20 March 2014
EMA/260303/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ebilfumin

International non-proprietary name: oseltamivir

Procedure No. EMEA/H/C/003717

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Table of contents

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Actavis Group PTC ehf submitted on 23 April 2013 a Marketing Authorisation application to the European Medicines Agency (EMA) for Ebilfumin, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004 – 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 March 2014.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference medicinal product for which a Marketing Authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indications:

- Treatment of influenza

  In patients one year of age and older who present with symptoms typical of influenza, when influenza virus is circulating in the community.

  Ebilfumin is indicated for the treatment of infants less than 1 year of age during a pandemic influenza outbreak (see section 5.2). The treating physician should take into account the pathogenicity of the circulating strain and the underlying condition of the patient to ensure there is a potential benefit to the child.

- 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 Ebilfumin 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.

Ebilfumin is indicated for post-exposure prevention of influenza in infants less than 1 year of age during a pandemic influenza outbreak (see section 5.2).

Ebilfumin is not a substitute for influenza vaccination.

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Tamiflu instead of non-clinical and clinical unless justified otherwise.

Information on paediatric requirements

Not applicable.

The chosen reference medicinal product is:

- Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:
  - Product name, strength, pharmaceutical form: Tamiflu, 30 mg, 45 mg & 75 mg, hard capsules
  - Marketing authorisation holder: Roche Registration Ltd
  - Date of authorisation: 20-06-2002
  - Marketing authorisation granted by: Community
  - Community Marketing authorisation number: EU/1/02/222/003, EU/1/02/222/004, EU/1/02/222/001

- Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:
  - Product name, strength, pharmaceutical form: Tamiflu, 30 mg, 45 mg & 75 mg, hard capsules
  - Marketing authorisation holder: Roche Registration Ltd
  - Date of authorisation: 20-06-2002
  - Marketing authorisation granted by: Community
  - Community Marketing authorisation number: EU/1/02/222/003, EU/1/02/222/004, EU/1/02/222/001

- Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:
  - Product name, strength, pharmaceutical form: Tamiflu 75 mg, hard capsules
  - Marketing authorisation holder: Roche Registration Ltd
  - Date of authorisation: 20-06-2002
  - Marketing authorisation granted by: Community
  - Community Marketing authorisation number: EU/1/02/222/001
  - Bioavailability study number(s): 2603/11

Scientific advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application

1.2. Manufacturer

Manufacturer(s) responsible for batch release

Actavis hf.
Reykjavikurvegur 78
IS- 220 Hafnarfjörðu
ICELAND

1.3. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was Milena Stain.

- The application was received by the EMA on 23 April 2013.
- The procedure started on 22 May 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 9 August 2013.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 05 September 2013.
- During the meeting on 16 - 19 September 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 19 September 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 October 2013.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 22 November 2013.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 05 December 2013.
- During the CHMP meeting on 16 - 19 December 2013, the CHMP agreed on a list of outstanding issues to be addressed by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 17 January 2014.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 28 January 2014.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 06 February 2014.
- During the CHMP meeting on 17 - 20 February 2014 the CHMP agreed on a second list of outstanding issues to be addressed by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 25 February 2014.

- The Rapporteur circulated the Assessment Report on the applicant's responses to the second List of Outstanding Issues to all CHMP members on 06 March 2014.
- During the meeting on 17 - 20 March 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Ebilfumin.

2. Scientific discussion

2.1. Introduction

Influenza is an acute viral infection that spreads easily from person to person and can affect anybody in any age group. Influenza circulates worldwide and causes annual epidemics that peak during winter in temperate regions. Influenza is thus a serious public health problem that causes severe illnesses and deaths for higher risk populations.

There are three types of seasonal influenza – A, B and C. Type A influenza viruses are further typed into subtypes according to different kinds and combinations of virus surface proteins. Among many subtypes of influenza A viruses, currently influenza A(H1N1) and A(H3N2) subtypes are circulating among humans.

Seasonal influenza is characterized by a sudden onset of high fever, cough (usually dry), headache, muscle and joint pain, severe malaise, sore throat and runny nose. The incubation period is about two days.

The most effective way to prevent the disease or severe outcomes from the illness is vaccination.

In addition, antiviral drugs for treatment and prevention of influenza are available. There are two classes of such medicines, 1) adamantanes (amantadine and remantadine), and 2) inhibitors of influenza neuraminidase (oseltamivir and zanamivir).

Ebilfumin (oseltamivir), a neuraminidase inhibitor, ATC Code: J05AH02, is a generic of the originator product Tamiflu. The active metabolite is a selective inhibitor of influenza virus neuraminidase enzymes, which are glycoproteins found on the virion surface. Viral neuraminidase enzyme activity is important both for viral entry into uninfected cells and for the release of recently formed virus particles from infected cells, and for the further spread of infectious virus in the body.

Ebilfumin is indicated for the treatment and prevention of influenza in patients one year of age and older and for the treatment and prevention of influenza in patients less than one year of age during a pandemic influenza outbreak. The indication proposed for Ebilfumin is the same as authorised for the Reference medicinal product.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard capsules containing 30 mg, 45 mg and 75 mg of oseltamivir as active substance.

Other ingredients are:

Capsule core
Pregelatinized starch (derived from maize starch)
Talc
Povidone (K-29/32)
Croscarmellose sodium
Sodium stearyl fumarate

Capsule shell-30 mg
Gelatin
Yellow iron oxide (E172)
Titanium dioxide (E171)

Capsule shell-45 mg
Gelatin
Titanium dioxide (E171)

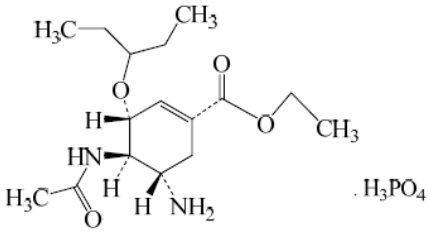
Capsule shell-75 mg
Cap:
Gelatin
Yellow iron oxide (E172)
Titanium dioxide (E171)
Body:
Gelatin
Titanium dioxide (E171)

Printing ink
Shellac Glaze-45% (20% esterified)
Black iron oxide (E172)
Propylene glycol (E1520)
Ammonium hydroxide 28% (E527)

The product is available in PVC/PE/PVDC/Al blisters or HDPE containers with LDPE lid (and a desiccant).

