THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR AKUCLAV (AMOXICILLIN SODIUM 1000 MG + CLAVULANATE POTASSIUM 200 MG) POWDER FOR SOLUTION FOR INJECTION

Version number 1.0
13 November 2023

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1. Introduction

Akuclav Powder for Solution for Injection is a generic medicine of Amoxicillin Sodium and Clavulanate Potassium. Akuclav Powder for Solution for Injection is a betalactam medicine belonging to J01CA04 Beta lactam antibiotics, Penicillin group. Akuclav Powder for Solution for Injection exerts is activity by inhibiting one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall resulting to cell lysis and death. Amoxicillin Sodium and Clavulanate Potassium Powder for Solution for Injection is approved in Tanzania for use in adults and children.

1.1 Product details

Registration number	TAN 20 HM 0422
Brand name	Akuclav
Generic name, strength and form	Amoxicillin Sodium 1000 mg and Clavulanate Potassium 200 mg Powder for Solution for Injection
ATC classification	J01CA04 Beta lactam antibiotics, Penicillin
Distribution category	POM
Country of origin	China
Associated product	State any other product of formulation, strength or site that is linked or associated with the product if applicable
Marketing Authorization Holder	North China Pharmaceutical Co.,Ltd, No.388 Heping East Road, Shijiazhuang Country: P.R. China. E-Mail: ncpcqa@163.com
Local Technical Representative	Moraf Pharmaceuticals Ltd, P O Box 21323, Kipande street, Kariakoo, Dar es Salaam, Tanzania. E-Mail: ali@morafpharmaceuticals.com

1.2 Assessment procedure

The application for registration of Akuclav was submitted on 06/02/2019. The product underwent full assessment. Assessment was completed in 2 rounds of evaluation. Akuclav was registered on 25/09/2020.

1.3 Information for users

Visual description of the finished product	A white or almost white powder
Primary packing material	Type-III glass vial with a grey butyl rubber stopper and 20 mm blue flip off seal
Secondary packing materials	

Shelf-life and storage condition	36 months Store below 30°C, protected from light and moisture
Route of administration	Intravenous
Therapeutic indications	Amoxicillin sodium and clavulanate potassium for injection is used in adults and children to treat the following infections: • severe ear, nose and throat infections • respiratory tract infections • urinary tract infections • skin and soft tissue infections including dental infections • bone and joint infections • intra-abdominal infections • genital organ infections in women. Amoxicillin sodium and clavulanate potassium for injection is used in adults and children to prevent infections associated with major surgical procedures.

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: Amoxicillin Sodium and Clavulanate Potassium Powder for Injection 1.2 G

Composition: Amoxicillin Sodium equivalent to Amoxicillin 1.0g and Clavulanate Potassium equivalent to clavulanic acid 200 mg

Pack size: 5 vials

Manufacturing details: batch number, manufacturing date, expiry date

Storage conditions: Store below 30°C, away from light and moisture

Manufacturer address: North China Pharmaceutical Co.,Ltd, No.388 Heping East Road, Shijiazhuang P.R. China.

Unique identifier: Not applicable.

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

The details of the primary pack include:
Brand name and strength: Amoxicillin Sodium and Clavulanate Potassium Powder for Injection 1.2 G
Manufacturing details: batch number, manufacturing date, expiry date
Name of manufacturer: North China Pharmaceutical Co.,Ltd

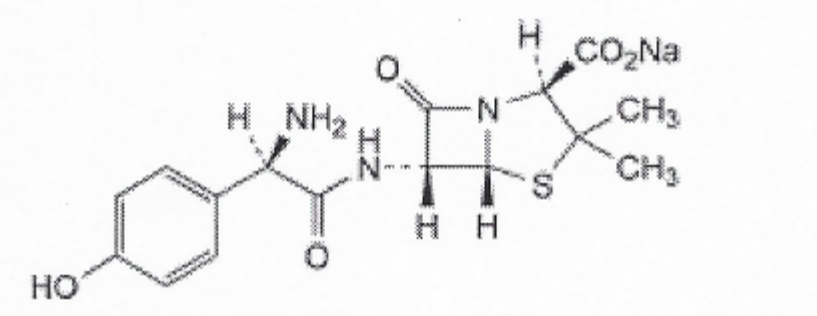
The content of the primary and secondary labels was aligned to the requirements of the Part V of the Compendium: Guidelines on Format and Content of Product Labels for Medicinal products. The label contains sufficient information for proper identification of the medicine and post marketing follow up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

3. Scientific discussion

Quality of Active Pharmaceutical Ingredient(s)

Amoxicillin Sodium (Sterile)
Information on quality of the API was submitted in form of full details.

General properties
Amoxicillin Sodium API is compendia in BP.
Molecular formula: $C_{16}H_{18}N_3NaO_5S$
Chemical name: Sodium (2S, 5R, 6R)-6-[[(2R)-2-amino-2-(4-hydroxyphenyl) acetyl] amino] -3, 3 -dimethyl-7-oxo-4-thia-1-azabicyclo [3 .2.0] heptane-2-carboxylate
Structure:



Critical physico-chemical properties of the API were very soluble in water, sparingly soluble in anhydrous ethanol, very slightly soluble in acetone.

Manufacture
The API manufacturing site, Zhuhai United Laboratories Co. Ltd, No. 2428, Anji Road, Sanzao Town, Jinwan District, Zhuhai, Guangdong 519 040, China was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by China Food and Drug

Administration. Amoxicillin Sodium 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 BP standards and ICHQ3A. The parameters monitored during quality control are: character, identification, pH, specific optical rotation, appearance of solution, related substances, N,N-dimethylaniline, 2-ethylhexanoic acid, water, sterility, bacterial endotoxins, visible particles, particulate matter, assay 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 Amoxicillin Sodium API is 36 months when packed in Aluminum tin sealed with inner lid containing butyl rubber sealing ring, then crimp on the aluminum cap and stored at below 25°C.

Potassium Clavulanate (Sterile)

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

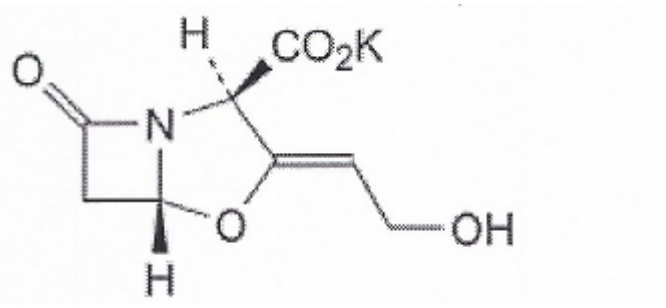
General properties

Potassium Clavulanate API is compendia in BP.

Molecular formula: $C_8H_8KNO_5$

Chemical name: Potassium (2R, 3Z, 5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo [3.2.0] heptanes-2-carboxylate

Structure:



Critical physico-chemical properties of the API were freely soluble in water, slightly soluble in ethanol (96%), very slightly soluble in acetone.

Manufacture

The API manufacturing site, Zhuhai United Laboratories Co. Ltd, No. 2428, Anji Road, Sanzao Town, Jinwan District, Zhuhai, Guangdong 519 040, China was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by China Food and Drug Administration. Potassium Clavulanate 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 BP standards and ICHQ3A. The parameters monitored during quality control are characters, Identification, bacterial endotoxin, sterility, pH, specific optical rotation, Absorbance, water, aliphatic amine, 2-ethylhexanoic acid, related substances, visible particles, particulate matter, residual solvents and assay. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system
The re-test period of Potassium Clavulanate API is 36 months when packed in Aluminum Tin with sealing ring Butyl Rubber and stored at 2 – 8 °C.

Amoxicillin Sodium and Clavulanate Potassium Sterile Blend

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

General properties
<Molecule> API is compendia in <USP/BP/JP/International Pharmacopeia>/<non-compendia>.
Molecular formula:
Chemical name:
Structure:

Critical physico-chemical properties of the API were **:** Freely soluble in water.

Manufacture
The API manufacturing site, Zhuhai United Laboratories Co. Ltd, No. 2428, Anji Road, Sanzao Town, Jinwan District, Zhuhai, Guangdong 519 040, China was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by China Food and Drug Administration. Amoxicillin Sodium and Clavulanate Potassium Sterile Blend API is manufactured by physical mixing of sterile Amoxicillin Sodium and sterile Clavulanate Potassium. Sufficient controls of quality of materials and in-process checks were employed throughout the manufacturing process.

Specifications
The API specifications were set as in-house standards and ICHQ3A. The parameters monitored during quality control are: Characters, Identification, Alkalinity, clarity of solution, colour of solution, visible particles, subvisible particles, Water, Clavulanate polymer and other fluorescent impurities, Related substances, Bacterial endotoxins, sterility, assay, ratio of amoxicillin and clavulanic acid, uniformity of assay 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 Amoxicillin Sodium and Clavulanate Potassium Sterile Blend API is 36 months when packed in Aluminum Tin with sealing ring Butyl Rubber and stored at 2°C – 8°C.

