EDA Assessment Report for human medicinal product

(Scientific Discussion)

Azibactocin 500mg Film Coated Tablets

(Azithromycin trihydrate)

Date: November 2023

I. Introduction

Based on the review of the quality, safety and efficacy data, the Egyptian Drug Authority have granted marketing authorization for "Azibactocin 500mg Film Coated Tablets" of MultiCare Egypt for Pharmaceutical Industries.

Azithromycin is a macrolide antibacterial drug indicated for mild to moderate infections caused by designated, susceptible bacteria:

- Acute bacterial exacerbations of chronic bronchitis in adults.
- Acute bacterial sinusitis in adults.
- Uncomplicated skin and skin structure infections in adults
- Urethritis and cervicitis in adults
- Genital ulcer disease in men
- Acute otitis media in pediatric patients (6 months of age and older)
- Community-acquired pneumonia in adults and pediatric patients (6 months of age and older).
- Pharyngitis/tonsillitis in adults and pediatric patients (2 years of age and older).

II. Quality Aspect

Drug Substance

- An APIMF (Applicant/ restricted part) has been submitted for evaluation.
- The drug substance is white or almost white powder, nonhygroscopic. It is practically insoluble in water, freely soluble in anhydrous ethanol and in methylene chloride.
- The synthesis of drug substance includes two steps with the formation of one intermediate. All starting materials, reagents, solvents are well controlled.
- The drug substance is elucidated via Elemental analysis, Mass spectroscopy, FT-IR, ^{1}H-NMR, ^{13}C-NMR, DEPT 135°, H-HCOSY, HMQC, HMBC, X -ray powder diffraction, DSC, TGA and the structure is well characterized.
- The drug substance specifications are in accordance with with USP Azithromycin Trihydrate monograph and include the following tests: description, solubility, Identification with IR & HPLC, Specific optical rotation, appearance of solution, crystallinity, water content, pH, residue on ignition, assay by HPLC, related substances & residual solvents. Microbiological tests are done as non-routine tests (Skip tests). All limits are acceptable.
- Analytical methods were adequately described and validated.
- The applicant provided batch analysis results of three drug substance batches demonstrating compliance with the current drug substance specification.

- Azithromycin is packed in an inner low-density polyethylene (LDPE) bag (Primary pack), twisted and closed tightly by a plastic locking tie as "Fiber drum" is used as secondary packaging. Container closure system is suitable to store API and comply with food grade packaging material and the specifications are acceptable.
- Stability of API have been submitted on 3 production batches under long-term conditions (25°C/60% RH- simulated commercial packaging), (30°C/75% RH -simulated commercial packaging) and under accelerated conditions (40°C/75% RH- simulated commercial packaging) respectively and conclude the conformity of specifications during the shelf life and storage conditions. The recommended storage conditions are "Preserve in tight containers, stored at temperature not exceeding 30 °C".

Medicinal Product

- **Product Description**
  - Azibactocin Film coated tablets are "light to dark pink" oblong biconvex plain film coated tablets with "white to off-white core".
  - The product is packed in: Carton box containing Aluminium/ opaque white PVC strip of 3 tablets.
  - **The excipients are:** Dibasic calcium phosphate anhydrous, Pregelatinized starch, Lactose monohydrate, Croscarmellose sodium, Sodium lauryl sulfate, Magnesium stearate (for tablet core). Hypromellose E5, Triacetin, Titanium dioxide, Red iron oxide (for tablet core).
- **Pharmaceutical development**, the development of the product has been described, the choice of excipients is justified and their functions explained. It was aimed to develop a product equivalent to the reference product. As Azithromycin is BCS Class II drug, the particle size was well controlled and selected by the applicant company to achieve the required dissolution properties. The appropriateness of the selected particle size limit is confirmed based on satisfactory bioequivalence study results.
- Overall, the choices of the packaging, manufacturing process, compatibility, overage physicochemical properties and microbiological attributes are justified.
- Manufacturing process, the manufacturing process is done by: Sifting, mixing, wet granulation, drying, sifting, blending, compression and coating. The process is done under sodium lamp.
- The manufacturing process was adequately validated according to relevant guidelines. Validation included three primary batches.
- Control of excipients, all excipients comply with with USP except for Red Oxide which follow "In-house" specifications and the specifications of the excipients are acceptable.
- Product specification includes the four universal tests for description, identification (HPLC, UV), assay, impurities and additional tests: mass uniformity, disintegration, dissolution, uniformity of dosage units, residual solvents & microbiological tests. All limits are acceptable.
- Analytical methods were adequately described and validated.