2.2.2. Active substance

The chemical name of oseltamivir phosphate *is* ethyl (3R,4R,5S)-4-acetamido-5-amino-3-(1-ethyl
propoxy)cyclohex-1-ene-1-carboxylate phosphate and has the following structure:



The structure of oseltamivir phosphate has been confirmed by means of CHN analysis, DSC analysis, UV, FT-IR, ^{1}H NMR and mass spectroscopy.

Oseltamivir phosphate is a white or almost white powder, slightly hygroscopic and freely soluble in water and in methanol, practically insoluble in methylene chloride.

Oseltamivir phosphate exhibits stereoisomerism due to the presence of three chiral centres; eight stereoisomers are therefore possible. The manufacturer consistently produces the R, R, S isomer. Enantiomeric purity is controlled routinely by specific optical rotation.

Several polymorphic forms exist of oseltamivir phosphate. Comparison of FT-IR spectra and Powder X-ray diffractogram with data of literature ensures that crystalline form A of oseltamivir phosphate is consistently manufactured. Form A was found to be the most stable form and easily formed. Stability studies of the active substance and finished product indicate no transition to a different polymorph.

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

There is a monograph of oseltamivir phosphate in the European Pharmacopoeia.

Manufacture

The active substance is sourced from one manufacturer.

Oseltamivir phosphate is synthesized in six main steps using a well-defined starting material with acceptable specification. No reprocessing, reworking or blending of batches is performed.

The characterisation of the active substance and its impurities (including potential genotoxic impurities) are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Specification

The active substance specification includes tests for appearance, identification (IR, optical rotation), assay (HPLC), impurities (HPLC), residual solvents (GC), water content (KF), heavy metals (Ph.Eur.), and residue on ignition (Ph. Eur.).

All parameters included in the specification are in line with the current Ph. Eur. monograph and applicable guidance.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Batch analysis data of three commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on three commercial scale batches of active substance from the proposed manufacturer stored in a container closure system representative of that intended for the market for 36 months under long term conditions at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided.

Stress and forced degradation studies have been performed. Oseltamivir phosphate is very sensitive to base, sensitive to acid, peroxide and water at 60 °C and only slightly sensitive to thermal effects and sun light.

The following parameters were tested: appearance, identification, water content, related substances, assay and polymorphism. The analytical methods used were the same as for release and were stability indicating.

The stability results indicate that the drug substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container and storage conditions.

2.2.3. Finished medicinal product

Pharmaceutical development

The aim of the development was to formulate hard gelatin capsules of oseltamivir with 30 mg, 45 mg and 75 mg bioequivalent to the reference product Tamiflu.

The pharmaceutical development was focused on: dose-proportional composition of 30 mg, 45 mg and 75 mg strengths; fast disintegration of the capsule with fast release and dissolution of the active substance; use of excipients described in the European Pharmacopoeia and compatible with the active substance and the definition of critical process parameters.

The qualitative composition and pharmaceutical form of Ebilfumin are the same as the reference product.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The Ebilfumin application concerns three strengths (30, 45 and 75 mg). A bioequivalence study has been performed on the 75 mg strength. The dissolution profiles of the *Ebilfumin* 75 mg capsule and of the reference Tamiflu 75 mg used in the bioequivalence study have been compared in order to demonstrate similarity.
The dissolution profiles of the other two strengths have also been compared to Ebilfumin 75 mg which has been used in the bioequivalence study (biobatch) as per the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr). Please also refer to 2.4.1 of this report."

Dissolution studies of the three strengths performed in the physiological range (pH 1.1, pH 4.5 and pH 6.8) confirmed that more than 85 % of the active substance dissolved within 15 minutes, similarly to the reference product. The batch used for the bioequivalence studies was manufactured at pilot scale but according to the commercial manufacturing process.

The suitability of the dissolution method used for batch release has been demonstrated.

A 6-month stability study demonstrated a similar impurity profile between Ebilfumin and the reference product.

The primary packaging is PVC/PE/PVDC/Al blisters or HDPE containers with LDPE lid (and a desiccant). The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

The pharmaceutical development section is adequately drawn up and contains all relevant data.

Adventitious agents

Gelatine obtained from bovine sources is used in the product. A valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

Manufacture of the product

The manufacturing process consists of 5 main steps: blending, wet granulation, blending of extragranular components, capsule filling and packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form, i.e. appearance, identification (HPLC, UV), uniformity of dosage units (Ph.Eur.), assay (HPLC), disintegration (Ph. Eur.), related substances (HPLC), dissolution (UV) and microbiological quality (Ph. Eur.).

Batch analysis results are provided for two pilot batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of two pilot batches of each strength of the finished product stored under long term conditions for 12 months at 25 ºC / 60% RH, for up to 6 months under accelerated conditions at 40 ºC / 75% RH, and for up to 9 months under intermediate conditions at 30 ºC / 75% RH according to the ICH guidelines were provided. The batches of medicinal product are representative to those proposed for marketing and were packed in primary packaging representative of those proposed for marketing.

Samples were tested for appearance, disintegration, assay, related substances, dissolution and microbial quality. The analytical procedures used are stability indicating.

Based on available stability data, the shelf-life the 30, 4 and 75 mg hard capsule as stated in the SmPC are acceptable.

In addition, satisfactory stability studies to support the shelf lives of pharmacy compounded suspensions as described in the SmPC were provided. All information regarding these pharmacy compounding suspensions, including dose recommendations for infants less than one year is therefore substantiated.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

Not applicable

2.3. Non-clinical aspects

2.3.1. Introduction

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. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity / environmental risk assessment

No Environmental Risk Assessment was submitted. Justification was provided by the applicant based on the assumption that there will be no significant increase of the amount of the active substance on the market and, therefore, no significant increase of environmental exposure. The CHMP agreed with this justification.

2.3.3. Discussion on non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of oseltamivir are well known. As oseltamivir is a widely used and well-known active substance, the Applicant did not provide additional non-clinical studies. Initial concerns about search-methodology were satisfactorily addressed. The CHMP did not consider that further non-clinical studies are necessary and that the overview based on literature review is appropriate.

2.3.4. Conclusion on the non-clinical aspects

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate. The MAH did not provide an ERA arguing that no increase in utilisation of the active substance is expected due to this generic application. The CHMP considered the applicant's justification for omission of any further environmental risk assessment acceptable. Section 5.3 of the SmPC is in line with the originator SmPC of Tamiflu.

2.4. Clinical aspects

2.4.1. Introduction

The applicant provided an overview on human pharmacology, efficacy and safety. Human pharmacology, efficacy and safety of oseltamivir are well known. The overview was based on appropriate scientific literature. In general, the clinical aspects of the generic product SmPC are in accordance with the reference product SmPC.

This is an application for hard capsules containing oseltamivir. To support the marketing authorisation application the applicant conducted a bioequivalence study with randomized, open label, two treatments, four periods, two sequences and cross-over fully replicate design under fasting conditions. This study is the pivotal study for supporting the application.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

The bioequivalence study was conducted with the 75 mg strength only. A biowaiver was requested for Ebilfumin 30 mg and Ebilfumin 45 mg.

General biowaiver-criteria are fulfilled according to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98) Rev. 1.:

1. The pharmaceutical products are manufactured by the same manufacturing process.

2. The qualitative composition of the different strengths is the same.

- The composition of the strengths is quantitatively proportional (Table 1)
- In vitro dissolution data are available and show similar dissolution rates (Table 2).

Comparison of dissolution profiles of Ebilfumin 30, 45 and 75 mg under CHMP-terms.

Table 1 Qualitative and quantitative composition of the Test product

Ingredient	Function	Strength (Label claim)					
		30 mg (165,000 – 1.650,000 capsules)		45 mg (110,000 – 1.100,000 capsules)		75 mg (132,000 – 1.320,000 capsules)	
CORE		Quantity per capsule (mg)	%*	Quantity per capsule (mg)	%*	Quantity per capsule (mg)	%*
Oseltamivir phosphate** -corresponding to oseltamivir	Active	39.4 30.0	39.4	59.1 45.0	39.4	98.5 75.0	39.4
Starch pregelatinised (1500)*	Filler/binder	48.6	48.6	72.9	48.6	121.5	48.6
Povidone (K-29/32)	Binder	4.0	4.0	6.0	4.0	10.0	4.0
Talc	Glidant	5.0	5.0	7.5	5.0	12.5	5.0
Croscarmellose sodium	Disintegrant	2.0	2.0	3.0	2.0	5.0	2.0
Sodium stearyl fumarate	Lubricant	1.0	1.0	1.5	1.0	2.5	1.0
Water, purified***	Granulation fluid	q.s.	-	q.s.	-	q.s.	-
Total capsule fill weight		***100.0 mg***	100%	***150.0 mg***	100%	***250. 0 mg***	100%

*each ingredient expressed as a percentage (w/w) of the total core or coating weight or w/v % for solutions

** The amount of Oseltamivir phosphate should be adjusted depending on the assay and water content, the amount of starch pregelatinised to be increased or decreased depending on changes made to the amount of Oseltamivir phosphate so that the total capsule weight remains constant.
*** **Granulated with purified water, removed during manufacture.**

Table 2: Comparison of dissolution profiles of Ebilfumin 30, 45 and 75 mg

Dissolution Medium			Collection Times (minutes)						f2
			5	10	15	20	25	30	
30 mg n = 12 D33427	pH= 1.2	0.1M HCl	60.7	89.7	93.1	93.6	93.7	93.7	-
	pH= 4.5	0.05M phosphate buffer	38.5	89.0	95.7	96.9	97.4	97.7	-
	pH= 6.8	0.05M phosphate buffer	36.9	91.5	99.2	100.6	101.2	101.5	-
45 mg n = 12 D33465	pH= 1.2	0.1M HCl	59.8	94.6	98.3	99.0	99.2	99.1	-
	pH= 4.5	0.05M phosphate buffer	43.9	81.7	93.0	94.0	94.4	94.6	-
	pH= 6.8	0.05M phosphate buffer	45.3	85.8	95.9	97.1	97.3	97.4	-
75 mg n = 12 D33428	pH= 1.2	0.1M HCl	55.6	89.3	96.6	98.6	99.1	98.9	-
	pH= 4.5	0.05M phosphate buffer	40.2	88.4	96.9	98.6	99.3	99.7	-
	pH= 6.8	0.05M phosphate buffer	39.5	88.2	99.2	101.2	101.6	101.6	-

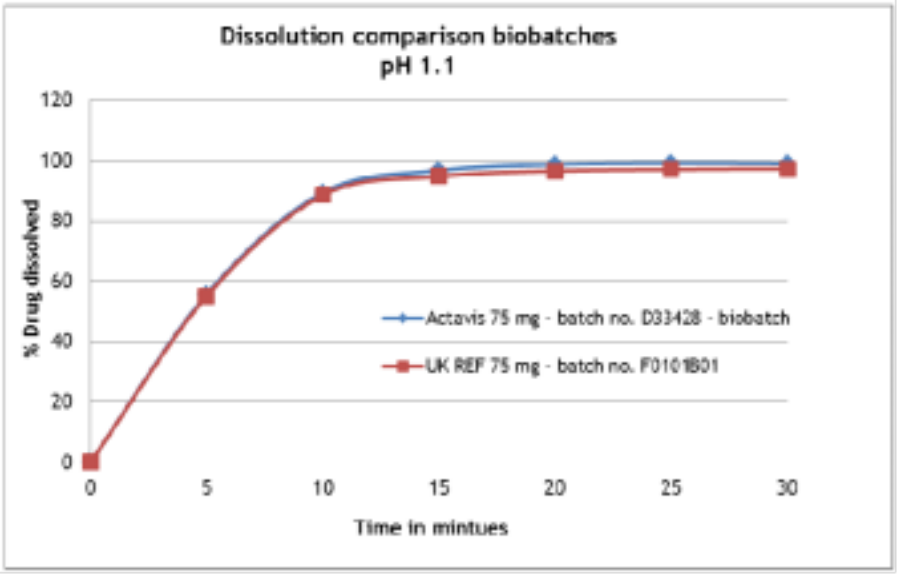
The similarity factor is not calculated as more than 85% is dissolved for all batches after 15 minutes and therefore the dissolution profiles are considered similar.

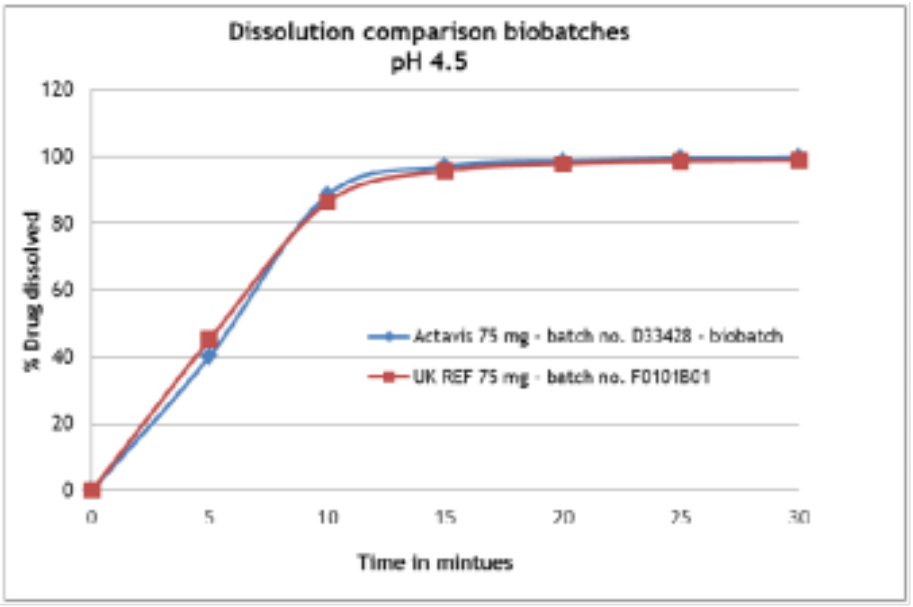
The pharmacokinetics over the therapeutic dose range is linear. Therefore, one bioequivalence study with the highest dose of 75 mg and a biowaiver for the additional strengths is considered adequate.

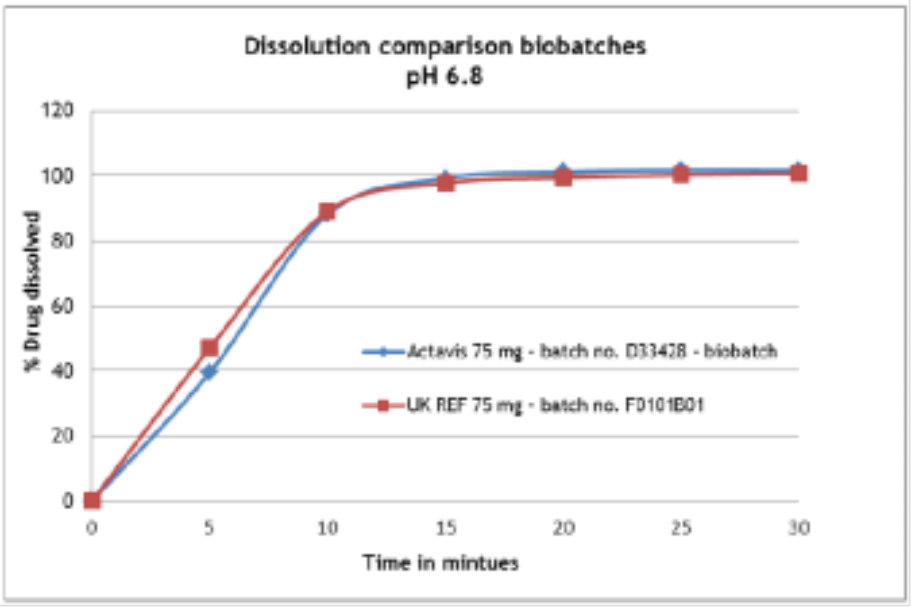
Results of *in vitro* dissolution tests of the bio-batches of the test product vs. reference product at three different buffers (pH 1.1, 4.5 and 6.8) reflect bioequivalence. More than 85 % of the drug is dissolved within 15 minutes at all pH values tested for test and reference product

Hence, similarity of dissolution profiles can be accepted as demonstrated without any further mathematical calculation.

For the reference product Tamiflu dissolution profiles were conducted for the 75mg strength. Results correspond to CHMP recommendations. Dissolution profiles of test and reference products are comparable (see figures on dissolution comparison of biobatches).


Dissolution comparison biobatches
pH 1.1
120
100
80
60
40
20
0
% Drug dissolved
0
5
10
15
20
25
30
Time in mintues
Actavis 75 mg - batch no. D33428 - biobatch
UK REF 75 mg - batch no. F0101B01


Dissolution comparison biobatches
pH 4.5
120
100
80
60
40
20
0
% Drug dissolved
0
5
10
15
20
25
30
Time in mintues
Actavis 75 mg - batch no. D33428 - biobatch
UK REF 75 mg - batch no. F0101B01



More than 85 % of the drug is dissolved within 15 minutes for all batches at all conditions. The dissolution profiles are therefore accepted as similar without further mathematical evaluation in compliance with Guideline on the Investigation of Bioequivalence CPMP/EWPQWP/1401/98 Rev. 1/Corr **.

Clinical studies

To support the application, the applicant has submitted a bioequivalence study.

2.4.2. Pharmacokinetics

Methods

Study design

Study No. 2603/11 was a randomized, open label, two treatment, four period, two sequence, single dose, crossover, fully replicate, bioequivalence study of Oseltamivir 75 mg capsules of Actavis Group PTC ehf, Iceland and Tamiflu (oseltamivir) 75 mg hard capsules of Roche Registration Limited, UK, in healthy adult subjects, under fasting conditions. Bioanalytical analysts were blinded to the randomization during the course of the analysis and until the results were processed by the statistical department and reported.

The study was conducted at Lotus Labs Pvt. Ltd., Mylapore, Chennai, India from 17 September 2012 to 28 September 2012. The study report is dated 27 November 2012.

A total of 32 healthy adult male subjects were enrolled into the study. Subjects were randomized into one of two sequences, each consisting of four periods [sequences TRTR resp. RTRT; T= oseltamivir 75 mg capsules of Actavis Group PTC ehf, R= Tamiflu (Oseltamivir) 75 mg hard

capsules of Roche Registration Limited]. Subjects were housed from the time of check-in (at least 11 hours before dosing) until after the 24 hours post dose blood draw in each period. After a supervised overnight fast of at least 10 hours, a single oral dose of the study product was administered with 240 mL of water. Subjects were dosed with the test or the reference product in each period as determined by the randomization schedule under fasting conditions. The 0.000 h sample was collected within a period of 1 hour before dosing and the post-dose blood samples were collected at 0.167, 0.333, 0.500, 0.750, 1.000, 1.250, 1.500, 1.750, 2.000, 2.500, 3.000, 3.500, 4.000, 6.000, 8.000, 12.000, 16.000 and 24.000 h after dosing in each period. Treatments were separated by a washout period of 3 days.

Test and reference products

	Test Product T	Reference Product P
Product	Oseltamivir 75 mg capsules	Tamiflu® 75 mg hard capsules [Oseltamivir]
Manufacturer	Actavis Group PTC ehf, Dalshraun 1, 220 Hafnarfjördur, Iceland	MA Holder: Roche Registration Limited, 6 Falcon Way, Shire Park, Welwyn Garden City, AL71TW, UK
Description	Hard gelatin Capsule, yellow cap, white body, oblong shaped, unmarked cap and body, opaque capsules	Hard gelatin oblong shaped opaque capsule with yellow coloured cap printed with "75 mg" in blue ink and white coloured body printed with "ROCHE" in blue colour ink
Batch No.	033428	F0101B01 on the carton F0101 on the blisters
Batch size	130.120 capsules	-
Manufacturing Date	11 June 2012	-
Expiry Date	-	12/2016
Retest Date	11 December 2012	-

The batch size of the test product is in line with the guidelines, in which a batch size is requested of at least 100.000 tablets and over 1/10th of the commercial batch size (132.000 – 1.320.000 capsules) and therefore appropriate.

Certificates of analysis for the test- and reference product were provided. The actual amount of oseltamivir phosphate according to the CoA was 73.5 mg for the test product and 72.4 mg for the reference product which is within the range of +/- 5%.

Results of in vitro dissolution tests of the bio-batches of the test product vs. reference product at three different buffers (pH 1.2, 4.5 and 6.8) reflect bioequivalence. More than 85% of the drug is dissolved within 15 minutes at all pH values tested for test and reference product (see information related to Exemption).

The applicant confirmed that the test product used in the bioequivalence study is identical to the product intended for marketing. The reference product was obtained from the UK market.

Population(s) studied

A total of 32 healthy adult male subjects were enrolled into the study. With the expected coefficient of variation for C_{max} not exceeding 30% and assuming the true ratio of C_{max} and AUC falling within 95% to 105%, the study should have at least 26 evaluable subjects to show bioequivalence with a power of 90% at a 5% level of significance. Expecting dropouts in the study 6 additional subjects were planned to be included in the study. 32 subjects were randomized to either test or reference product sequence in the four periods of the study. Three subjects dropped out and thus 29 subjects received both the test and reference products twice in the four periods and completed the study. However, 31 subjects completed at least 2 periods of the study, one for each formulation.

One subject did not check-in for period II, one subject was withdrawn due to AE (Decrease in Haemoglobin) and one subject did not check in for period IV.

Subjects had to be healthy, adult subjects (of either sex), aged between 18 and 45 years (inclusive); body mass indices between 18.5 and 30.0 kg/m^2 (inclusive).

All subjects had to be in compliance with the inclusion and exclusion criteria described in the protocol and were judged eligible for enrolment in this study, based on demographic data, medical history, general physical examination including vital signs measurements, ECG, chest X-ray, haematology, biochemistry, serology as well as urine analysis.

The subjects enrolled in the study were South Asians. There was no direct data available on Oseltamivir and its metabolite oseltamivir carboxylate for comparison from Caucasian population to the observed data in the current study but the applicant discussed adequately the influence of major drug metabolizing enzymes on Oseltamivir. The South Asians (India, Bangladesh, and Pakistan) are similar to Caucasians as far as the distribution and activity of major drug metabolizing enzymes are concerned.

Davies (2010) stated that “Overall, there are no clinically relevant differences in the pharmacokinetics of oseltamivir or OC between healthy volunteers and infected patients; this applies in adults of different sexes, ages and weights. Equally, ethnicity does not appear to affect the pharmacokinetics of the prodrug or active metabolite.”

The main purpose of using a cross over design was to provide a basis for separating treatment effects from other effects like gender or ethnicity. The influence of known or unknown confounding covariates is strongly reduced because each crossover patient serves as his or her own control.

Analytical methods

The analyte was oseltamivir phosphate, which is a prodrug of the active metabolite oseltamivir carboxylate.

Internal standard was Oseltamivir-D3; samples were extracted from a 500 µL aliquot of sodium fluoride and potassium oxalate human plasma by solid-phase extraction. The extracted samples were injected into a liquid chromatograph; detection method used was tandem mass spectrometry detector.

Quantitation is determined by peak area ratio method. A weighted ($1/x^2$) linear regression is performed to determine the concentration of the analytes.

The validated calibration range for the assay of oseltamivir phosphate is from 0.498 ng/mL to 131.211 ng/mL.

Sample reassays / repeats for oseltamivir were done on 10 samples (0.43% of total study samples); 7 samples were reassayed due to sample concentration above upper limit of quantitation; 3 samples were reassayed due to variation in internal standard. All reassays are in accordance with the presented SOP and the relevant guideline.

Incurred sample reanalysis (ISR) of oseltamivir has been performed on 178 samples (~ 7.68% of total samples analysed); 177 out of 178 ISR samples (~99.44%) were within 20% from the mean value.

Representative chromatograms (subjects 11-14, 16-17, ~18.75%) were provided.

The analytical method for the determination of oseltamivir in human plasma and respective validations are described adequately; the validation was basically performed according to the requirements of the EMA "Guideline on bioanalytical method validation" (EMEA/CHMP/EWP/192217/2009). Acceptance criteria are in a plausible range and were fulfilled. Provided chromatograms are acceptable; ISR has been investigated satisfactory.

The pro-drug oseltamivir phosphate was measured for all pharmacokinetic-analyses. This approach is endorsed considering the parent compound being more sensitive to detect differences between formulations in absorption rate.

The bioanalytical method demonstrates acceptable performance and is suitable for the determination of oseltamivir in human plasma over the calibration range.

Pharmacokinetic variables

The following parameters were calculated:

1. AUC_{0-t} using the linear trapezoidal rule
2. $AUC_{0-¥}$ by adding the quantity C_{last}/K_{el} to AUC_{0-t}.
3. C_{max}

The primary endpoints are defined as AUC_{0-t} and C_{max}.

Statistical methods

Log-transformed pharmacokinetic parameters were to be analyzed using a linear mixed-effects model. The model included treatment, period and sequence as fixed effects and subjects nested within sequence as random effect. Individual AUC parameters were calculated using the trapezoidal rule. Differences of LSMeans were to be calculated for log-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} values. 90% confidence intervals for these differences were to be calculated, and further be expressed by taking the antilog of the values obtained in order to get 90% confidence intervals on the normal scale. The 90% confidence interval was to lie within 80% to 125% for

AUC_{0-t}. For C_{max} the 90%-confidence interval was to lie within an acceptance range 79.70%-125.46%, defined according to the reference intra-subject variability (ISCV).