Quality of the Finished Pharmaceutical Product

Formulation

Akuclav is a a white or almost white powder in 25ml glass vial. Akuclav contains Amoxicillin Sodium and Clavulanate Potassium sterile blend with no excipients.

Manufacture

The finished product was manufactured at North China Pharmaceutical Co., Ltd., No. 388 Heping East Road, Shijiazhuang, P.R. China. The compliance of the site to TMDA GMP standards was confirmed through site inspection on 10-11 June 2018.

Specifications

The FPP is compendia in BP. The manufacturer controls the quality of the finished product as per BP and ICHQ3B requirements. The parameters monitored during quality control are: description, identification, alkalinity, water, clavulanate polymer and other fluorescent impurities, clarity of solution, color of solution, visible particles, particulate matter, related substance, uniformity of mass, content of clavulanic acid, content of amoxicillin, bacterial 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 3 batches of the finished product stored at 30℃±2℃/75%±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 25ml tubular glass vial, butyl rubber stoppers, flip-off caps at Store below 30°C.

Safety and efficacy information

Safety and efficacy of Akuclav was established through reliance on the innovator product.

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. Akuclav 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

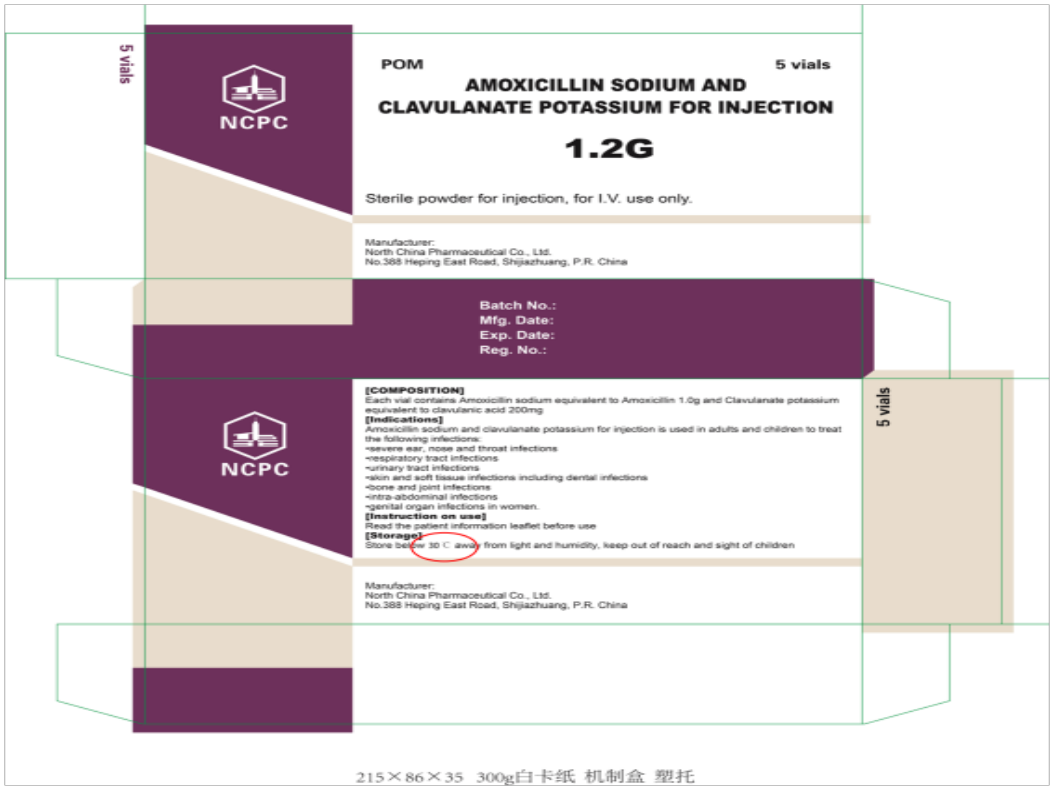
Re-registration applications

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




Batch No.:
Mfg. Date:
Exp. Date:
Reg. No.:
NCPC
POM
AMOXICILLIN SODIUM AND CLAVULANATE POTASSIUM FOR INJECTION 1.2G
(Amoxicillin 1g/clavulanic acid 200mg)
Sterile Powder for Injection, for I.V. use only
Read the patient information leaflet before use
Store below 30 C away from light and humidity,
keep out of reach and sight of children
Manufacturer:
North China Pharmaceutical Co., Ltd.
No.388 Heping East Road, Shijiazhuang, P.R. China
70*35mm 不干胶