

### SCIENTIFIC DISCUSSION

<b>Name of the Finished Pharmaceutical Product:</b>	Oseltamivir Capsules 75 mg*
<b>Manufacturer of Prequalified Product:</b>	Cipla Ltd. Plot No .S-103 – S-105, S-107 –S-112, L-147,L-147-1 Verna Industrial Estate, Verna, Salcette - Goa. Pin 403 722 India
<b>International Nonproprietary Name:</b>	Oseltamivir
<b>Pharmaco-therapeutic group (ATC Code):</b>	Antivirals for systemic use, neuraminidase inhibitors (J05AH02)
<b>Therapeutic indication:</b>	Oseltamivir Capsules 75 mg 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 under local DRA responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

## 1. Introduction

Oseltamivir Capsules 75 mg is indicated for the treatment and prophylaxis of both Influenza virus A and Influenza virus B infection.

- For the treatment of influenza in adults and children one year of age or older, who present with symptoms typical of influenza, when influenza virus is circulating in the community. Efficacy has been demonstrated when treatment is initiated within two days of first onset of symptoms. This indication is based on clinical studies of naturally occurring seasonal influenza in which the predominant infection was influenza A.
- Post exposure prevention in individuals one year of age or older following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community.
- In exceptional situations (e.g. in case of a mismatch between the circulating and vaccine virus strains, and a pandemic situation) seasonal prevention could be considered in individuals one year of age or older.

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 a 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.

The quality specifications of oseltamivir phosphate are in line with ICH Q3A(R2) and are considered adequate for the control of its quality. All methods in the specification have been satisfactorily described and all the key methods validated. The limits have been justified by reference to batch analyses data, which confirm both compliance with the proposed specification and consistency between batches.

Based on the results of stability testing conducted according to the requirements of WHO, a retest period of 24 months was approved for the API, if stored in the original container at a temperature below 25°C.

### Other ingredients

Other ingredients used in the capsule content formulation include croscarmellose sodium, pregelatinised starch, sodium stearyl fumarate and talc, all of compendial grade. The capsule shell contains gelatin, iron oxide yellow, titanium dioxide, sodium lauryl sulphate, liquid paraffin while the printing ink contains shellac, black iron oxide and propylene glycol.

### Finished Pharmaceutical Product (FPP)

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

Oseltamivir Capsules 75 mg are hard gelatin capsules consisting of a white body spin printed with "75" and a yellow cap. Imprints are black. The capsules contain white to off-white free flowing powder. The capsules are packaged in white, induction-sealed, HDPE bottles fitted with child-resistant closures and containing a silica gel bag desiccant (pack size: 30 capsules) or in clear PVC/PE/PVDC-aluminium blister cards (pack size: one card containing 10 capsules per box).

#### *Pharmaceutical development*

The development of the final composition of Oseltamivir Capsules 75 mg has been described. A micronised grade of the API is used to obtain uniform distribution of the API. The fill powder is manufactured by a wet granulation process, using conventional pharmaceutical technology. Dehydrated ethanol is used as granulating solvent. All the manufacturing processes and in-process controls are satisfactorily described.

Validation data presented for three primary batches demonstrated the consistency of the process. The applicant committed to validate not less than the first three commercial batches prior to the marketing of the FPP to assure that production processes are well controlled. The proposed specifications, analytical methods with validation, and batch quality control results ensure consistent quality for this finished pharmaceutical product.

#### *Stability testing*

Stability studies have been performed at 25°C/60%RH and 30°C/65%RH as long-term storage conditions and at accelerated conditions. Based on the data a shelf-life of 24 months has been allowed for the FPP when stored below 25°C.

#### 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.

Bioequivalence study comparing Oseltamivir capsules 75 mg (containing oseltamivir phosphate equivalent to oseltamivir 75 mg) of Cipla Ltd., India with Tamiflu® capsule (containing oseltamivir phosphate equivalent to oseltamivir 75 mg) of Roche, UK in healthy male human subjects. (Study no. 05-12-042).

The objective of the study was to compare the bioavailability of the stated oseltamivir 75 mg capsule manufactured by Cipla Ltd., India (test drug) with the same dose of the reference product (Tamiflu, Roche) 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 75 mg  
(oseltamivir 75 mg)  
Batch no. X60154.
- Treatment R: Reference – 1 capsule Tamiflu  
(oseltamivir 75 mg)  
Batch no. B113612.

A 5-day wash-out period was observed between the two study periods. Serial blood samples (1 pre-dose sample and 24 samples within 72 h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C<sub>max</sub> and t<sub>max</sub> for bioequivalence evaluation. Drug concentrations of 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 9.3 ng/ml for oseltamivir carboxylate.

The study was performed with 34 participants; data generated from a total of 30 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 $\pm$ SD (* )	Reference (R) arithmetic mean $\pm$ SD (* )	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
$t_{\max}$ (h)	0.98 $\pm$ 0.81	1.03 $\pm$ 1.09	-	-
$C_{\max}$ (ng/ml)	71 $\pm$ 29 (66)	75 $\pm$ 28 (70)	94.7	81.5 – 110.1
AUC <sub>0-t</sub> (ng.h/ml)	160 $\pm$ 36 (156)	164 $\pm$ 36 (160)	97.5	92.9 – 102.3
AUC <sub>0-inf</sub> (ng.h/ml)	167 $\pm$ 37 (163)	171 $\pm$ 36 (168)	97.2	92.9 – 101.5

\* geometric mean

#### Oseltamivir carboxylate

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean $\pm$ SD (* )	Reference (R) arithmetic mean $\pm$ SD (* )	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
$t_{\max}$ (h)	4.9 $\pm$ 1.3	5.0 $\pm$ 1.4	-	-
$C_{\max}$ (ng/ml)	389 $\pm$ 102 (377)	380 $\pm$ 108 (366)	102.8	97.3 – 108.7
AUC <sub>0-t</sub> (ng.h/ml)	4546 $\pm$ 1035 (4443)	4508 $\pm$ 1002 (4411)	100.7	97.1 – 104.5
AUC <sub>0-inf</sub> (ng.h/ml)	4899 $\pm$ 1005 (4807)	4931 $\pm$ 1013 (4836)	99.4	96.2 – 102.8

\* geometric mean

#### Conclusions:

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 Capsules 75 mg 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 Capsules 75 mg 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 virological and immunological 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 SPC (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 SPC. 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 Capsules 75 mg has shown to be bioequivalent to Tamiflu<sup>®</sup> (Roche).

### Efficacy and Safety

Regarding clinical efficacy and safety, Oseltamivir Capsules 75 mg 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 Oseltamivir Capsules 75 mg was acceptable for the following indication: “**the treatment and prophylaxis of Influenza infection**” and has advised to include Oseltamivir Capsules 75 mg, manufactured at, Cipla Ltd. Goa Plot S-103 –S105 S-107 – S-112,L-147,L-147-1,Verna Industrial Estate, Verna, Salcette - Goa, Pin 403 722 GOA, India in the list of prequalified medicinal products.