European Medicines Agency
Evaluation of Medicines for Human Use

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Product name: **TAMIFLU**
Procedure No: **EMEA/H/C/402/X/44**

SCIENTIFIC DISCUSSION

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1. Introduction

This application for Tamiflu 30 mg hard capsules is a line extension for the addition of new dosage strength to the existing Marketing Authorisation for Tamiflu 75 mg hard capsules (EU/1/02/222/001). Tamiflu 12 mg/ml powder for oral suspension (EU/1/02/222/002) is also authorised at the same time as Tamiflu 75 mg hard capsules.

The active substance of Tamiflu, oseltamivir, is a pro-drug of the active metabolite, oseltamivir carboxylate. Oseltamivir has been investigated for its ability to inhibit neuraminidase activity in influenza A and B viruses. Oseltamivir is a selective inhibitor of influenza virus neuraminidase enzymes, which are glycoproteins found on the virion surface. Viral neuraminidase enzyme activity is essential for the release of recently formed virus particles from infected cells and the further spread of infectious virus in the body. Inhibition of this viral surface glycoprotein enzyme is expected to hinder the release of virions from infected cells which may lead to reduction in viral replication and to attenuation of the infection.

Tamiflu was originally tested as hard capsules for oral administration in strength of 75 mg. In order to extend the treatment to children and to patients who cannot swallow capsules, a powder for oral suspension containing 12 mg/ml of oseltamivir freebase was developed.

Tamiflu is approved for the following indication:
"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 influenza in which the predominant infection was influenza A (see section 5.1 of SPC).
Prevention of influenza:
- Post exposure prevention in adults and adolescents 13 years of age or older following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community.
- 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. 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 adults and adolescents 13 years of age or older.
Tamiflu 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 taking into consideration variability of epidemiology and the impact of the disease in different geographical areas and patient populations".

In view of pandemic preparedness and due to the excellent stability of the capsule formulation, the MAH has developed appropriate strengths that could be stockpiled. For these reasons the MAH decided to develop the lower dose capsules containing 30 mg of oseltamivir by filling the appropriately lower amount of the same encapsulation mixture as that used for 75 mg capsules into smaller capsule shells.

2. Quality aspects

Introduction

Tamiflu is currently presented as 75 mg hard capsules in PVC/PE/PVDC/Alu blister packs of 10 capsules and as 12 mg/ml powder for oral suspension packaged in amber glass bottle with a tamper-evident child-resistant closure containing 30gr of the powder.
The MAH introduced a new strength of 30 mg hard capsules packaged in PVC/PE/PVDC/Alu blister packs of 10 capsules.

Active Substance

Oseltamivir phosphate, (3R,4R,5S)-4-acetylamino-5-amino-3-(1-ethylpropoxy)1-cyclohexene-1-carboxylic acid, ethyl ester, phosphate (1:1), is a non-hygroscopic pro-drug of the active metabolite, oseltamivir carboxylate. It is freely soluble in water. The drug substance oseltamivir phosphate has been appropriately characterized and fully described and was already approved within the Tamiflu 75 mg capsules marketing Authorization Application. The manufacturing process and process controls are the same as approved in the dossier of Tamiflu 75 mg capsules and as IB variations. The validations of analysis methods have been satisfactorily described previously. The specifications are previously assessed and approved and therefore considered to be justified. The proposed re-test period has been approved in connection with IB variation of Tamiflu 75 mg capsules and testing of three production batches will be continued up to the end of the re-test period.

Medicinal Product

- *Pharmaceutical Development*

Based on the approved dosing scheme for paediatric population a new strength of 30 mg capsules have been developed covering the whole range of body weight in children, who are able to swallow capsules.
The 30 mg capsules are direct weight multiples of the 75 mg capsules. The lower dose capsules are manufactured by filling into smaller capsule shells the requisite lower amount of the exact same encapsulation mixture as that used for the 75 mg capsules. The drug product is an immediate-release hard gelatine capsule, showing rapid dissolution of drug substance from capsules. The excipients used are of pharmacopoeial standard and widely used in pharmaceutical dosage dorms. Their selection followed compatibility tests with the drug substance and are the same as those used in the approved 75 mg strength.

