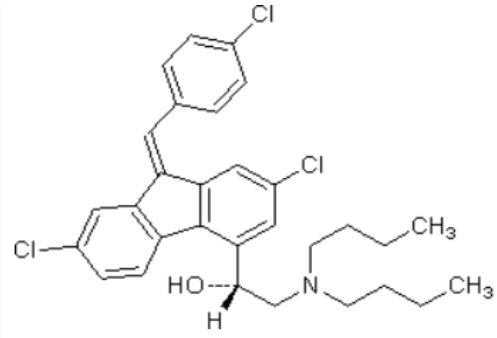
General Information

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 S Kant Healthcare Ltd., Plot No. 1802 To 1805, IIIrd Phase, GIDC, Vapi- 396195, Dist: Valsad, Gujarat, India, Vital laboratories Ltd, Plot No:1416-18 & 1507, IIIrd Phase, GIDC, Vapi-396195, Dist: Valsad, Gujarat, India, and Calyx Chemicals and Pharmaceuticals Ltd.MIDC, Tarapur-401 506, Boisar.The manufacturing complies with GMP requirements as evidenced by the GMP certificates issued by Gujarat Food and Drug Control Administration and Maharashtra Food and Drug 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, heavy metal, loss on drying, sulphated ash, related substances, assay, bulk density, tap density, 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 double polyethylene bag properly sealed with strip and labelled and further kept in HDPE container with storage condition 'Preserve in well closed containers'.

Quality of the Finished Pharmaceutical Product

Formulation

Lariact 20 mg/ 120 mg is a yellow coloured, circular uncoated flat beveled edges tablet, having break line on one side and another side plain.

Lariact 20 mg/ 120 mg contains the API Artemether and Lumefantrine and other ingredients listed here after: microcrystalline cellulose, maize starch, hypromellose e15 (hydroxy propyl methyl cellulose e-15), polysorbate 80, purified water, crospovidone, purified talc, colloidal anhydrous silica, 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 S Kant Healthcare Limited, Plot No. 1802-1805, G.I.D.C. Phase III, VAPI 396 195. Gujarat, India. The compliance of the sites to TMDA GMP standards was confirmed through site inspection on 06 October, 2018.

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, tablet thickness and diameter, friability, hardness, disintegration time, dissolution (HPLC detection), 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 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 36 months when stored in Aluminium-PVDC/PVdC blister pack with storage condition 'Store in a dry place below 30°C.Protect from light'.

Safety and efficacy information

Safety and efficacy of Lariact 20 mg/120 mg was established through a bioequivalence trial.

BE trial report number SKL/AMLT/008/13 was submitted.

Study title	A single-dose, randomized, two-sequence, two-treatment, two-way crossover study to assess bioequivalence of 'Artemether 20 mg and Lumefantrine 120 mg tablets manufactured by S Kant Healthcare Limited and Coartem (Artemether and Lumefantrine) manufactured by Novartis Pharmaceuticals corporation in healthy adult male human subject under fed condition	
Study design	An open label, randomized, two-treatment, two-period, two-sequence, single dose, crossover, comparative bioequivalence study in healthy adult human male subjects under fed conditions	
Study site	L.T.M.M. College and General Hospital, Sion, Mumbai, India	
Study dates	21/04/2013 to complete	
Primary objective	To compare the rate and extent of absorption of two formulations i.e. Artemether 20 mg and Lumefantrine 120 mg Tablets manufactured S Kant Healthcare Limited and Coartem (Artemether and Lumefantrine) manufactured by Novartis Pharmaceuticals corporation in healthy adult male human subject under fed condition	
Secondary objective	To monitor the safety of the two formulations i.e. Artemether 20 mg and Lumefantrine 120 mg Tablets manufactured S Kant Healthcare Limited and Coartem (Artemether and Lumefantrine) manufactured by Novartis Pharmaceuticals corporation in healthy adult male human subject under fed condition	
Number of participants	Planned: 44 subjects Enrolled: 44 subjects Dosed: 44 subjects Withdrawn – 00 subjects Completed: 44 subjects, Bio-sample analyzed: 44 subjects Pharmacokinetic and statistical data analyzed: 44 subjects	
Monitored parameters	Tmax, Cmax, AUC0→t, AUC0→∞, AUC% Extrapolation Kel and T1/2	
	Test Product	Reference product

Investigational medicinal products	Strength: 20/120 mg Batch number: AR3003 Expiry date: 02/2015	Strength: 20/120 mg Batch number: X1627 Expiry date: 12/2014
Analytical method	LC-MS/MS method was used for the determination of plasma concentration of analytes	
Statistical method	SAS® software Version	

Efficacy results are summarized as follows:

For Artemether

Parameter	Test	Reference	90 % Confidence interval	DF	CV (%)
LnAUC0-t	24.2422	24.7297	91.11 – 105.47	42	20.62
LnAUC0-inf	29.1392	29.1924	91.11– 105.47	42	20.79
LnCmax	2.7057	2.7061	96.15 – 103.96	42	10.94

