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) 75mg Capsules*.
Manufacturer of the Prequalified Product:	Strides Arcolab Limited 36/7, Suragajakkanahalli, Indlavadi Cross, Anekal Taluk, Bangalore-562 106, INDIA. Tel.: 91-80- 67840600 Fax: 91-80- 67840606
Active Pharmaceutical Ingredient (API):	Oseltamivir phosphate
Pharmaco-therapeutic group (ATC Code):	Antivirals for systemic use, neuraminidase inhibitors (J05AH02)
Therapeutic indication:	Oseltamivir (as phosphate) 75mg Capsules is indicated for the treatment and prophylaxis of Influenza virus A and Influenza virus B infection.

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

1. Introduction

Oseltamivir (as phosphate) 75mg Capsules is indicated for the treatment and prophylaxis of both Influenza virus A and Influenza virus B infection in adults and children.

The appropriate use of Tamiflu for prevention of influenza should be determined on a case-by-case basis by the circumstances and the population requiring protection.

2. Assessment of Quality

The assessment was done according to SOP 20 of the WHO Prequalification programme.

Active Pharmaceutical Ingredient (API)

Oseltamivir phosphate, (3R,4R,5S)-4-acetylamino-5-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid, ethyl ester, phosphate (1:1) is pro-drug of the active metabolite, oseltamivir carboxylate. It is highly water soluble and non-hygroscopic.

The Ph.Int. monograph for Oseltamivir phosphate has been adopted by WHO's Expert Committee on Specifications for Pharmaceutical Preparations for addition to the Fourth edition of the Ph.Int., Second Supplement.

Detail on the multi-step synthesis of oseltamivir phosphate – including control of the starting materials, intermediates, reagents and solvents – has been assessed through WHO's APIMF procedure. The critical parameters have been identified and in-process controls are set at each stage to check the reaction completion and other critical process parameters. Prospective process validation performed on three consecutive batches demonstrated that the manufacturing process is reproducible and robust.

The specifications of oseltamivir phosphate include tests for description, solubility, identification, water content (KF), heavy metals, related substances (HPLC), assay (HPLC), residual solvents, particle size and visible foreign matter. 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 content formulation include croscarmellose sodium, povidone, pre-gelatinised starch, sodium stearyl fumarate and talc. The capsule shell contains gelatin, iron oxide (red and yellow) and titanium dioxide, while the printing ink contains iron oxide black, potassium hydroxide and shellac.

Finished Pharmaceutical Product (FPP)

Product specification

Each capsule contains 98.50mg oseltamivir phosphate equivalent to 75mg oseltamivir.

Oseltamivir (as phosphate) 75mg Capsules are size '2' hard gelatin capsules with cream cap and brown body, printed 'OP' on cap and '75' on body in black. The capsules contain white to off-white free flowing powder. The capsules are packaged in blisters constructed from plain aluminium blister foil and clear PVC/PVdC coated PVC (pack size: 10 capsules per blister card, one blister card per carton).

Pharmaceutical development and manufacture

The development of the final composition of Oseltamivir (as phosphate) 75mg Capsules has been described. The objective was to develop a stable, robust and a reproducible dosage form, bioequivalent to the innovator product Tamiflu® 75mg hard capsule. Comparative dissolution testing in multi BCS media was used to target the in vitro release properties of the innovator product.

The fill powder is manufactured by a non-aqueous wet granulation process, using conventional pharmaceutical technology. During process development the manufacturing steps and critical process parameters were identified. Validation data presented for four batches demonstrated the consistency of the process.

The finished product specifications are regarded adequate for ensuring consistent product quality and include tests for description, identification (HPLC and TLC), average fill weight, uniformity of fill weight, uniformity of dosage units (by weight variation), disintegration time, dissolution, related substances (HPLC), water content, residual solvents (GC), microbial limits and assay (HPLC).

Stability testing

Stability studies have been conducted on the four batches used in the process validation studies at 25°C/60%RH and 30°C/75%RH as long-term storage conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product. The data showed little change with time and were well within the agreed specifications at all storage conditions. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

Conclusions

The quality part of the dossier is accepted.