The chosen primary packaging adequately protects the product during the proposed shelf-life. The stability profile for the 30 mg capsules is anticipated to be similar to that of the 75 mg capsules.
Bioequivalence has been demonstrated between the 75 mg capsules and the powder for oral suspension with study WP16225. The 75 mg capsules used in the bioequivalence study fulfilled the requirements for a rapidly dissolving immediate release dosage form, i.e. at least 85% of drug substance was dissolved within 15 minutes.
In order to demonstrate the equivalence of the 30 mg and 75 mg capsules, comparative dissolution studies were performed. The dissolution profiles of the validation batches of 30 mg capsules were compared with that of the 75 mg capsules batch used in study WP16225.
The 30 mg capsules comply with the requirements for a fast dissolving immediate release dosage form. After 15 minutes more than 85% of drug substance is dissolved each time; therefore for the assessment of their equivalence the calculation of the f_2-factor is not necessary. The 30 mg capsules are considered equivalent to the 75 mg with regard to their *in-vitro* performance. Hence, based on the linear pharmacokinetics they are also considered equivalent to Tamiflu powder for oral suspension at the respective doses.

- *Adventitious Agents*

Neither the excipients nor the active substance is derived from human or animal origin. Certificates of Suitability have been provided for the gelatine capsule which is of ruminant origin.

- *Manufacture of the Product*

The manufacture of the drug product involves conventional pharmaceutical operations such as wet granulation, drying, milling, final blending and capsule filling. It is robust and ensures consistent product quality based on a validated process. The capsule filling process for the 30 mg capsules uses equipment applying the same operation principles as is used for the 75 mg capsules. The encapsulation process was validated for each of the dosage strengths to ensure that with the smaller capsule size and the lower fill-mass the requirements for homogeneity are still fulfilled.

- *Product Specification*

The product specification contains the relevant tests and limits for a product of this type. Tests include appearance and size of capsule, appearance and colour of capsule content, identification of capsule colorants, identification of the active substance (HPLC & TLC), uniformity of dosage units by mass variation (Ph. Eur.), degradation products (HPLC), weight uniformity (Ph.Eur.), dissolution (Ph.Eur.), and microbial limits (Ph.Eur).

- *Stability of the Product*

6 months stability data on three validation batches of Tamiflu 30 mg capsules manufactured on commercial scale stored in the proposed packaging material under 30ºC/75% RH and 40ºC/75% RH. The storage conditions of 30ºC/75% RH used in stability studies instead of 30ºC/65% RH or 25ºC/60% RH can be considered acceptable.
The results of 6 months show that the specifications were met in both storage conditions. The following parameters studied: appearance and colour of capsule contents, dissolution, degradation products and assay, using validated analytical methods.
Photostability studies presented in connection with the dossier of Tamiflu 75 mg capsules showed that the drug product does not need protection from light. Those studies can also be considered sufficient for Tamiflu 30 mg capsules.

Comparative stability results of Tamiflu 30 mg and 75 mg capsules after storage for 6 months at 40ºC/75% RH in the proposed packaging material were presented. The results show that no significant differences have been found in 6 months at 40ºC/75% RH between the batches. Equivalent long-term stability behaviour as for the 75 mg capsules is therefore expected for the 30 mg. The shelf-life of 5 years has been approved for Tamiflu 75 mg capsules based on the real-time 60 months stability data.
In conclusion, based on the stability data for 75 mg capsules and on 6-month data at 30ºC/75% RH and 40ºC/75% RH for 30 mg capsules, the proposed shelf life and storage conditions for the drug product as stated in the SPC are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

All relevant information on development, manufacture and control of the drug substance and drug product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of all the important quality characteristics of the product. It can be reasonably concluded that the product should have a satisfactory and uniform performance in the clinic. At the time of the CHMP opinion, there were no unresolved quality issues, which could have a negative impact on the Benefit Risk balance of the product.

3. Non-clinical aspects

No pre-clinical data was submitted.

4. Clinical aspects

- *Pharmacokinetics*

The drug product is an immediate-release hard gelatine capsule. As stated above, the manufacturing conditions are the same for all capsule strengths, the same excipients are used, including the coating, and the specifications are the same as those approved for Tamiflu 75 mg capsules.

