

This part reflects the scientific knowledge and the information about this product available at the time of prequalification. Thereafter, updates may have become necessary which are included in parts 1 to 5 and, if related to pharmaceutical issues, also documented in part 8 of this WHOPAR.

SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product:	Oseltamivir (as phosphate) 30 mg Capsules*
Manufacturer of Prequalified Product:	Macleods Pharmaceuticals Limited Block No. 2 Village Theda P.O. Lodhi Majra Tehsil Baddi, Dist.: Solan Himachal Pradesh, 174101 India Tel: +91-1795 661400 Fax: +91-1795 661452
Active Pharmaceutical Ingredient (API):	Oseltamivir (as phosphate)
Pharmaco-therapeutic group (ATC Code):	Antivirals for systemic use, neuraminidase inhibitors (J05AH02)
Therapeutic indication:	Oseltamivir (as phosphate) 30 mg Capsules is indicated for the treatment of symptoms of influenza and for the prevention of influenza as detailed in the summary of product characteristics

* Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

1. Introduction

Oseltamivir (as phosphate) 30 mg Capsules is indicated for the treatment of symptoms of influenza and for the prevention 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 (3R,4R,5S)-4-(acetylamino)-5-amino-3-(1-ethylpropoxy)cyclohex-1-ene-1-carboxylate dihydrogen phosphate, is highly water soluble and slightly hygroscopic. It is manufactured in a multistep process from a well-defined starting material. Potential and actual impurities, including genotoxic impurities, were characterised and discussed with respect to their origin. The API shows polymorphism; one polymorphic form, Form A, is consistently produced and does not change during stability testing.

The API specifications are pharmacopoeial based and include tests for description, solubility, identification (IR, HPLC and phosphates), specific optical rotation, residue on ignition, heavy metals, water content (KF), related substances (HPLC and LCMS), assay (HPLC), loss on drying, residual solvents (GC), particle size and polymorphism (XRPD).

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 packaging.

Other ingredients

The capsule fill powder contains pregelatinized starch, croscarmellose sodium, povidone, talc and sodium stearyl fumarate. The capsule shells contain gelatin, iron oxide red, iron oxide yellow and titanium dioxide, while the imprint ink contains shellac and FD&C Blue # 2 Aluminium Lake (Indigo Carmine). Sodium stearyl fumarate is not of animal origin. A CEP was submitted for gelatin used in the manufacture the capsule shells. It meets the EU criteria for products with risk of transmitting animal spongiform encephalopathies.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

Oseltamivir (as phosphate) 30 mg Capsules are light yellow cap and light yellow body size '4' hard gelatin capsules, containing white to off white granules, with "30 mg" on cap and "M 53" on body imprinted with blue ink. The capsules are packaged in clear PVC/PE/PVdC-Al blisters.

The development of the final composition of the multisource product has been described. The objective was to develop a stable and robust dosage form, bioequivalent to the WHO comparator product Tamiflu® of the same strength. The comparator product was characterised to define a quality target product profile, including dissolution. The selection of excipients was based on their compatibility with oseltamivir phosphate, similarity with the comparator product and their suitability to achieve the desired characteristics of the formulation. Due to the poor flow properties of the API a dry mixing process during encapsulation was not considered. The fill powder is manufactured via a wet granulation process (organic solvent), using conventional pharmaceutical technology. Satisfactory in-process controls have been established.

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

Specifications

The product specifications are pharmacopoeial based and include tests for description, identification (HPLC, UV), average net content (mg), dissolution (UV detection), uniformity of dosage units (by weight variation), organic impurities (HPLC), assay (HPLC), water content (KF), residual solvent (GC) and microbial limits.

Stability testing

Stability studies have been conducted on samples stored at 30°C/75%RH (zone IVb) as long-term storage condition and for 6 months at accelerated conditions (40°C/75%RH) in the packaging proposed for marketing of the product. The product proved to be stable with a slight increase in water content and in degradation products, though well within justified limits. No significant change was observed at accelerated conditions. 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 Bio-Equivalence

The following bioequivalence study has been performed in 2014 according to internationally accepted guidelines.

Bioequivalence study of single dose of Oseltamivir (as Phosphate) 75 mg Capsules manufactured by Macleods Pharmaceuticals Ltd., India in comparison with Tamiflu® (oseltamivir phosphate) capsules 75 mg distributed by Genentech, Inc. USA in healthy, adult, human subjects under fasting condition (study no. BEQ-1261-OSEL-2014).

The objective of the study was to compare the bioavailability of the stated Oseltamivir (as Phosphate) 75 mg Capsules manufactured by/for Macleods Pharmaceuticals Ltd., India (test drug) with the reference formulation Tamiflu® (Genentech, Inc.) 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 capsule Oseltamivir (as Phosphate) 75 mg Capsules
Batch no. BOS302A.
- Treatment R: Reference – 1 capsule Tamiflu®
(oseltamivir 75 mg)
Batch no. 531738.

A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 29 samples within 48h 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 2.1 ng/ml for oseltamivir.

The study was performed with 72 participants; data generated from a total of 48 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)	0.82 ± 0.57	0.94 ± 0.97	-	-
C _{max} (ng/ml)	87 ± 45 (77)	84 ± 44 (74)	103.5	93.7 – 114.4

AUC _{0-t} (ng.h/ml)	147 ± 40 (142)	141 ± 39 (137)	103.7	100.5 – 107.0
AUC _{0-inf} (ng.h/ml)	153 ± 40 (148)	148 ± 40 (143)	103.4 The results of the study show	100.3 – 106.7

* geometric mean

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 Capsules, meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Tamiflu® (Genentech, Inc.).

A biowaiver was granted for the additional 30 and 45 mg capsule strengths (Macleods Pharmaceuticals Ltd., India) in accordance to WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the Oseltamivir Phosphate 30 and 45 mg capsule were determined to be qualitative essential the same, the ratio of active ingredient and excipients between the strengths is considered essential the same and the dissolution profiles between the formulations for the API was determined the same.

4. Summary of Product Safety and Efficacy

Oseltamivir (as phosphate) 30 mg Capsules has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the innovator product. Oseltamivir (as phosphate) 30 mg Capsules fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance.

The clinical safety of this product is considered to be acceptable when guidance and restrictions in the summary of product characteristics are taken into account. Reference is made to the Summary of Product Characteristics (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 Oseltamivir (as phosphate) 30 mg Capsules is used in accordance with the summary of product characteristics (SmPC).

Bioequivalence

Oseltamivir (as phosphate) 30 mg Capsules fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance.

Efficacy and Safety

Regarding clinical efficacy and safety, Oseltamivir (as phosphate) 30 mg Capsules is considered effective and safe to use when the guidance and restrictions in the SmPC are taken into consideration.

Benefit Risk Assessment

Based on the WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit-risk profile of Oseltamivir (as phosphate) 30 mg Capsules was acceptable for the treatment of symptoms of influenza and for the prevention of influenza as detailed in the summary of product characteristics and has advised to include Oseltamivir (as phosphate) 30 mg Capsules, manufactured at Macleods Pharmaceuticals Ltd, Himachal Pradesh, India in the list of prequalified medicinal products.