COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Oseltamivir Zentiva 30 mg, 45 mg and 75 mg hard capsules

(oseltamivir)

NL/H/4650/001-003/DC

Date: 25 May 2020

This module reflects the scientific discussion for the approval of Oseltamivir Zentiva 30 mg, 45 mg and 75 mg hard capsules. The procedure was finalised at 19 March 2020. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Oseltamivir Zentiva 30 mg, 45 mg and 75 mg hard capsules, from Zentiva k.s.

Treatment of influenza
Oseltamivir is indicated in adults and children including full term neonates 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.

Prevention of influenza

- Post-exposure prevention in individuals 1 year of age or older following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community.
- The appropriate use of oseltamivir for prevention of influenza should be determined on a case by case basis by the circumstances and the population requiring protection. 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.
- oseltamivir is indicated for post-exposure prevention of influenza in infants less than 1 year of age during a pandemic influenza outbreak.

Oseltamivir is not a substitute for influenza vaccination.

The use of antivirals for the treatment and prevention of influenza should be determined on the basis of official recommendations. Decisions regarding the use of oseltamivir for treatment and prophylaxis should take into consideration what is known about the characteristics of the circulating influenza viruses, available information on influenza drug susceptibility patterns for each season and the impact of the disease in different geographical areas and patient populations.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Tamiflu 30 mg, 45 mg and 75 mg, hard capsules which have been registered in the EEA by Roche Registration GmbH since 20 May 2002 through a centralised procedure (EU/1/02/222).

The concerned member states (CMS) involved in this procedure were Germany, France and Spain.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Oseltamivir Zentiva is a hard gelatin capsule:

- Oseltamivir Zentiva 30 mg is a capsule with a light-yellow opaque body with a black band imprinted with “M” and a light-yellow opaque cap imprinted with “30 mg”. Each capsule contains oseltamivir phosphate equivalent to 30 mg of oseltamivir.
- Oseltamivir Zentiva 45 mg is a capsule with a grey opaque body with a black band imprinted with “M” and a grey opaque cap imprinted with “45 mg”. Each capsule contains oseltamivir phosphate equivalent to 45 mg of oseltamivir.
- Oseltamivir Zentiva 75 mg is a capsule with a grey opaque body with a black band imprinted with “M” and a light-yellow opaque cap imprinted with “75 mg”. Each capsule contains oseltamivir phosphate equivalent to 75 mg of oseltamivir.

The hard capsules are packed in PVC/PE/PVdC – Al blisters.

The excipients are:
Capsule core - pregelatinized starch (derived from maize starch), povidone K-30, croscarmellose sodium, talc and sodium stearyl fumarate
Capsule shell - gelatin, titanium dioxide (E171), yellow iron oxide (E172)[for 30 mg and 75 mg], red iron oxide (E172)[for 30 mg and 75 mg] and black iron oxide (E172)[for 45 mg and 75 mg]
Printing ink - Black ink TEK SW 9008: shellac, propylene glycol, concentrated ammonia solution, black iron oxide (E172) and potassium hydroxide.

II.2 Drug Substance

The active substance is oseltamivir phosphate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white powder, which is freely soluble in water and in methanol, practically insoluble in methylene chloride. Oseltamivir phosphate is manufactured as crystalline Form-A. The active substance consists of three asymmetric carbon atoms; hence eight stereo isomers are possible. The manufacturer produces the R, R, S-isomer. It is slightly hygroscopic.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible

Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Additional testing is specified in the CEP for residual solvents and an impurity. The finished product manufacturer also controls the particle size of the drug substance and the polymorphic form. The particle size has been justified. Batch analytical data demonstrating compliance with this specification have been provided for four batches.

Stability of drug substance
The active substance is stable for 3 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their function explained. The formulation optimisation studies carried out are acceptable. The dissolution conditions are in line with the Ph.Eur and the recommendations given in the Guideline on the investigation of bioequivalence CPMP/EWP/QWP/1401/98/Rev.1/Corr**) and are therefore acceptable. Comparative *in-vitro* dissolution profile data between the batches of the test product and the reference product Tamiflu in pH 1.2, 4.5 and 6.8 phosphate buffer has been provided. In pH 1.2, 4.5 and 6.8, dissolution is rapid and the dissolution profiles between test and reference products can be considered as being similar since more than 85% of active substance is dissolved within 15 minutes. To support the application, a bioequivalence study has been performed with the 75 mg strength of the finished product, and a biowaiver for the other strengths has been requested. In pH 1.2, 4.5 and 6.8, more than 85% of the active is released within 15 minutes for the 75 mg bio-batch strength and the additional strengths of the test product, so the profiles can be considered as similar. Overall, the pharmaceutical development has been adequately performed.

