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	[IN018 trade name][*]
Manufacturer of Prequalified Product	MSN Laboratories Private Limited Formulations Division, Unit-II Survey Nos. 1277, 1319 to 1324 Nandigama (Village & Mandal) Rangareddy District Telangana 509228 India
Active Pharmaceutical Ingredient(s) (API)	Oseltamivir (as phosphate)
Pharmaco-therapeutic group (ATC Code)	Antivirals for systemic use: neuraminidase inhibitors (J05AH02)
Therapeutic indication	[IN018 trade name] is indicated in adults and children for the treatment and post-exposure prophylaxis of influenza

1. Introduction

IN018 trade name] is indicated in adults and children for the treatment and post-exposure prophylaxis of influenza, as detailed in the summary of product characteristics.

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)

Oseltamivir phosphate, ethyl (3*R*,4*R*,5*S*)-4-(acetylamino)-5-amino-3-(1-ethylpropoxy)-cyclohex-1-ene-1-carboxylate dihydrogen phosphate is a white to off-white powder.

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

A CEP (Certificate of Suitability) issued by the EDQM was submitted, ensuring good manufacturing control and applicability of the Ph.Eur. monograph to control quality of the API. Additional user requirements include particle size distribution and polymorphic form (form A).

Stability testing was conducted according to the requirements of WHO. The proposed re-test period is justified based on the stability results, when the API is stored in the original packing material.

Other ingredients

Other ingredients used in the capsule core formulation include pregelatinised starch, povidone, croscarmellose sodium, talc and sodium stearyl fumarate. The capsule shell contains gelatin, iron oxide red (E172), iron oxide yellow (E172), iron oxide black (E172) and titanium dioxide (E171), while the printing ink contains shellac (E904), iron oxide black (E172) and potassium hydroxide (E525). The suppliers of gelatin provided EDQM-CEPs demonstrating TSE/BSE-compliance of this excipient. BSE/TSE compliance declarations were provided for the other ingredients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

Each capsule contains 39.40 mg oseltamivir phosphate equivalent to 30 mg oseltamivir.

[IN018 Trade name] are size "4" hard gelatin capsules, each having a light-yellow, opaque colour body, with black colour band, imprinted with "M" and having a light-yellow, opaque colour cap imprinted with "30 mg". The capsules, filled with white to off-white powder, are packaged in clear transparent PVC/PE/PVDC -Alu blister cards.

Three capsule strengths, proportionally similar in capsule fill composition were developed: 75mg, 45 mg and 30 mg. The different strengths showed very rapid dissolution in the main BCS media, similar to the comparator product.

The development of the final composition of the multisource product has been described. The objective was to develop a solid oral dosage form, bioequivalent to the comparator product, Tamiflu® capsules of the same strength. The selection of excipients was based on the comparator product (qualitatively the same) and API-excipient compatibility studies. Due to the poor flow of oseltamivir phosphate API, roller compaction process was chosen for manufacturing of the finished pharmaceutical product. Formulation trials were performed to optimize the concentration of excipients and process parameters, resulting in a product with the desired physicochemical characteristics including dissolution profile similarity with the comparator product. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The finished product specifications include tests for description, identification of API (HPLC, retention time and PDA detection) and colourants, average blend fill mass, average mass of filled capsule, weight, uniformity of dosage units (by mass variation), water determination (KF), dissolution (UV detection), assay (HPLC), related substances (HPLC) and microbiological enumeration. The test procedures have been adequately validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH as long-term storage conditions and for six months at 40°C/75%RH as accelerated conditions in the packaging intended for marketing of the product. The product proved to be quite stable at these conditions, with no apparent negative trend. The data support the proposed shelf life at the storage conditions as stated in the SmPC.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2018 according to internationally accepted guidelines:

An open-label, balanced, randomized, single-dose, two-treatment, two-period, two-sequence, two-way crossover, oral bioequivalence study of Oseltamivir phosphate capsules 75 mg of MSN Laboratories Private Limited, India and Tamiflu® (oseltamivir phosphate) capsules 75 mg of Genetech USA, Inc., a member of the Roche Group, USA, in healthy, adult, human subjects under fasting conditions. (Study no. 040-BE-2017).

The objective of the study was to compare the bioavailability of the stated oseltamivir phosphate 75 mg capsule manufactured by/for MSN Laboratories Private Limited, India (test drug) with the reference formulation Tamiflu® (Genetech USA) 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 Oseltamivir (as phosphate) 75 mg capsule (oseltamivir [as phosphate] 75 mg) Batch no. DC1711005A.
Treatment R:	Reference – 1 tablet Tamiflu® (oseltamivir [as phosphate] 75 mg) Batch no. 633177.

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 22 samples within 36 hours post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for oseltamivir were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 0.5 ng/mL for oseltamivir.

The study was performed with 52 participants. Data generated from a total of 50 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Oseltamivir

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)**	0.67 (0.17 – 3.5)	0.67 (0.33 – 5.0)	-	-
C_{max} (ng/mL)	97 ± 39 (90)	90 ± 32 (84)	106.4	97.8 – 115.8
AUC_{0-t} (ng.h/mL)	184 ± 40 (180)	176 ± 37 (173)	104.3	101.5 – 107.2
AUC_{0-inf} (ng.h/mL)	187 ± 40 (182)	179 ± 37 (175)	104.1	101.3 – 107.0

* geometric mean; **median (range)

The results of the study show that preset acceptance limits of 80-125 % are met by both AUC and C_{max} values regarding oseltamivir. Accordingly, the test oseltamivir (as phosphate) 75 mg capsule meets the criteria for bioequivalence with regards to the rate and extent of absorption, and is therefore, bioequivalent to the reference Tamiflu® (Genetech USA, Inc).

A biowaiver was granted for the additional 30 mg and 45 mg capsule strengths (MSN Laboratories Private Limited, India), in accordance to the WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the oseltamivir (as phosphate) 30 mg and 45 mg capsules were determined to be qualitative essential the same, the ratio of active ingredient and excipients between the strengths was considered essential the same and the dissolution profiles between the formulations for the API were determined the same.

4. Summary of product safety and efficacy

[IN018 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, [IN018 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Tamiflu® (Genetech USA, Inc.) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [IN018 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 [IN018 trade name] is used in accordance with the SmPC.

Bioequivalence

[IN018 trade name] fulfilled all criteria for waiving an *in vivo* bioequivalence study as per relevant WHO guidance. Hence, [IN018 trade name] and Tamiflu® 30 mg capsules (Genetech USA, Inc) can be considered bioequivalent.

Efficacy and Safety

Regarding clinical efficacy and safety, [IN018 trade name] is considered effective and safe to use when the guidance and restrictions in the Summary of Product Characteristics 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 [IN018 trade name] was acceptable for the following indication: **'treatment and post-exposure prophylaxis of influenza in adults and children'**, and has advised that the quality, efficacy and safety of [IN018 trade name] allow inclusion of [IN018 trade name], manufactured at MSN Laboratories Private Limited, Formulations Division, Unit-II, Survey Nos. 1277, 1319 to 1324, Nandigama (Village & Mandal), Rangareddy District, Telangana 509228, India, in the list of prequalified medicinal products.