TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR AZUNATE (ARTESUNATE 60 MG) POWDER FOR INJECTION.

Version number 0.1,

March 2022

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1. Introduction

Azunate is an artemsinin derivative medicine belonging to P01BE03 - Artemisinin and derivatives, plain group. Azunate exerts is activity by causing cleavage of endoperoxide bridge in the pharmacophore of DHA and therefore generates reactive oxygen species (ROS), which increases oxidative stress and causes malarial protein damage via alkylation. In addition, Artesunate potently inhibits the essential Plasmodium falciparum exported protein 1 (EXP1), a membrane glutathione S-transferase. As a result, the amount of glutathione in the parasite is reduced. Azunate is approved in Tanzania for use in adults and children.

1.1 Product details

Registration number	TAN 21 HM 0132
Brand name	Azunate
Generic name, strength and form	Artesunate Powder for Injection of 60 mg
ATC classification	P01BE03 - Artemisinin and derivatives, plain
Distribution category	POM
Country of origin	India
Associated product	Not Applicable
Marketing Authorization Holder	Macleods Pharmaceuticals Limited. 304, Atlanta Arcade, Marol Church road, Andheri (East), **India.**
Local Technical Representative	RK Pharmaceuticals (Tz)Limited Plot No 326, Dar es Salaam

1.2 Assessment procedure

The application for registration of Azunate was submitted on 06/09/2019, the product underwent full assessment. Assessment was completed in two rounds of evaluation. Azunate was registered on 29/03/2021.

1.3 Information for users

Visual description of the finished product	White powder in a clear 10 mL USP type-III glass vial sealed with 20 mm grey bromo butyl rubber plugs and 20 mm chocolate brown flip off aluminum seal.
Primary packing material	10 mL USP Type-III glass vial with 20 mm Grey Bromo-butyl rubber stopper.
Secondary packing materials	1 x 10 mL co-packed with 1 mL ampoule of Sodium Bicarbonate and 5 mL ampoule of Sodium Chloride in a cardboard box with a multi-folded package leaflet.
Shelf-life and storage condition	24 months Do not store above 30°C. Store in dry place protected from light. Do not refrigerate or freeze

	The reconstituted and diluted solutions should be store below 30°C and to be use with 1 hour.
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 was not provided as this product is POM which is used to patients with severe malaria (most cases hospitalized) and it is not meant for long term use.

Container labels
The product label information is presented in English. Details in the secondary pack label include:
Brand name: Azunate
Composition: Artesunate 60 mg
Pack size: USP Type III Glass Vial of 10 mL with 20 mm Grey Bromo-butyl Rubber Stopper co-packed with 1 mL ampoule of Sodium Bicarbonate and 5 mL ampoule of Sodium Chloride in a cardboard box with a multi-folded package leaflet.

Manufacturing details: batch number, manufacturing date, expiry date and manufacturing license number

Storage conditions: Do not store above 30°C, in dry place, protected from light. Do not refrigerate or freeze

Manufacturer address: Macleods Pharmaceuticals Limited, Phase I, Unit II, Plot No. 25 – 27, Survey No. 366, Premier Industrial Estate, Kachigam, Daman – 396210, India

Unique identifier: None
Special warnings/precautions or instructions for use: Keep out of reach of children, do not put the solution in an IV drip

The details of the primary pack include:
Brand name and strength: Azunate
Manufacturing details: TMDA registration number

Name of manufacturer: Macleods Pharmaceuticals 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.

The product was approved without the inclusion of a space for printing registration number. This was approved because this requirement is now under revision and therefore it has not been enforced for products being approved current.

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 proof WHO prequalification and the corresponding required information.

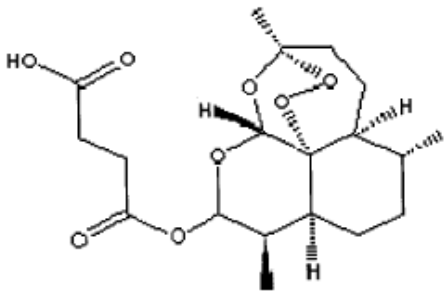
General properties

Artesunate API is compendial drug substance having an official monograph in the International Pharmacopeia

Molecular formula: $C_{19}H_{28}O$

Chemical name: (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:

Very slightly soluble in water, very soluble in dichloromethane, freely soluble in ethanol (~750g/l)& acetone. Artesunate API was considered as a highly soluble API as it has Dose/solubility volume of less than 250 ml. The drug product will be administered in solution form and hence physical properties like polymorphism and PSD are not critical.

Manufacture

The API manufacturing site Mangalam Drugs and Organics Ltd., Unit-1, Plot No. 187, 2nd Phase, G.I.D.C., Vapi, 396 195, Gujarat, India was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by the Food & Drugs Control Administration, Gujarat State, India. Artesunate 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 ICHQ3A. The parameters monitored during quality control are: physical appearances, solubility, Identification, pH, specific optical rotation, water content, sulphated ash, heavy metals, related substances (impurities), assay and clarity of the solution. 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 24 months when packed in white LDPE bag and secondary packing in black LDPE bag in HDPE container and stored at or below 25°C, protected from moisture and light.

Quality of the Finished Pharmaceutical Product

Formulation

Azunate is a fine white powder filled and sealed in aluminum bullet container with rubber bung & aluminum seal (canister set) co-packed with 1 mL ampoule of Sodium Bicarbonate and 5 mL ampoule of Sodium Chloride in a cardboard box with a multi-folded package leaflet. Azunate contains Artesunate and other ingredients listed here after; ethanol and water for injection. 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 Macleods Pharmaceuticals Limited, Phase I, Unit II, Plot No. 25 – 27, Survey No. 366, Premier Industrial Estate, Kachigam, Daman – 396210, India. The compliance of the site to TMDA GMP standards was confirmed through site inspection on 20th April, 2020.

Specifications

The FPP is a compendial product having an official monograph in an international pharmacopeia and USP. The manufacturer controls the quality of the finished product as per US pharmacopeia, In-house and ICHQ6A requirements. The parameters monitored during quality control are: description, identification, average fill weight, uniformity of mass, pH value, water content, clarity of solution, particulate matter, reconstitution time, related substances, assay, endotoxin and sterility. 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°C ± 2°C / 75% ± 5% RH for 24 months and 40°C ± 2°C/75 ± 5 % RH for 6 months. Based on the stability data presented, the approved shelf-life is 24 months when stored in Glass Vial USP Type III closed with 20 mm Grey Bromo-butyl Rubber Plugs and sealed with 20 mm Chocolate Brown flip off Aluminum Seal.

Safety and efficacy information

Azunate Powder for injection is a parental formulation and therefore fulfils the exemption for demonstrating therapeutic. The composition of Azunate for infusion manufactured by Macleods Pharmaceuticals Ltd is the same as the originator product, Artesunate Powder for injection manufactured by Guilin Pharmaceuticals Limited. Therefore, it was considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product.

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. Azunate was recommended for registration.

5. Post-approval updates

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

Mfg. Lic. No : 00115
Batch No. / Lot :
Mfg. Date /
Date de fabrication :
Expiry Date /
A utiliser avant :

Artesunate for Injection Ph. Int. 60 mg
Artésunate pour injection Ph. Int. 60 mg

POM **Azunate**

Injection 60 mg

I.M./I.V. USE
Single use only
Utilisation I.M./I.V.
Seulement pour usage unique

STERILE

MACLEODS

Composition
Each vial contains:
Sterile Artesunate Ph. Int. 60 mg

The pack contains 1 ml ampoule of Sodium Bicarbonate Injection USP 5 % w/v and 5 ml ampoule of Sodium Chloride Injection BP 0.9 % w/v Reconstituted and diluted solution should be store below 30°C and to be use within 1 hour

Dosage: As prescribed by the Physician See package insert for complete prescribing information

Do not store above 25°C, in dry place, protected from light. Do not refrigerate or freeze.

Keep out of reach of children

Registration No.:

A-The Vial Artesunate
B-Sodium bicarbonate injection ampoule
C-Sodium Chloride injection larger ampoule

Instructions for use:

Step 1:
Add B to A and mix well until the solution becomes clear

Step 2:
Add C Sodium Chloride BP

For I.V. use:
Add 5 ml of Sodium Chloride Injection BP 0.9 % w/v to the vial. Mix and inject by slow I.V. route over 3-5 minutes.

Do not put the solution in an I.V. drip

For I.M. Use:
Add 2 ml of Sodium Chloride Injection BP 0.9 % w/v to the vial. Mix and inject by I.M. use.

For batch details of sodium chloride injection and Sodium bicarbonate injection refer respective ampoules

A-Le flacon d'Artesunate
B-Ampoule de bicarbonate de sodium injectable
C-Ampoule plus grande contenant le chlorure de sodium injectable

Mode d'emploi :

Étape 1 : Ajouter B à A et bien mélanger jusqu'à ce que la solution devienne clair.

Étape 2 :
Ajouter C du chlorure de sodium BP

Pour usage intraveineux :
Ajouter 5 ml de chlorure de sodium injectable BP 0,9 % p/v dans le flacon. Mélanger et injecter par voie intraveineuse lente sur une durée de 3 à 5 minutes.

Ne pas mettre la solution dans une perfusion intraveineuse.

Pour utilisation intramusculaire :
Ajouter 2 ml de chlorure de sodium injectable BP 0,9 % p/v dans le flacon. Mélanger et injecter par voie intramusculaire.

Pour les détails sur les lots d'injection de chlorure de sodium et d'injection de bicarbonate de sodium, se reporter aux ampoules respectives.

Composition :
Chaque flacon contient :
Artésunate stérile Ph. Int. 60 mg

Le paquet contient une ampoule de 1 ml de bicarbonate de sodium injectable USP 5 % p/v et une ampoule de 5 ml de chlorure de sodium injectable BP 0,9 % p/v La solution reconstituée et diluée doit être conservée à une température inférieure à 30°C et doit être utilisée dans l'heure qui suit.

Dosage : Tel que prescrit par le médecin. Voir la notice de l'emballage pour les renseignements thérapeutiques complets.

Ne pas stocker au-dessus de 25°C, dans un endroit sec, à l'abri de la lumière.
Ne pas mettre au réfrigérateur ni au congélateur.

Tenir hors de portée des enfants

MACLEODS
Manufactured in India by /
Fabriqué en Inde par:
MACLEODS PHARMACEUTICALS LTD.
Plot No. 25-27, Survey No. 366, Premier Industrial Estate, Kachigam, Daman -396210 (U.T.)
Off: Alkaria Arcade, Mind Church Road, Andheri (E), Mumbai - 400 059.

- PANTONE 2935 CVC
- PANTONE 151 CVC
- PANTONE 179 CVC
- BLACK

Composition : Chaque flacon contient :
Artésunate stérile Ph. Int. 60 mg

Le paquet contient une ampoule de 1 ml de bicarbonate de sodium injectable USP 5 % p/v et une ampoule de 5 ml de chlorure de sodium injectable BP 0,9 % p/v
La solution reconstituée et diluée doit être conservée à une température inférieure à 25°C et doit être utilisée dans l'heure qui suit.

Dosage : Tel que prescrit par le médecin. Voir la notice de l'emballage pour les renseignements thérapeutiques complets.

Artesunate for Injection 60 mg
Artésunate pour injection Ph. Int. 60 mg

POM **Azunate**

Injection 60 mg

I.M./I.V. USE Single use only
Utilisation I.M./I.V.
Seulement pour usage unique
STERILE

MACLEODS

Ne pas stocker au-dessus de 25°C, dans un endroit sec, à l'abri de la lumière. Ne pas mettre au réfrigérateur ni au congélateur.

Tenir hors de portée des enfants

MACLEODS

Manufactured in India by :/
Fabriqué en Inde par:
MACLEODS
PHARMACEUTICALS LTD.
Off.: Atlanta Arcade, Marol Church Road, Andheri (E), Mumbai - 400 059.

Mfg. Lic. No. : DD/115
Batch No. / Lot :
Mfg. Date /
Date de fabrication :
Expiry Date /
A utiliser avant :

- PANTONE 2935 CVC
- PANTONE 151 CVC
- PANTONE 179 CVC
- BLACK