THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR ARGESUN™ 30, 60, 120 (ARTESUNATE 30 MG, 60 MG AND 120 MG) POWDER FOR INJECTION

Version number 1.0
14 October 2023

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1. Introduction

Argesun is a generic medicine of Artesunate powder for injection. Argesun is an antimalarial medicine belonging to P01BE03-antimalarial group. Argesun exerts is activity by activation involving iron-mediated cleavage of the endoperoxide bridge of DHA to generate an unstable organic free radical followed by alkylation, where the free radical binds to malarial proteins leading to destruction of parasite membrane. Argesun is approved in Tanzania for use in adults and children.

1.1 Product details

Registration number	Argesun 120: TAN 20 HM 0421 Argesun 60: TAN 20 HM 0409 Argesun 30: TAN 20 HM 0417
Brand name	Argesun 30, 60 and 120
Generic name, strength and form	Artesunate for injection 30 mg Artesunate for injection 60 mg Artesunate for injection 120 mg
ATC classification	P01BE03-antimalarial
Distribution category	POM
Country of origin	China
Associated product	Solvents- Sodium Bicarbonate and Arginine Injection)
Marketing Authorization Holder	Shanghai Fosun Pharmaceutical Development Co., Ltd, Room 350, No.5 Kangshi road, Kangqiao Town, Pudong New District (Kangqiao), Shanghai, China E-Mail: shiliang@fosunpharma.com
Local Technical Representative	Tridem Pharma Tanzania Limited P.O Box 23145, Keko-Mwanga, Dar es Salaam, Tanzania E-Mail: bensonaloyce@guilinpharma.com

1.2 Assessment procedure

The application for registration of Argesun was submitted on 27/02/2020. The product underwent full assessment. Assessment was completed in 1 rounds of evaluation. Argesun was registered on 25/09/2020.

1.3 Information for users

Visual description of the finished product	White crystalline powder
Primary packing material	Artesunate 120: The primary packs are colourless, type I glass vials with gray colored type I rubber stoppers and aluminium lid with a purple flip-off plastic cover.

	Artesunate 60: The primary packs are colourless, type I glass vials with gray colored type I rubber stoppers and aluminium lid with a blue flip-off plastic cover. Argesun 30: Colourless, type I glass vials with gray colored type I rubber stoppers and aluminium lid with a green flip-off plastic cover
Secondary packing materials	
Shelf-life and storage condition	36 months After reconstitution: 1 hour Do not store above 30°C
Route of administration	IM & IV
Therapeutic indications	Treatment of severe malaria caused by Plasmodium falciparum, in adults and children.

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: Argesun injection

Composition: Artesunate for injection 120 mg, Artesunate for injection 60 mg, Artesunate for injection 30 mg

Pack size: <primary & secondary pack>

Manufacturing details: batch number, manufacturing date, expiry date

Storage conditions: Store below 30°C, the reconstituted solution should be stored below 30°C and should be used within 1 hour.

Manufacturer address: Guilin Pharmaceutical Co., Ltd, No. 43, Qilidian Road, Guilin 541004, China

Unique identifier: <state the unique identification used>

Special warnings/precautions or instructions for use: <include warnings or IFU if applicable>

The details of the primary pack include:

Brand name and strength: Argesun injection

Manufacturing details: batch number, manufacturing date, expiry date

Name of manufacturer: <name only>

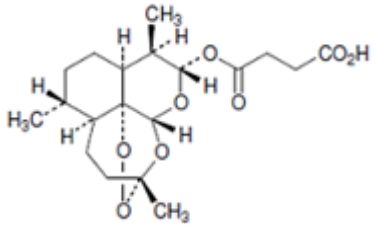
The content of the primary and secondary labels was aligned to the requirements of the Part V of the Compendium: Guidelines on Format and Content of Product Labels for Medicinal products. The label contains sufficient information for proper identification of the medicine and post marketing follow up of the product.
Describe any approved deviation to the requirements and the justification for the deviation.

3. Scientific discussion

Quality of Active Pharmaceutical Ingredient(s)

Artesunate
Information on quality of the API was submitted in form of full details.

General properties
Artesunate API is compendia in non-compendia.
Molecular formula: $C_{19}H_{28}O_8$
Chemical name: (3R,5aS,6R,8aS,9R,10S,12R,12aR)-Decahydro-3,6,9–trimethyl-3,12-epoxy-12H-pyrano[4,3-j]- 1,2- benzodioxepin-10-ol,hydrogen succinate.
(3R,5aS,6R,8aS,9R,10S,12R,12aR)-3,6,9-trimethyldecahydro-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin-10-yl hydrogen butanedioate.
Structure:



Critical physico-chemical properties of the API were Artesunate is very slightly soluble in water; very soluble in dichloromethane, freely soluble in ethanol.

Manufacture
The API manufacturing site, Guilin Pharmaceutical Co., Ltd.; located in No.43 Qilidian Road,Guilin, China was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by China Food and Drug Administration (CFDA). Artesunate API is manufactured by <chemical/fermentation> synthesis using <conventional/novel> 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 Ph and in-house standards and ICHQ3A. The parameters monitored during quality control are: description, identification, impurities,

assay, specific optical rotation,heavy metals, residue on ignition, water, particle size distribution, pH, clarity and color of solution, residual solvent, bacterial endotoxin, 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 Artesunate API is 36 months when packed in transparent PE bags and one layer of black PE bag and stored at 30℃.