- Batch Analysis from the proposed production site were provided for 3 primary batches, demonstrating compliance with the release specifications.
- Container closure system is suitable to store FPP and comply with food grade packaging material and the specifications are acceptable.
- Stability of FPP have been submitted on three primary batches under long-term conditions (30°C/65% RH -commercial packaging) and under accelerated conditions (40°C/75% RH-commercial packaging) respectively and conclude the conformity of specifications during the shelf-life and storage conditions. The recommended storage conditions are "To be stored at temperature not exceeding 30° C"
- Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies, a declaration/certificate of TSE/BSE free is submitted for substances of animal origin.

Conclusion:
Based on the review of CTD quality module and other supplementary documents; from the quality point, the product is approved.

III. Non-Clinical

No new preclinical data have been submitted with this application. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application. An Environmental Risk Assessment has not been performed as this product is intended for generic substitution and therefore will not result in an increase of risk to the environment during use, storage and disposal.

IV. Clinical Aspects

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Introduction
Azithromycin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria in order to prevent the development antimicrobial resistance and maintain the efficacy of azithromycin. Azithromycin is indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the microorganisms.

Pharmacokinetics

Bioequivalence Study

The bioequivalence study was conducted on the test product Azibactocin 500mg film coated tablets (Azithromycin trihydrate 500mg) manufactured by: MultiCare Egypt for Pharmaceutical Industries, relative to the reference product Zithromax® 500mg film coated tablets (Azithromycin trihydrate 500mg) produced by: Pfizer Pharma GmbH, Berlin, administered to healthy participants.

Design

Randomized Single Oral Dose, Open-Label, Two-Treatment, Two-Sequence, Two Period, crossover bioequivalence study with a washout period of two weeks between periods under fasting conditions in healthy participants.

On randomized manner each subject received single oral dose from test & reference products directly into mouth administrated by 240 ml water after overnight fasting (at least 8-10 hours in fasting) according to the randomization sheet.
Blood Sampling: pre-dose blood sample were withdrawn at 0.00,0.25,0.5,0.75,1,1.25,1.5,1.75,2,2.25,2.5,3,3.5 3.5,4,5,7,9,11, 24, 48 &72 hours after dosing.

Analytical Methods

All procedures used to perform the bio-analyses of Azithromycin trihydrate 500mg in subject samples were executed according to international guidelines and official publications.

CRO developed an adequately validated method to ensure data integrity, Accuracy and Precision of data generated during sampling, sample treatment and bioanalyses.

Results

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range) of **Azithromycin trihydrate 500mg** under fast conditions.

Treatment N=36	**AUC0-72 (ng.h/ml)**	**Cmax (ng/ml)**	**Tmax (h)**	**$T_{1/2}$ (h)**
Test	3078.60	525.25	2.50	29.62
Reference	2828.98	524.59	2.50	31.69
***Ratio (90%) CI**	112.534 (102.759-123.238)	105.077 (94.668-116.630)	--------	---------

*ln-transformed values

Conclusion

The 90% confidence intervals calculated for C_{max}, AUC $_{0\text{-}t}$ and AUC $_{0\text{-}inf}$ are within the bioequivalence acceptance range of 80 % - 125 %.

Based on this study demonstrated that Azithromycin trihydrate 500mg in product dosage form of The Test Product Azibactocin 500mg Film Coated Tablets Manufactured by MultiCare Egypt for Pharmaceutical Industries relative to The Reference Product Zithromax® 500mg Film Coated Tablets (Azithromycin trihydrate 500mg) Produced by: Pfizer Pharma GmbH, Berlin, administered to healthy participants on 36 participants.