Results

Table 4 Pharmacokinetic parameters for oseltamivir (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-t)}$	145.60	27.933	145.46	33.128
$AUC_{(0-\infty)}$	147.82	27.651	147.97	33.041
C_{max}	68.7	33.017	63.03	25.034
T_{max}*	1.13	1.026	0.92	0.739
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (* median, range)			

Table 5 Statistical analysis for oseltamivir (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-t)}$	101.53	98.44 – 104.72	8.00
C_{max}	105.93	96.25 – 116.59	30.52
* estimated from the Residual Mean Squares			

Based on the obtained pharmacokinetic parameters of oseltamivir, the reference and test product are considered bioequivalent with respect to the extent and rate of absorption. The 90% confidence intervals for AUC_{0-t} and C_{max} are within the predefined acceptance ranges.

The mean residual area was lower than 20% for all treatments indicating that the duration of sampling was sufficient.

Safety data

There were four adverse events reported in the study which all four were considered related to study products. The following adverse events (AEs) were reported during the study: Headache, body pain and decrease in haemoglobin. Among the four related adverse events, one adverse event was assessed to be related to the test product, two adverse events were assessed to be related to the reference product and one adverse event (decrease in haemoglobin in one subject) could not be attributed to either the test or the reference product as the abnormal lab result was detected during the end of period II study safety procedure and evaluation of safety lab results. All adverse events were moderate in intensity except one AE which was mild in intensity and resolved completely without sequelae. There were no serious adverse events in the study.

The safety profile of the test product is acceptable and comparable with the safety profile of the reference product. Both formulations were well tolerated, with no major side effects.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product subject of the generic application has not been marketed in any country.

2.4.5. Discussion on clinical aspects

According to the Guideline on the Investigation of Bioequivalence (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) the study design of the BE-study 2603/11 is appropriate for an immediate release product and the pharmacokinetic variables studied are adequate.

The general biowaiver criteria are met and the pharmacokinetics over the therapeutic dose range is linear. Therefore, a biowaiver for the additional strengths (30 mg and 45 mg) is acceptable.

The methodological aspects of the design of study 2603/11 are fully appropriate. This applies to the single-dose cross-over as well as the fully replicate study design. A replicate study design was necessary, as the Applicant had pre-planned for possible widening of the bioequivalence criteria for C_{max} in line with EMA Guideline CPMP/EWPQWP/1401/98 Rev. 1/Corr **. An open label-design is acceptable, but the blinding of the bioanalytical analyst is considered necessary and therefore supported.

The sample size justification did not consider the 2 sequence, four period study design. However, the approach was conservative and is considered acceptable. The CV used for sample size calculation was very much in line with the CV finally observed in the study. The final analysis included all subjects with a sufficient number of evaluable samples, i.e. out of the 32 subjects included into the trial only one subject was excluded from the statistical analyses, as this subject did not have PK values for both treatments. This approach is in line with EMA Guideline CPMP/EWP/QWP/1401/98 Rev. 1/Corr ** and therefore is considered appropriate.

The statistical analysis model applied was not fully pre-specified in the study protocol, as it turned out during the responses submitted during the evaluation. While this is considered a deficiency it is nevertheless concluded that the model allowing for a subject-by-formulation interaction resulted in conservative estimates in support of bioequivalence and thus the results are acceptable. The primary endpoints are appropriately defined as AUC_{0-t} and C_{max} in line with the EMA Guideline CPMP/EWP/QWP/1401/98 Rev. 1/Corr **. The calculation of the 90% confidence intervals as well as the equivalence acceptance ranges are in line with EMA guidance. The rules for widening the acceptance range for C_{max} are appropriately defined and with an observed ISCV of 30.52% for the reference it is appropriate that the acceptance range for C_{max} can be widened to 79.70%-125.46%. Though it is not fully clear how the ISCV for the reference was estimated, any considerations on widening are not relevant as the 90% confidence interval for C_{max} lies clearly within the standard 80%-125% acceptance range.

The selection of healthy volunteers as study population is in line with the BE Guideline and is considered ethical with regard to the study medication. The inclusion and exclusion criteria are clearly stated in the protocol as well as the criteria for subject withdrawal. Furthermore, criteria for restrictions, prohibitions, concomitant medication, subject screening, investigations and post study procedures are defined.

The reported protocol deviations and the deviations in the blood sampling schedule are not considered relevant for the overall results.

The withdrawal of one subject due to AE is in line with the defined criteria and considered appropriate.

No gender specific effects are stated in the innovator's SmPC or in the published literature. Davies (2010) stated that "Overall, there are no clinically relevant differences in the pharmacokinetics of oseltamivir or OC between healthy volunteers and infected patients; this applies in adults of different sexes, ages and weights. Equally, ethnicity does not appear to affect the pharmacokinetics of the prodrug or active metabolite."

In order to obtain a study population as homogenous as possible the non-inclusion of females in the BE study may be justified and accepted. The applicant also discussed the impact of a fully replicate crossover study design on ethnic, gender or race differences.

The main purpose of using a cross over design was to provide a basis for separating treatment effects from other effects like gender or ethnicity. The influence of known or unknown confounding covariates is strongly reduced because each crossover patient serves as his or her own control. Therefore, the Applicant argued that establishing bioequivalence in one ethnic group can be bridged to other ethnic groups. In conclusion, the bioequivalence study conducted in South Asians was justified and accepted by the CHMP.

2.4.6. Conclusions on clinical aspects

The objective of the provided pharmacokinetic study was to assess the bioequivalence of Oseltamivir 75 mg hard capsules manufactured by Actavis and Tamiflu 75 mg hard capsules of Roche Registration Limited, UK, in healthy adult subjects under fasting conditions.

Based on the results obtained Oseltamivir 75 mg hard capsules of Actavis Group PTC ehf., Iceland and Tamiflu 75 mg capsules of Roche Registration Limited, UK, are considered bioequivalent. The results of study 2603/11 with 75 mg formulation can be extrapolated to the other strengths (30 mg and 45 mg), according to conditions outlined in the relevant Guidelines.

The safety of the formulations was also assessed on the basis of clinical and laboratory examinations at different time points at the beginning, during and at the end of the study and registration of adverse events and/or adverse drug reactions. The test and reference product were clinically comparable in their safety profile.

The application contains also an adequate review of published clinical data.

All data regarding safety and efficacy available of the reference medicinal product also apply for this generic product.

2.5. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk management plan

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Additional risk minimisation measures

No additional risk minimisation measures will be necessary for the safe and effective use of the medicinal product.

