European Medicines Agency

London, 27 July 2009

ASSESSMENT REPORT
FOR
TAMIFLU

International Non-proprietary Name:
oseltamivir

Procedure No. EMEA/H/C/000402/II/0068

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

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1. Introduction

On 27 April 2009 the World Health Organization (WHO) raised the level of influenza pandemic alert from the current phase 3 to phase 4 based on the emergence of a new Influenza A (H1N1) virus and its widespread presence in Mexico and the United States of America (USA).

On 29 April 2009, the WHO raised the level of influenza pandemic alert to phase 5, based on assessment of available information and following expert consultations. Advice was given to all countries to activate their pandemic preparedness plans and to monitor unusual outbreaks of influenza-like illness and severe pneumonia.

There are presently four antiviral drugs available for treatment of influenza and these belong to two classes: adamantane inhibitors (amantadine and rimantadine) and neuraminidase inhibitors (oseltamivir and zanamivir). The novel influenza virus detected in humans has been found to be resistant to amantadine and rimantadine. Laboratory testing however indicated that these viruses may be susceptible to oseltamivir (Tamiflu) and zanamivir (Relenza).

Tamiflu is a centrally authorised product with a marketing authorisation valid since 20 June 2002.

Tamiflu is indicated in the 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. It is also indicated in post-exposure prevention in individuals one year of age or older. Tamiflu is approved as hard capsules and powder for oral suspension.

Considering the spread of the novel Influenza A (H1N1) and the potential clinical need in case of a declared pandemic, the EMEA requested that dosing recommendations in children younger than 1 year of age for oseltamivir should be investigated, therefore, the Executive Director of the European Medicines Agency (EMEA) presented on 30 April 2009, a request for a CHMP opinion under Article 5(3) of Regulation (EC) No 726/2004.

In May 2009 the European Medicines Agency has given guidance on the use of Tamiflu (oseltamivir) in children under one year of age in the case of a declared influenza A/H1N1 pandemic.

- During an officially declared influenza A/H1N1 pandemic the benefits of the use of Tamiflu outweigh its risks in the treatment of children under the age of one year.
  - The recommended dosage for treatment is 2 to 3 mg per kg body weight twice daily.
  - The recommended dosage for prophylaxis is 2 to 3mg per kg body weight once daily and should not exceed 10 days.
- Hospitalisation of children below 1 year of age in case of an Influenza A/H1N1 pandemic, including the children below 3 months of age, is recommended by the CHMP. However it should follow recommendations from Member States depending on the local situation.

During its plenary meeting held in June 2009, the CHMP was of the opinion that Tamiflu Product Information must be updated to include recommendations on the use of Tamiflu for children below 1 year of age in the context of the Novel Influenza (H1N1) pandemic.

On 17 July 2009, the MAH submitted this type II variation II/68 in order to extend the therapeutic indication of Tamiflu to include treatment of children between 6 and 12 months of age in case of pandemic influenza.

2. Clinical aspects

- Rationale for the proposed change

During its plenary meeting held in June 2009, the CHMP was of the opinion that Tamiflu Product Information must be updated to include recommendations on the use of Tamiflu for children below 1 year of age in the context of the Novel Influenza (H1N1) pandemic.

Reference is made to the Article 45 (1) of the Regulation (EC) No 1901/2006 of the European Parliament and of the Council, stating:

> *"1. By 26 January 2008, any paediatric studies already completed, by the date of entry into force, in respect of products authorised in the Community shall be submitted by the marketing authorisation holder for assessment to the competent authority.*
> *The competent authority may update the summary of product characteristics and package leaflet, and may vary the marketing authorisation accordingly. Competent authorities shall exchange information regarding the studies submitted and, as appropriate, their implications for any marketing authorisations concerned.*
> *The Agency shall coordinate the exchange of information".*

In the view of the EMEA, the following 2 studies fall under the scope of the above mentioned provision as they were already completed by its date of entry into force:

- Final Summary of Japanese Retrospective Surveillance and Prospective Studies in Children Less than 1 Year of Age,
- The Completed NIH Chart Review - CASG 113 FSR submitted by the MAH in June 2007.