For Lumefantrine

Parameter	Test	Reference	90 % Confidence interval	DF	CV (%)
Ln AUC0-t	2.965	2.985	97.86 – 100.00	42	4.34
Ln AUC0-inf	3.149	3.151	97.80– 100.00	42	5.55
Ln Cmax	0.708	0.78	96.81 – 100.00	42	14.32

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, Artemether 20 mg and Lumefantrine 120 mg tablets manufactured by S Kant Healthcare Limited is equivalent and interchangeable with Coartem (Artemether and Lumefantrine) manufactured by Novartis Pharmaceuticals corporation 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 Practice, the benefit of the product outweighs the risks associated with its use when used in accordance to the summary of product characteristics. Lariact 20 mg/120 mg 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

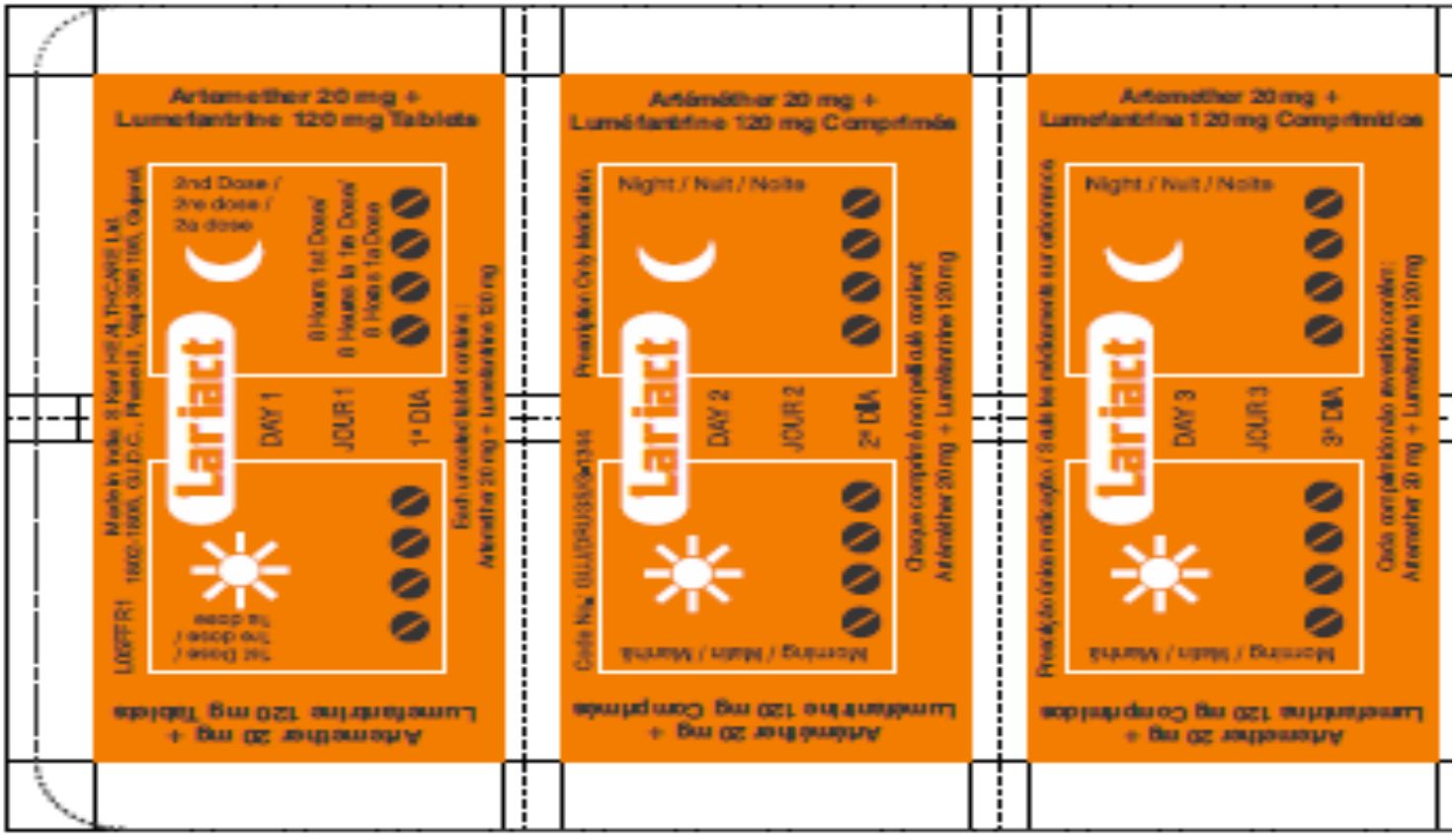
NA

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;