This part outlines the scientific assessment and knowledge about this product at the time of prequalification. Updates to this information are included in parts 1 to 5 and 8 of this WHOPAR.

SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product	[NT020 trade name]*
Manufacturer of Prequalified Product	Rusan Pharma Ltd. Khasra No. 122 MI, Central Hope Town, Selaqui, District: Dehradun - 248197 Uttarakhand India
Active Pharmaceutical Ingredient(s) (API)	Azithromycin (as dihydrate)
Pharmaco-therapeutic group (ATC Code)	Antibacterials for systemic use, macrolides (J01FA10)
Therapeutic indication	[NT020 trade name] is indicated for the treatment of yaws in adults, adolescents, and children ≥6 months. It is also indicated in adults and adolescents for susceptible bacterial infections, including cholera, enteric fever (typhoid and paratyphoid), gonorrhoea, chlamydia trachomatis infections (including sexually transmitted infections and trachoma), and acute dysentery.

1. Introduction

[NT020 trade name] is indicated for the treatment of yaws (≥6 months) and, in adults and adolescents, for susceptible bacterial infections including cholera, enteric fever, gonorrhoea, Chlamydia trachomatis infections, and acute dysentery.

Treatment regimens should align with the latest WHO recommendations and be supported by other authoritative guidance, including official advice on the appropriate use of antibacterial agents.

2. Assessment of quality

The assessment was done in accordance with the requirements of WHO's *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*.

Active pharmaceutical Ingredient (API)

A certificate of suitability issued by the EDQM was submitted for azithromycin ensuring good manufacturing control and applicability of the respective Ph.Eur monograph to control the quality of the API. Additional user requirements for azithromycin include test for particle size distribution, the limits of which were set on the data obtained for the API batch used in the manufacture of the FPP biobatch.

* Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility.

Other ingredients

Other ingredients used in the core tablet formulation include dicalcium phosphate, pregelatinized starch, croscarmellose sodium, hypromellose, sodium lauryl sulfate, magnesium stearate and lactose monohydrate, all being conventional pharmaceutical ingredients complying with the requirements of the pharmacopoeia. The commercially sourced proprietary film-coating mixture contains hypromellose, titanium dioxide, macrogol/PEG, talc and sodium lauryl sulphate. Lactose monohydrate is of bovine origin. TSE/BSE free certificates from the suppliers have been provided for the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white, round, film-coated tablet. It is biconvex (rounded on top and bottom) with a flat edge. The tablet is plain on both sides. The tablets are packaged in clear colourless plastic (PVC) or (PVC/PVDC) on aluminium foil blister cards.

The goal of the formulation development strategy was to obtain a robust, stable immediate release product bioequivalent to the WHO recommended comparator product, Zithromax 500mg film-coated tablets. The excipients were selected based on the comparator product and API-excipient compatibility data. Due to the poor flow property and compressibility of azithromycin, wet granulation was selected as the manufacturing process for the finished pharmaceutical product. Various experiments were performed to select and optimize the concentration of excipients and process parameters to obtain tablets of desired characteristics. Satisfactory in-process controls have been established.

According to a risk evaluation by the applicant, the FPP has no potential to contain nitrosamine impurities and hence no risk was identified.

Specifications

The finished product specifications include tests for description, identification (IR and HPLC), average weight of tablet, uniformity of weight, thickness, diameter, disintegration time, dissolution (HPLC detection), moisture content, uniformity of dosage units (by weight variation), related substances (HPLC), assay (HPLC) and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH (zone IVb) as long-term storage conditions and for six months at 40°C/75%RH as accelerated storage conditions in the packaging proposed for marketing of the product. The product proved to be quite stable at these storage conditions, with little degradation observed. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2021/2022 according to internationally accepted guidelines.

An open label, randomized, balanced, single-dose, two treatments, two period, two sequence, two way, crossover, truncated, oral bioequivalence study of Azithromycin 500 mg film-coated tablets of Rusan Pharma Ltd., India with Zithromax 500 mg film-coated tablets marketing authorization holder Laboratories Pfizer, Lda. Lagoons Park. Building 10 2740-271 Porto Salvo Portugal in normal healthy adult human subjects under fasting conditions (study no. 0.23/20).

The objective of the study was to compare the bioavailability of the stated Azithromycin 500 mg tablet manufactured by/for Rusan Pharma Ltd., India (test drug) with the reference formulation Zithromax 500 mg tablet (Pfizer) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T: Test – 1 tablet Azithromycin 500 mg (azithromycin 500 mg) Batch no. 28542101.
Treatment R: Reference – 1 tablet Zithromax 500 mg (azithromycin 500 mg) Batch no. 040002.

A 28-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 24 samples within 72h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for azithromycin were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 2 ng/mL for azithromycin.

The study was performed with 48 participants; data generated from a total of 45 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for azithromycin as well as statistical results are summarised in the following table:

Azithromycin

Pharmacokinetic Parameter	**Test formulation (T)** arithmetic mean ± SD (geometric mean)	**Reference (R)** arithmetic mean ± SD (geometric mean)	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional** 90% CI (ANOVAlog)
t_{max} (h)	2.37 ± 1.10	2.56 ± 1.09	-	-
C_{max} (ng/mL)	502 ± 173 (474)	517 ± 159 (487)	97.3	88.1 – 107.4
AUC_{0-t} (ng·h/mL)	4097 ± 1214 (3910)	4184 ± 1104 (4017)	97.3	90.1 – 105.2
AUC_{0-inf} (ng·h/mL)	4996 ± 1601 (4737)	5004 ± 1328 (4797)	98.7	91.2 – 107.0

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding azithromycin. Accordingly, the test Azithromycin 500 mg tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Zithromax 500 mg tablet (Pfizer).

4. Summary of product safety and efficacy

[NT020 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. According to the submitted data on quality and bioavailability, [NT020 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Zithromax 500 mg tablet (Pfizer). for which benefits have been proven in terms of clinical efficacy. The clinical safety of [NT020 trade name] is

considered acceptable when guidance and restrictions stated in the summary of product characteristics (SmPC) are considered. Refer to the SmPC (WHOPAR part 4) for data on clinical safety.

5. Benefit risk assessment and overall conclusion

Quality

Physicochemical and biological aspects relevant to the uniform pharmaceutical characteristics have been investigated and are controlled in a satisfactory way. The quality of this product is considered to lead to an acceptable clinical performance when [NT020 trade name] is used in accordance with the SmPC.

Bioequivalence

[NT020 trade name] has been shown to be bioequivalent with Zithromax 500 mg tablet (Pfizer).

Efficacy and Safety

Regarding clinical efficacy and safety, [NT020 trade name] is considered effective and safe to use when the guidance and restrictions in the SmPC are taken into consideration.

Benefit Risk Assessment

Based on WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit–risk profile of [NT020 trade name] was acceptable for the following indication: 'for the treatment of yaws in adults, adolescents, and children ≥6 months. It is also indicated in adults and adolescents for susceptible bacterial infections, including cholera, enteric fever (typhoid and paratyphoid), gonorrhoea, chlamydia trachomatis infections (including sexually transmitted infections and trachoma), and acute dysentery', and would allow inclusion of [NT020 trade name], manufactured at Rusan Pharma Ltd., Khasra No. 122 MI, Central Hope Town, Selaqui, District: Dehradun – 248197, Uttarakhand, India in the list of prequalified medicinal products.