Arginine

Information on quality of the API was submitted in form of full details.

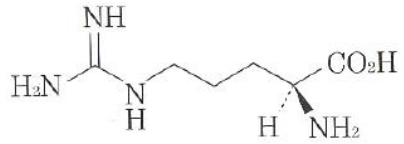
General properties

Arginine API is compendia in USP/BP.

Molecular formula: $C_6H_{14}N_4O_2$

Chemical name: (2S)-2-Amino-5 guanidinopentanoic acid

Structure:



Critical physico-chemical properties of the API were freely soluble in water and in formic acid, practically insoluble in ethanol (99.5).

Manufacture

The API manufacturing site, Shanghai Ajinomoto Amino Acid Co., Ltd.; located in No. 718, East Rongle Road, Songjiang District, Shanghai 201613, China was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by China Food and Drug Administration (CFDA). L-Arginine API is manufactured by purification of crude L-Arginine. Sufficient controls of quality of materials and in-process checks were employed throughout the manufacturing process.

Specifications

The API specifications were set as per USP and in-house standards and ICHQ3A. The parameters monitored during quality control are: description, identification, residue on ignition, chloride ,sulfate , iron , heavy metal ,, related substances, specific rotation , loss on drying, microbial limit, assay and bacterial endotoxin. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Arginine API is 36 months when packed in polyethylene bag and stored at 25°C.

Quality of the Finished Pharmaceutical Product

Formulation

Argesun is a white crystalline powder in type I glass vials. It is co-packed with Sodium Bicarbonate and Arginine Injection ampoules. Argesun contains Artesunate with no excipients.

Manufacture

The finished product was manufactured at Guilin Pharmaceutical Co., Ltd, No. 43, Qilidian Road, Guilin 541004, China . The compliance of the site to TMDA GMP standards was confirmed through desk-review on 04 June 2020.

Specifications

The FPP is compendia in International Ph. The manufacturer controls the quality of the finished product as per International Ph, in-house and ICHQ3B requirements. The parameters monitored during quality control of Artesunate sterile powder are: appearance, identification, specific optical rotation heavy metals, residual on ignition, water, pH, related substances, bacterial endotoxin, sterility, residual organic solvent, particle size distribution, visible particles (light inspection), residual on ignition, clarity and color of solution, assay. The parameters monitored during quality control of Artesunate for injection are: description, identification, clarity and color of solution, pH, insoluble particulate matter, water, filling quantity variation, content uniformity, visible particles, related substances, bacterial endotoxin, sterility, assay .Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on 3 batches of the finished product stored at 30℃±2, 70%±5%RH for 36 months and 40℃±2℃; 75%±5%RH for 6 months. Based on the stability data presented, the approved shelf-life is 36 months when stored in glass vial and a rubber stopper pressed with an aluminum-plastic cap at below 30℃.

Safety and efficacy information

No studies were conducted because the produt is for parenteral administration.

4. Benefit-Risk Assessment and Conclusion

On basis ofthe 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. Argesun 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

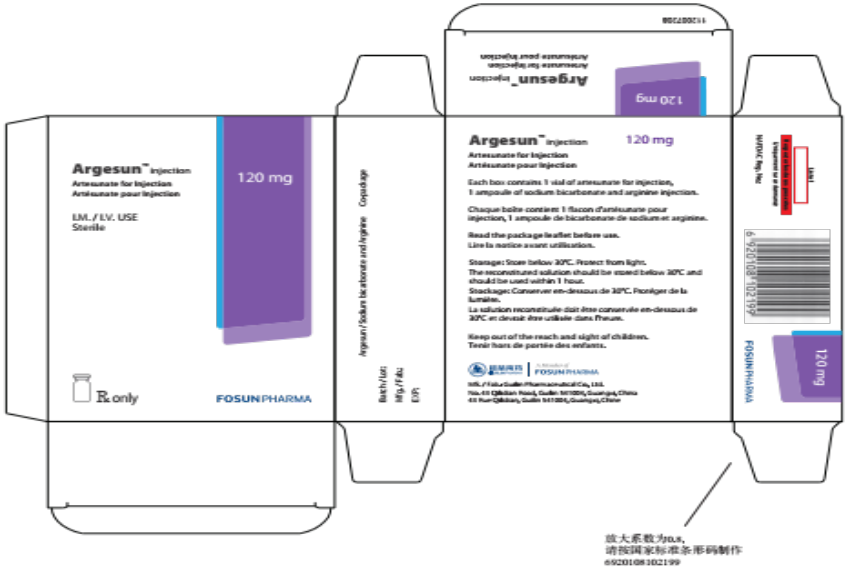
Re-registration applications

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 label



Argesun™ injection

Artesunate for Injection
Arésunate pour Injection

120mg I.M. / I.V. USE ℞ only

Storage: Store below 30°C. Protect from light.
The reconstituted solution should be stored below 30°C and should be used within 1 hour.

Stockage: Conserver en-dessous de 30°C.
Protéger de la lumière.
La solution reconstituée doit être conservée en-dessous de 30°C et devrait être utilisée dans l'heure.

1vial /box × **boxes/carton**
1 flacon /boîte × **boîtes/carton**

112007210

Argesun Co-package

Batch / Lot.:

Mfg. / Fab.:

EXP:

Sodium bicarbonate and arginine

Batch / Lot.:

NAFDAC Reg. No.:

Made in China