Obligation to conduct post-authorisation measures

Not applicable.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 4.0, the PRAC considers by consensus that the risk management system for oseltamivir (Ebilfumin) in the treatment and prevention of influenza is acceptable.

Safety concerns

The applicant identified the following safety concerns in the RMP:

Table 2.1 Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Skin disorders (rash, urticaria, erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis)
	Gastrointestinal bleeding and haemorrhagic colitis
	Hepato-biliary disorders (hepatitis, elevated liver enzyme)
	Cardiac arrhythmia
	Visual disturbance
	Development of oseltamivir-induced viral resistance
	Neuropsychiatric events
Important potential risks	Exposure during pregnancy
	Exposure of infants through breastfeeding
	Potential drug-drug interactions (probenecid, chlorpropamide, methotrexate, phenylbutazone, clopidogrel)
Important missing information	Use in children with hepatic and renal impairment
	Use in patients receiving dialysis treatment
	Treatment of influenza in immunocompromised patients
	Exposure in children < 1 year of age
Areas of special interest under influenza pandemic situation	Use in pregnant women
	Use in breastfeeding women
	Use in young children
	Lack of efficacy/development of resistance
	Medication errors
	Neuropsychiatric ADRs
	Fatal ADRs
	Counterfeit drugs and product defects
Summary of safety concerns	
Important identified risks	Skin disorders (rash, urticaria, erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis)
	Gastrointestinal bleeding and haemorrhagic colitis
	Hepato-biliary disorders (hepatitis, elevated liver enzyme)

Summary of safety concerns	
	Cardiac arrhythmia
	Visual disturbance
	Development of oseltamivir-induced viral resistance
	Neuropsychiatric events
Important potential risks	Exposure during pregnancy
	Exposure of infants through breastfeeding
	Potential drug-drug interactions (probenecid, chlorpropamide, methotrexate, phenylbutazone, clopidogrel)
Important missing information	Use in children with hepatic and renal impairment
	Use in patients receiving dialysis treatment
	Treatment of influenza in immunocompromised patients
	Exposure in children < 1 year of age
Areas of special interest under influenza pandemic situation	Use in pregnant women
	Use in breastfeeding women
	Use in young children
	Lack of efficacy/development of resistance
	Medication errors
	Neuropsychiatric ADRs
	Fatal ADRs
	Counterfeit drugs and product defects

The PRAC agreed.