3. Assessment of Bioequivalence

The following bioequivalence study has been performed in 2006 according to internationally accepted guidelines.

A randomized, single dose, open label, two period, two treatment, two sequence, crossover bioequivalence study of Oseltamivir Phosphate capsules 75 mg manufactured by Strides Arcolab Ltd, India with Tamiflu® (oseltamivir phosphate) capsules 75 mg manufactured by F. Hoffmann – La Roche Ltd., Basel, Switzerland in healthy male subjects under fasting condition (study no. US/AHD/06/010).

The objective of the study was to compare the bioavailability of the stated oseltamivir 75 mg capsule manufactured by Strides Ltd., India (test drug) with the same dose of the reference formulation (Tamiflu, Roche) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, 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 75 mg (oseltamivir 75 mg) Batch no. 7202743
Treatment R:	Reference – 1 capsule Tamiflu (oseltamivir 75 mg) Batch no. B1120

A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 23 samples within 48 h 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 and oseltamivir carboxylate were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 2 ng/ml for oseltamivir and about 15 ng/ml for oseltamivir carboxylate.

The study was performed with 48 participants; data generated from a total of 42 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Oseltamivir

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVA log)
t_{max} (h)	1.13 ± 0.88	0.85 ± 0.53	-	-
C_{max} (ng/ml)	94 ± 35 (87)	93 ± 31 (87)	100.2	90.7 – 110.7
AUC_{0-t} (ng.h/ml)	223 ± 61 (216)	219 ± 59 (212)	101.9	97.4 – 106.5
AUC_{0-inf} (ng.h/ml)	235 ± 70 (227)	232 ± 71 (222)	101.9	95.9 – 108.3

* geometric mean

Oseltamivir carboxylate

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)	4.5 ± 0.9	4.6 ± 0.9	-	-
C_{max} (ng/ml)	520 ± 156 (497)	507 ± 149 (482)	103.0	100.0 – 106.0
AUC_{0-t} (ng.h/ml)	5589 ± 1364 (5404)	5411 ± 1351 (5215)	103.6	101.0 – 106.3
AUC_{0-inf} (ng.h/ml)	5880 ± 1377 (5699)	5736 ± 1380 (5547)	102.7	100.2 – 105.4

* geometric mean

The pharmacokinetic data for oseltamivir carboxylate are considered supportive and indicated a comparable bioavailability between Test and Reference.
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 product Oseltamivir 75 mg capsule meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference Tamiflu® (Roche).

4. Summary of Product Safety and Efficacy

Oseltamivir (as phosphate) 75mg Capsules has been shown to conform to the same appropriate standards of quality, efficacy and safety as those required for the innovator`s product. According to the submitted data on quality and bioavailability it is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Tamiflu® (Roche) for which benefits have been proven in terms of clinical and virological efficacy.

The clinical safety of this product is considered to be acceptable when guidance and restrictions presented in the Summary of Product Characteristics are taken into consideration. Reference is made to the SmPC (WHOPAR part 4) for data on clinical safety.

5. Benefit Risk Assessment and Overall Conclusion

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Bioequivalence

Oseltamivir (as phosphate) 75mg Capsules has shown to be bioequivalent to Tamiflu® (Roche).

Efficacy and Safety

Regarding clinical efficacy and safety, Oseltamivir (as phosphate) 75mg Capsules is considered effective and safe to use when the guidance and restrictions presented in the Summary of Product Characteristics are taken into consideration.

Benefit Risk Assessment

Based on the WHO assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered by consensus that the benefit risk profile of was acceptable for the following indication: "**the treatment and prophylaxis of Influenza infection"** and has advised to include Oseltamivir (as phosphate) 75mg Capsules, manufactured at Strides Arcolab Limited 36/7, Suragajakkanahalli, Indlavadi Cross, Anekal Taluk, Bangalore-562 106, India in the list of prequalified medicinal products.