Besides dissolution testing (see 3.3 Quality aspects), no bioequivalence studies between the 30 mg and the 75 mg capsules or the powder for oral suspension have been performed. The 30 mg are dose-proportional to the 75 mg capsules and exhibit equivalent dissolution properties. The 30 mg capsules have the same coating and homogenous content than the 75 mg capsules.

The pharmacokinetics of oseltamivir phosphate (prodrug) and oseltamivir carboxylate (active metabolite) were studied in the original marketing authorisation application of Tamiflu 75mg capsules

submitted in 2001. The conclusions adopted by the CHMP when the Opinion was adopted in March 2002 remain valid. It can be summarised as follow:

- Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate (pro-drug) and is extensively converted by predominantly hepatic esterases to the active metabolite (oseltamivir carboxylate). In healthy humans, at least 75% of an oral dose enters the systemic circulation as the active metabolite. Plasma concentrations of both the prodrug and the active metabolite are proportional to dose and are unaffected by co-administration of food.
- The pharmacokinetics is similar in children although the elimination is faster than in adults and adolescents. Oseltamivir has a wide therapeutic window. Thus, no bioequivalence studies are needed.

The bioequivalence surrogate inference is in line with the CHMP Note for Guidance on Bioavailability and Bioequivalence.

Hence, based on the linear pharmacokinetics they are also considered equivalent to Tamiflu 12mg/ml powder for oral suspension.

- *Dosing regimen*

Tamiflu 30 mg capsule was developed to be administered mainly to children of 1 year of age or older, even if it can as well be administered to adults for specific reasons. The recommended dose for these 30 mg capsules is identical to the weight-adjusted dosing regimens recommended for children of 1 year of age or older for Tamiflu 12mg/ml powder for suspension and should read in section 4.2 of the SPC:

Treatment The recommended dose of Tamiflu is indicated in the table below. The following weight-adjusted dosing regimens are recommended for children 1 year of age or older:

Body Weight	**Recommended dose for 5 days**
≤ 15 kg	30 mg **twice** daily
> 15 kg to 23 kg	45 mg **twice** daily
> 23 kg to 40 kg	60 mg **twice** daily
> 40 kg	75 mg **twice** daily

Prophylaxis: The recommended prophylactic dose of Tamiflu is indicated in the table below. The following weight-adjusted dosing regimens are recommended for children 1 year of age or older.

Body Weight	**Recommended dose for 10 days**
≤ 15 kg	30 mg **once** daily
> 15 kg to 23 kg	45 mg **once** daily
> 23 kg to 40 kg	60 mg **once** daily
> 40 kg	75 mg **once** daily

- *Clinical efficacy aspects*

No clinical efficacy data was submitted.

- *Clinical safety aspects*

No safety study was submitted when the MAH applied for this line extension for Tamiflu 30 mg capsule in February 2007.

The report of the study **ML16864**, a post-marketing retrospective surveillance study of pregnant women exposed to oseltamivir observed from May 2002 to December 2006, was provided by Chugai Pharmaceuticals Co. Ltd. in the response to the D120 LOQ adopted in June 2007. This surveillance

was performed for the purpose of investigating data pertaining to safety, including data on whether or not the pregnant women and the babies born to them suffered any adverse drug reaction.

In this study ML16864, 17 cases were identified and 73 were included in the safety analysis. The outcome of the pregnancy in 2 cases was unknown. Among the neonates and foetuses in the 73 cases, the incidence of serious adverse events was 8.22% (6/73); and the number of episodes of a serious adverse event was 7 (2 episodes of spontaneous abortion; and 1 episode each of threatened abortion, hydrops foetalis, premature baby, cleft lip and palate, and ventricular septal defect).

The current approved SPC for Tamiflu advises that *Tamiflu should be used during the pregnancy only in those cases in which the benefits outweigh the risks.* The CHMP concluded that an overview of all pregnancy data available for oseltamivir is submitted in the context of the next PSUR (submission planned 20 November 2007) in order to better assess the need to update the section 4.6 of the SPC (see annex 4.6 Letter of undertaking dated 13 July 2007) .

5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

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

Risk Management Plan

The MAA submitted a risk management plan for Tamiflu 30mg capsules.

Tamiflu RMP version 1.0 was submitted as part of the 30 mg capsules application dossier in February 2007.
The MAH submitted the table "Summary of the risk management plan" as agreed on 17 July 2007 as part of a new version (Version 1.1) of the risk management plan. The MAH intends to submit a revised risk management plan for all formulations of Tamiflu in September 2007.

Safety issue	**Proposed pharmacovigilance activities**	**Proposed risk minimisation activities**
Dehydration secondary to vomiting and diarrhoea (children)	Close observation through routine pharmacovigilance system	Vomiting and diarrhoea listed in 4.8 of the SPC.
Fructose intolerance (children)	Close observation through routine pharmacovigilance system	Warning in section 4.4 of the SPC "Patients with rare hereditary problems of fructose intolerance should not take this medicine."
Skin disorder (skin rash, urticaria, multiforme, Stevens-Johnson epidermal necrolysis)	Close observation through routine pharmacovigilance system	Listed in section 4.8 of the SPC.
Development of viral resistance	Regular monitoring of the potential for the emergence of Tamiflu resistance in the circulating influenza virus populations. Periodic Resistance Reports from NISN and annual update of Roche resistance report via the PSUR.	Statement on viral resistance in section 5.1 of the SPC.

Liver and biliary system disorder (hepatitis, elevated liver enzymes)	Close observation through routine pharmacovigilance system	Listed in section 4.8 of the SPC.
Neuropsychiatric events/delirium	Close observation through routine pharmacovigilance system	Listed in section 4.8 of the SPC.
Important potential risks		
Exposure of infants through lactation	Close observation through routine pharmacovigilance system	Statement in section 4.6 of the SPC.
Medication error (confusion with new doses of 30 mg and 45 mg capsules)	Close observation through routine pharmacovigilance system	Instructions in section 4.2 of the SPC.
Off-label use (other viral infections)	Close observation through routine pharmacovigilance system	
Important missing information		
Hepatic and renal impairment in children	The MAH is currently addressing the feasibility of a clinical development program in this patient cohort including adults. Safety will be obtained from the immunompromised treatment and prophylaxis protocols. PK data will be generated for any children recruited who have hepatic or renal impairment.	Statement in section 4.2 of the SPC "There is insufficient clinical data available in children with renal impairment to be able to make any dosing recommendation."
Immunocompromised children and adults	Close observation through routine pharmacovigilance system; Clinical trials NV20234 and NV20235 are ongoing	There is insufficient evidence to make any recommendations.
Children <1 year of age	The safety information obtained from two surveillance studies conducted in Japanese infants below the age of 1 year do not indicate any increased reporting of events. Currently the MAH is collaborating with the NIH/CASG study group in setting up a trial in children less than 1 year of age.	Statement in section 4.1 of the SPC that only indicated in children > 1 year of age.

The CHMP, having considered the data submitted in the application, is of the opinion that the risks of the 30 mg capsules are the same as for the 75mg capsules. One potential concern is the use of reduced oseltamivir doses by adults (on purpose or by mistake) which might lead to inefficacy. The MAH commits to address this potential risk in any material they produce. It is important that the safety assessment of the 30 mg capsules is synchronised with the approved formulations of Tamiflu, including the RMP and related safety commitments including resistance reporting, interaction studies, information on pregnancies, etc.

6. Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of the 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. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

Safety

Within the dossier submitted in February 2007 the MAH did not provide any new safety data. The only safety information provided was a surveillance study on pregnant women. The assessment of this study needs to be put in the context of the overall picture of the use of Tamiflu in case of pregnancy. Therefore the MAH should commit to submit all available safety data on pregnancy in the context of the next PSUR for submission in November 2007. On the basis on the safety data provided, the CHMP concluded that there is no safety issue, which has a negative impact on the Benefit Risk balance of the product.

User consultation

User consultation is not necessary

Risk-benefit assessment

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- Routine pharmacovigilance was adequate to monitor the safety of the product.
- No additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Tamiflu 30mg, Capsule, hard in the treatment and prevention of influenza was favourable and therefore recommended the granting of the marketing authorisation.