Pharmacovigilance plans

The PRAC, having considered the data submitted, was of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Table 2.4: Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Skin disorders (rash, urticaria, erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis)	A warning is included in section 4.8 Adverse reactions in studies investigating oseltamivir for treatment and prevention of influenza in adults and adolescents or through post-marketing surveillance **Skin and subcutaneous tissue disorders:** *Uncommon:* Rash, Urticaria *Rare:* Erythema multiforme, Stevens-Johnson syndrome, Toxic epidermal necrolysis	None proposed
Gastrointestinal bleeding and haemorrhagic colitis	A warning is included in section 4.8 **Gastrointestinal disorders:** *Rare*: Gastrointestinal bleedings, Haemorrhagic colitis	None proposed
Hepato-biliary disorders (hepatitis, elevated liver enzyme)	A warning is included in section 4.8 Adverse reactions in studies investigating oseltamivir for treatment and prevention of influenza in adults and adolescents or through post-marketing surveillance **Hepatobilary disorders:** *Uncommon:* Elevated liver enzymes *Rare:* Hepatitis Description of selected adverse reactions Hepato-biliary system disorders, including hepatitis and elevated liver enzymes in patients with influenza-like illness. These cases include fatal fulminant hepatitis/hepatic failure.	None proposed
Cardiac arrhythmia	A warning is included in section 4.4 and 4.8 Section 4.4 Cardiac / respiratory disease Efficacy of oseltamivir in the treatment of subjects with chronic cardiac disease and/or respiratory disease has not been established. No difference in the incidence of complications was observed between the treatment and placebo groups in this population (see section 5.1). Section 4.8 Adverse reactions in studies investigating oseltamivir for treatment and prevention of influenza in adults and adolescents or through post-marketing surveillance **Cardiac disorders**: *Uncommon*: Cardiac arrhythmia	None proposed
Visual disturbance	A warning is included in section 4.8 Adverse reactions in studies investigating oseltamivir for	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	treatment and prevention of influenza in adults and adolescents or through post-marketing surveillance **Eye disorders**: *Rare*: Visual disturbance	
Development of oseltamivir-induced viral resistance	Text is included in SPC section 5.1 Oseltamivir-resistant viruses isolated from oseltamivir-treated patients and oseltamivir-resistant laboratory strains of influenza viruses have been found to contain mutations in N1 and N2 neuraminidases. Resistance mutations tend to be viral sub-type specific. Since 2007 resistance associated H275Y mutation in seasonal H1N1 strains has become widespread. The susceptibility to oseltamivir and the prevalence of such viruses appear to vary seasonally and geographically. In 2008, H275Y was found in > 99 % of circulating H1N1 influenza isolates in Europe. The 2009 H1N1 influenza ("swine flu") was almost uniformly susceptible to oseltamivir, with only sporadic reports of resistance in connection with both therapeutic and prophylactic regimens.	None proposed
Neuropsychiatric events	A warning is included in section 4.4 and 4.8: <u>Section 4.4</u> <u>Neuropsychiatric events</u> Neuropsychiatric events have been reported during administration of oseltamivir in patients with influenza, especially in children and adolescents. These events are also experienced by patients with influenza without oseltamivir administration. Patients should be closely monitored for behavioural changes, and the benefits and risks of continuing treatment should be carefully evaluated for each patient (see section 4.8). <u>Section 4.8</u> Adverse reactions in studies investigating oseltamivir for treatment and prevention of influenza in adults and adolescents or through post-marketing surveillance. **Psychiatric disorders:** *Rare*: Agitation, Abnormal behaviour, Anxiety, Confusion, Delusions, Delirium, Hallucination, Nightmares, Self-injury **Nervous system disorders:** *Very common*: Headache, *Common*: Insomnia, *Uncommon*: Altered level of consciousness, Convulsion Adverse reactions in studies investigating Oseltamivir for treatment and prevention of influenza in children (age/weight-based dosing [30 mg to 75 mg o.d.])	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Nervous system disorders: *Common*: Headache Description of selected adverse reactions *Psychiatric disorders and nervous system disorders* Influenza can be associated with a variety of neurologic and behavioural symptoms which can include events such as hallucinations, delirium, and abnormal behaviour, in some cases resulting in fatal outcomes. These events may occur in the setting of encephalitis or encephalopathy but can occur without obvious severe disease. In patients with influenza who were receiving Oseltamivir, there have been postmarketing reports of convulsions and delirium (including symptoms such as altered level of consciousness, confusion, abnormal behaviour, delusions, hallucinations, agitation, anxiety, nightmares), in a very few cases resulting in self-injury or fatal outcomes. These events were reported primarily among paediatric and adolescent patients and often had an abrupt onset and rapid resolution. The contribution of Oseltamivir to those events is unknown. Such neuropsychiatric events have also been reported in patients with influenza who were not taking Oseltamivir.	
Exposure during pregnancy	A warning is included in section 4.6 Pregnancy While no controlled clinical studies have been conducted on the use of oseltamivir in pregnant women, there is limited data available from post-marketing and retrospective observational surveillance reports. These data in conjunction with animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal or postnatal development. Pregnant women may receive oseltamivir, after considering the available safety information, the pathogenicity of the circulating influenza virus strain and the underlying condition of the pregnant woman.	None proposed
Exposure of infants through breast-feeding	A warning is included in section 4.6 and 5.3 Section 4.6 Breast-feeding In lactating rats, oseltamivir and the active metabolite are excreted in milk. Very limited information is available on children breast-fed by mothers taking oseltamivir and on excretion of oseltamivir in breast milk. Limited data demonstrated that oseltamivir and the active metabolite were detected in breast milk, however the levels were low, which	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	would result in a sub-therapeutic dose to the infant. Considering this information, the pathogenicity of the circulating influenza virus strain and the underlying condition of the breastfeeding woman, administration of oseltamivir may be considered, where there are clear potential benefits to breastfeeding mothers. Section 5.3 In lactating rats, oseltamivir and the active metabolite are excreted in the milk. Limited data indicate that oseltamivir and the active metabolite are excreted in human milk. Extrapolation of the animal data provides estimates of 0.01 mg/day and 0.3 mg/day for the respective compounds.	
Potential drug-drug interactions (probenecid, chlorpropamide, methotrexate, phenylbutazone, clopidogrel)	A warning is included in section 4.5 Pharmacokinetic properties of oseltamivir, such as low protein binding and metabolism independent of the CYP450 and glucuronidase systems (see section 5.2), suggest that clinically significant drug interactions via these mechanisms are unlikely. Probenecid No dose adjustment is required when co-administering with probenecid in patients with normal renal function. Co-administration of probenecid, a potent inhibitor of the anionic pathway of renal tubular secretion, results in an approximate 2-fold increase in exposure to the active metabolite of oseltamivir. Renal elimination Clinically important drug interactions involving competition for renal tubular secretion are unlikely, due to the known safety margin for most of these substances, the elimination characteristics of the active metabolite (glomerular filtration and anionic tubular secretion) and the excretion capacity of these pathways. However, care should be taken when prescribing oseltamivir in subjects when taking co-excreted agents with a narrow therapeutic margin (e.g. chlorpropamide, methotrexate, phenylbutazone).	None proposed
Use in children with hepatic and renal impairment	None proposed	None proposed
Use in patients receiving dialysis treatment	A warning is included in section 4.2: Dose adjustment regimens for patient receiving dialysis treatment are suggested in this section.	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Treatment of influenza in immunocompromised patients	A warning is included in section 4.4: Immunocompromised patients The efficacy of oseltamivir in either treatment or prophylaxis of influenza in immunocompromised patients has not been firmly established.	None proposed
Exposure in children < 1 year of age	A warning is included in section 5.2: *Infants less than 1 year of age:* Limited pharmacokinetic and safety data are available for infants less than 1 year of age. Pharmacokinetic modelling was undertaken using these data in addition to data from studies in adults and infants and children 1 year of age or older. The results demonstrate that doses of 3 mg /kg twice daily for infants aged 3 to 12 months and 2.5 mg /kg twice daily for infants aged between 1 and 3 months provide exposures similar to those shown to be clinically efficacious in adults and infants and children 1 year of age or older (see sections 4.1 and 4.2). There are currently no data available in infants less than 1 month of age using oseltamivir.	None proposed
Areas of special interest under influenza pandemic situations	Guidance on indications and posology under influenza pandemic situations is included in the SmPC: Section 4.1 Ebilfumin is indicated for the treatment of infants less than 1 year of age during a pandemic influenza outbreak. The treating physician should take into account the pathogenicity of the circulating strain and the underlying condition of the patient to ensure there is a potential benefit to the child. The appropriate use of Ebilfumin 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. Ebilfumin is indicated for post-exposure prevention of influenza in infants less than 1 year of age during a pandemic influenza outbreak. Section 4.2 The recommended treatment dose for infants less than 1 year of age is between 2 mg/kg twice daily and 3 mg/kg twice daily during a pandemic influenza outbreak. This is based upon limited pharmacokinetic and safety data indicating that	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	these doses provide plasma drug exposures in the majority of patients similar to those shown to be clinically efficacious in older children and adults. Recommended age-adjusted dosing regimens for infants below 1 year of age are included in this section. The recommended prophylaxis dose for infants less than 1 year of age during a pandemic influenza outbreak is half of the daily treatment dose. This is based upon clinical data in infants and children 1 year of age or older and adults showing that a prophylaxis dose equivalent to half the daily treatment dose is clinically efficacious for the prevention of influenza. Recommended age-adjusted dosing prophylaxis regimens for infants below 1 year of age are included in this section.	

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The CHMP endorsed the PRAC advice without changes.

PSUR submission

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Tamiflu. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of oseltamivir 30 mg, 45 mg and 75 mg hard capsules. The reference product Tamiflu is indicated for treatment and prevention of influenza. No non-clinical studies have been provided for this application but an adequate summary of the available non-clinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active

substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with a randomized, open label, two treatment, four period, two sequence, single dose, crossover, fully replicate, bioequivalence study. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Ebilfumin met the protocol-defined criteria for bioequivalence when compared with the Tamiflu. The point estimates and their 90 % confidence intervals for the parameters AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance ranges. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Ebilfumin in the treatment and prevention of influenza and therefore recommends the granting of the marketing authorisation.

Conditions or restrictions regarding supply and use

Medicinal products subject to medical prescription

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

  At the time of granting the marketing authorisation, the submission of periodic safety update reports is not required for this medicinal product. However, the marketing authorisation holder shall submit periodic safety update reports for this medicinal product if the product is included in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83 and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.