Additionally the CHMP also considered the following data:

- Drug safety report 1032998 which evaluates literature, preclinical data and cases of maternal exposure recorded in the Roche oseltamivir safety database.
- Poster presentation describing German retrospective survey – Influenza in Infants – Experience with Oseltamivir, H Skopnik and K. Siedler, Klinikum Worms, Klinik fur Kinder- und Jugendmedizin, Gabriel-von-Seidl-Straβe 81, D-67550 Worms
- Amendment 1 of Clinical study report MV21118 (A double-blind, randomized, placebo-controlled study of early oseltamivir treatment of influenza in children 1-3 years of age)
- NIH/NIAID collaborative antiviral study group (23 April 2009)
- Evaluation sheet used to perform a structured retrospective analysis of the medical records of children admitted to Worms Hospital with a diagnosis of influenza and treated with oseltamivir with the parents' fully informed consent over 5 consecutive influenza seasons (2003–2007)

- Analysis of data submitted

The following information was submitted by the MAH for oseltamivir on 1st May 2009 and assessed by the CHMP in the frame of the Article 5(3) procedure:

- Drug safety report 1032998 which evaluates literature, preclinical data and cases of maternal exposure recorded in the Roche oseltamivir safety database.
- Poster presentation describing German retrospective survey – Influenza in Infants – Experience with Oseltamivir, H Skopnik and K. Siedler, Klinikum Worms, Klinik fur Kinder- und Jugendmedizin, Gabriel-von-Seidl-Straβe 81, D-67550 Worms
- Final Summary of Japanese Retrospective Surveillance and Prospective Studies in Children Less than 1 Year of Age
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- NIH/NIAID collaborative antiviral study group (23 April 2009)
- Evaluation sheet used to perform a structured retrospective analysis of the medical records of children admitted to Worms Hospital with a diagnosis of influenza and treated with

oseltamivir with the parents' fully informed consent over 5 consecutive influenza seasons (2003–2007).

Additionally, the Completed NIH Chart Review - CASG 113 FSR submitted by the MAH in June 2007 was also taken into consideration.

Assessment of the data can be found in the assessment report of the Article 5(3) procedure published on the EMEA website at the following addresses:
http://www.emea.europa.eu/humandocs/PDFs/EPAR/tamiflu/28766209en.pdf
http://www.emea.europa.eu/humandocs/PDFs/EPAR/tamiflu/32609509en.pdf

- Results and Discussion

Based on the available data, the MAH provided on 17 July 2009 dosing recommendations down to 6 months of age, taking into account the large safety data from prospective and retrospective surveillance studies in 2477 children < 1 year of age, of which more than 300 are 3-6 months of age and 100 are < 3 months. The MAH has limited pharmacokinetic data from a PK/PD study which indicates that using a dose of 3 mg/kg in children 6-12 months of age provides plasma drug exposures in the majority of patients similar to those shown to be clinically efficacious in older children and adults.
However, the MAH has insufficient PK data in children < 6 months of age at this time to provide more precise dosing recommendations in this very young population.

Therefore, in response to the CHMP request, the MAH proposed to update sections 4.1, 4.2, 4.4, 4.8, and 5.2 of the SPC, and Sections 3 and 4 of the PL for both capsules and suspension with information on treatment of children aged between 6 and 12 months during a pandemic influenza.

It should be noted that due to time constraints, the MAH was not in a position to submit an updated version of the Risk Management Plan (RMP) to include this new population. The CHMP agreed that the RMP would be submitted in August 2009 for assessment.