Manufacturing process
The manufacturing process involving sifting, blending, compaction, milling (sizing of granules), lubrication, capsule filling and packaging and has been validated according to relevant European guidelines. Process validation data on the product have been presented

for three production scale batches of each capsule strength batches in accordance with the relevant European guidelines.

Control of excipients

All excipients comply with the specifications of the respective Ph. Eur. monographs, current edition. In addition to the Ph. Eur. tests, pregelatinized starch, croscarmellose sodium and sodium stearyl fumarate are also subject to additional in-house tests. Specifications for functionality-related tests on pregelatinized starch and croscarmellose sodium have been provided. Relevant functionality-related quality aspects of the excipients croscarmellose sodium, talc and sodium stearyl fumarate, that may be relevant for the product manufacturing process, were appropriately discussed. The specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, identification of colouring agents, average blend fill mass, average mass of filled capsule, uniformity of dosage units, disintegration time, water determination, dissolution, assay, related substances, impurities and microbial examination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three production scale batches for each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three batches for each strength stored at 25°C/60% RH (24 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). A photostability study was performed on one batch of each strength of the drug product in line with ICH guideline ICH Q1B. The results from the photostability study indicate that there were no out of specification results for the parameters tested in samples directly exposed. On basis of the data submitted, a shelf life was granted of 3 years when stored below 30°C. For the storage of the pharmacy compounded suspension a shelf life of 10 days when stored below 25°C could be granted.

Specific measures for the prevention of transmission of animal spongiform encephalopathies

Except for the empty hard gelatine capsule shells, no materials derived from animal and/or human origin are used in the manufacture of Oseltamivir Zentiva. The MAH submitted CEPs issued by the EDQM for gelatin used in the manufacturing of the hard capsules. This is acceptable in line with Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3). TSE/BSE certificates for the active pharmaceutical ingredient and excipients from the respective suppliers for all excipients are provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Oseltamivir Zentiva has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Oseltamivir Zentiva is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Tamiflu which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Oseltamivir is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Oseltamivir Zentiva 75 mg hard capsules (Zentiva k.s., Czech Republic) is compared with the pharmacokinetic profile of the reference product Tamiflu 75 mg, hard capsules (Roche Registration GmbH, Germany).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions with the EU reference product. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

A biowaiver has been requested for the lower strengths. All the proposed products were manufactured by the same process and the composition of the different strengths is qualitatively the same. The composition of the different strengths is dose proportional. Dissolution data have been provided at a pH 1.2, 4.5 and 6.8 showing comparable dissolution. Hence, all conditions have been met and a biowaiver has been granted.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 52 healthy male subjects, aged 20-44 years. Each subject received a single dose (75 mg) of one of the 2 oseltamivir formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected at pre-dose and at 0.17, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 36 and 48 hours after administration of the products.

The design of the study is acceptable. According to the SmPC, the capsules can be taken with or without food. As such, the fasting condition applied in the study is considered adequate.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

One subject withdrew his consent after dosing in the first period, nine subjects were withdrawn due to adverse events (vomiting) and two subjects did not report to the facility during admission of second period. Therefore, a total of 40 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of oseltamivir under fasted conditions.

Treatment N=40	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	149 ± 32	151 ± 32	63 ± 28	0.51 (0.27 – 4.0)	2.3 ± 0.7
Reference	144 ± 30	146 ± 30	62 ± 29	0.75 (0.5 – 3.0)	2.5 ± 0.9
***Ratio (90% CI)**	1.04 (1.01 – 1.07)	--	1.04 (0.92 – 1.17)	--	--
CV (%)	8.5	--	31.5	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Oseltamivir Zentiva is considered bioequivalent with Tamiflu. The results obtained for the 75 mg capsule could be extrapolated to the 30 and 45 mg capsules.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Oseltamivir Zentiva.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	- Development of oseltamivir-induced viral resistance
Important potential risks	- Exposure during pregnancy
Missing information	- Treatment of influenza in immunocompromised patients

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Tamiflu. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Oseltamivir Zentiva 30 mg, 45 mg and 75 mg hard capsules have a proven chemical-pharmaceutical quality and are generic forms of Tamiflu 30 mg, 45 mg and 75 mg, hard capsules. Tamiflu is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Oseltamivir Zentiva with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 19 March 2020.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse