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) Capsules 75 mg*
Manufacturer of Prequalified Product:	Mylan Laboratories Limited Plot No. H-12 & H-13 MIDC, Waluj Industrial Area Aurangabad 431 136 Maharashtra, India
Active Pharmaceutical Ingredient (API):	Oseltamivir (as phosphate)
Pharmaco-therapeutic group (ATC Code):	Antivirals for systemic use, neuraminidase inhibitors (J05AH02)
Therapeutic indication:	Oseltamivir (as phosphate) Capsules 75 mg 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 (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

1. Introduction

Oseltamivir (as phosphate) Capsules 75 mg 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 according to SOP 20 of the WHO Prequalification programme.

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 according to the BCS. The API is described in the Ph.Int, Ph.Eur and USP.

The API is manufactured in a multi-step process from a well-defined starting material. The starting material, intermediates, reagents and solvents are adequately controlled. 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 and HPLC), water content (KF), specific optical rotation, heavy metals, organic impurities (HPLC), assay (HPLC), residual solvents, polymorphic form (XRPD), palladium content (AAS) and methyl and ethyl methanesulfonate (GC-MS). The test methods have been satisfactorily described and validated.

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 croscarmellose sodium, povidone, pregelatinised starch, sodium stearyl fumarate and talc. The capsule shell contains gelatin and titanium dioxide (E171) , D&C yellow #10 (E104) and FD&C yellow # 6 (Sunset yellow FCF, E110), while the printing ink contains black iron oxide (E172), potassium hydroxide, propylene glycol and shellac.

Finished pharmaceutical product (FPP)

Each capsule contains 98.53 mg oseltamivir phosphate equivalent to 75 mg oseltamivir.

Oseltamivir (as phosphate) Capsules 75 mg are ‘size 2’ hard gelatin capsules with yellow opaque cap and white opaque body imprinted axially with ‘MYLAN’ over ‘OS3’ in black ink on both cap and body. The capsules are filled with white to off-white powder. The capsules are packaged in white HDPE bottles with white opaque polypropylene screw cap and in PVC or Triplex blisters.

Pharmaceutical development and manufacture

The development of the final composition of the multisource product has been described. The objective was to develop a stable, robust and a reproducible dosage form, bioequivalent to the innovator product Tamiflu® of the same strength. The selection of excipients was based on past manufacturing experience, the composition of the comparator product (qualitatively the same) and API-excipient compatibility studies. Due to the very poor flow properties of the API a dry mixing process during encapsulation was not considered. The process selected entails dry granulation, milling and lubrication. The final lubricated granules are then filled in the empty hard gelatine capsule shells. Satisfactory in-process controls have been established.

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

Specifications

The finished product specifications are regarded adequate for ensuring consistent product quality and include tests for description, identification of the API (HPLC and TLC) and colorants, average fill

weight, uniformity of dosage units (by weight variation), dissolution (HPLC detection), related substances (HPLC), water content, microbial limits and assay (HPLC).

Stability testing

Stability studies have been conducted at 30°C/75%RH as long-term storage conditions and for six months at accelerated conditions in the packaging proposed for marketing the product. The data showed a slight increase of degradation products, though well within justified limits. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

Conclusions

The quality part of the dossier is accepted.

3. Assessment of Bioequivalence

The following bioequivalence study was performed in 2012 according to internationally accepted guidelines.

A randomised, balanced, open-label, two-treatment, two-period, two-sequence, single-dose, crossover, bioequivalence study of Oseltamivir Phosphate capsules 75 mg of Mylan Laboratories Limited (formally known as Matrix Laboratories Limited), with Tamiflu® (oseltamivir phosphate) capsules 75 mg of Roche Laboratories Inc, in normal, healthy, adult, male and female human subjects under fasting conditions (study No. ARL/11/526).

The objective of the study was to compare the bioavailability of the stated Oseltamivir Phosphate 75 mg capsules manufactured by Matrix Laboratories Limited, India (test drug) with the same dose of the reference formulation (Tamiflu®, Roche Laboratories Inc) and to assess bioequivalence. The comparison was performed as a single-centre, open-label, randomised, crossover study in healthy male 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 phosphate 75 mg (oseltamivir phosphate 75 mg) Batch No. 1085225
Treatment R	Reference – 1 capsule Tamiflu® (oseltamivir phosphate 75 mg) Batch No. U4071

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 20 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 analysed using a validated LC-MS/MS method. The limit of quantification was stated to be about 2 ng/ml for oseltamivir.

The study was performed with 36 participants; data generated from a total of 36 subjects were used for analysis to establish pharmacokinetic parameters and to 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} (hour)	0.72 ± 0.37	0.66 ± 0.20	–	–
C_{max} (µg/ml)	104 ± 39 (96)*	101 ± 44 (93)*	104.0	89.9–120.2

AUC_{0-t} (µg·hour/ml)	200 ± 51 (192)*	209 ± 57 (201)*	95.5	86.3–105.8
AUC_{0-inf} (µg·hour/ml)	206 ± 51 (198)*	215 ± 57 (208)*	95.6	86.7–105.4
* geometric mean				

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 capsule Oseltamivir Phosphate 75 mg meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Tamiflu® (Roche Laboratories Inc).

A biowaiver was granted for the additional strengths Oseltamivir Phosphate 30 mg and 45 mg (Matrix Laboratories Limited, India) in accordance to WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the Oseltamivir 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 is considered essentially the same and the dissolution profiles between the formulations for the APIs were determined the same.

4. Summary of Product Safety and Efficacy

Oseltamivir (as phosphate) Capsules 75 mg 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) Capsules 75 mg 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) Capsules 75 mg is used in accordance with the summary of product characteristics (SmPC).

Bioequivalence

Oseltamivir (as phosphate) Capsules 75 mg 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) Capsules 75 mg 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) Capsules 75 mg was acceptable for 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) Capsules 75 mg, manufactured at Mylan Laboratories Limited, Waluj Industrial Area, Aurangabad, India in the list of prequalified medicinal products.