Additionally, Roche committed in June 2009 to provide an analysis of available PK data together with any analysis/new information from the ongoing US NIH (WP-20749) study to the CHMP/EMEA in September 2009.
In the frame of the adoption of the CHMP opinion for the variation II/68, the MAH was requested to commit to submit a type II variation to update the Product Information in line with the analysis of the available PK data including recommendations for 0-6 months of age by 1st September 2009.

In June 2009, Roche also committed to conduct a study in Europe to test mixing and dosing instructions (extemporaneous solution) for:
- children above 1 year of age based on the current approved dose, which equates to 3mg/kg for 1 to 2 years old.
- children below 1 year of age based on the dose of 2-3mg/kg as recommended by the CHMP in May 2009.

In a teleconference held on 16 July 2009, Roche proposed:
- to use 2 different capsule strengths, 75 mg and 30 mg, but not 45 mg as the 45 mg capsule would equate to the 30 mg capsule in terms of size, opening difficulties, dosing volumes etc.
- to conduct this study in 2 Member states, one English speaking country and one non-English speaking country.

The protocol of this mixing and dosing study should be submitted to the CHMP and the EMEA by 27 July 2009 for a quick assessment.

Within this upcoming type II variation to be submitted on the 1st September 2009, the MAH should also amend the Product Information in line with the results of this mixing and dosing study to give clear guidance on the way to prepare an oral formulation from the capsules and to dose appropriately for children.

- Conclusions and Benefit / Risk Assessment

Further to discussions during its plenary meeting held in July 2009, the CHMP agreed that the proposal from the MAH could be accepted at this stage. However the MAH should commit to submit a type II variation on the 1st September 2009 to update Tamiflu Product Information in line with the analysis of the available PK data including dose recommendations for children less than 6 months of age and to include all available data and to propose a wording for the use of Tamiflu in post-exposure prophylaxis in children.

The CHMP concluded that overall data suggest that the benefit of using Tamiflu for the treatment of children between 6 and 12 months of age outweighs the risk in the context of a pandemic influenza.

The CHMP decided that Tamiflu Product Information should therefore be updated to include recommendations of dose to treat children between 6 and 12 months of age in the context of a pandemic influenza.

- Changes to the Product Information

When discussing the Product Information of Tamiflu oral suspension, the following comments were made:

- Tamiflu oral suspension is prepared by adding 52 ml of water to the powder for oral suspension. The recommended dosing for children aged 6-12 months is based on a concentration of 10 mg/ml and the dose is administered in millilitres with a 3 ml graduated syringe. However, the recommended dose for older children above 15 kg and adults is administered with a syringe graduated for dose in milligrams. To avoid confusion, the dosing should be revised to be based on millilitres, irrespective of the patient age, and only syringes graduated for volume should be used. As a concentration of 10 mg/ml is used for the calculation of the dose it can be assumed that the true concentration of the drug product is 10 mg/ml.
- The concentration of the oral suspension is 12 mg/ml while the calculation and dosing are based on a 10 g/ml concentration, which will be very confusing for the user. The MAH should give the true concentration and ensure that the table "*Dosing Scheme of Tamiflu Preparation as a Function of the Patient's*" in the SPC is correct.
- The table "*Dosing Scheme of Tamiflu Preparation as a Function of the Patient's*" in section 4.2 of Tamiflu oral suspension SPC stops at 10 kg for children below 1 year of age with 30 mg per. The MAH should consider that some less than 1 year children may be heavier than 10 kg. The table should be completed accordingly.

The MAH should take into account these above-mentioned comments when amending the Product Information for the oral suspension through the type II variation to be submitted in September 2009.

The sections 4.1, 4.2, 4.4, 4.8, and 5.2 of the SPC, and the sections 3 and 4 of the PL have been updated for 30, 45 and 75 mg capsules and for the oral suspension to add dose recommendations for treatment of children aged between 6 and 12 months in the context of a pandemic influenza.

Conclusion

On 23 July 2009 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Labelling and Package Leaflet.