European Medicines Agency

London, 24 September 2009

ASSESSMENT REPORT FOR TAMIFLU

International Non-proprietary Name:
oseltamivir

Procedure No. EMEA/H/C/000402/II/0070

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 6 months 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.

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

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.

During its plenary meeting held in July 2009, the type II variation II/68 was concluded and the CHMP adopted a positive opinion to extend the therapeutic indication of Tamiflu to include treatment of children between 6 and 12 months of age in case of a pandemic influenza.

On the 11th of September 2009, the MAH submitted this type II variation II/70 in order to extend the therapeutic indication of Tamiflu to include treatment of children between 1 and 6 months of age and prophylaxis of children less than 1 year of age in the case of a pandemic influenza.

It should be noted that in parallel the MAH submitted a type II variation II/71 to include in the Product Information (PI) some recommendations on the preparation of an extemporaneous solution and the dosing for children less than 1 year of age.

2. Clinical aspects

2.1. 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.

On the 17th of July 2009, the MAH submitted this type II variation II/68 in order to extend the use of Tamiflu to the treatment of children between 6 and 12 months of age in case of pandemic influenza. The MAH provided on 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 had access to limited pharmacokinetic data from an ongoing NIH study "*A Pharmacokinetic/Pharmacodynamic and Safety Evaluation of Oseltamivir (Tamiflu) for the Treatment of Children Less Than 24 Months of Age with Confirmed Influenza Infection*" (CASG 114), which indicated 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 or higher to those shown to be clinically efficacious in older children and adults.
However, at that time the MAH had access to insufficient PK data in children < 6 months of age to provide dosing recommendations in this very young population.

In the frame of the adoption of the CHMP opinion for the variation II/68, the MAH committed to submit a type II variation by 1st September 2009 to update the Product Information in line with the analysis of the available PK data including recommendations for 0-6 months of age and to propose a wording for the use of Tamiflu in post-exposure prophylaxis in children, which is the scope of this type II variation II/70.

2.2. Analysis of data submitted

- **Extension of the therapeutic indication to include treatment of children between 0 and 6 months of age in case of pandemic influenza**

- Description of the data

In the frame of the type II variation II/68 to extend the therapeutic indication to include treatment of children between 6 and 12 months of age in case of pandemic influenza adopted by the CHMP in July 2009 (Commission Decision granted 9 September 2009), the MAH submitted additional information on the ongoing NIH study CASG 114. This study CASG 114 is a prospective, age-stratified pharmacokinetic/pharmacodynamic and safety evaluation of oseltamivir therapy in children less than 24 months of age with confirmed influenza infection. Between 48 and 108 infants with confirmed influenza are expected to be enrolled into one of five age cohorts see table 1 below.

The table 1 - Enrolment scheme.

Cohort	Age	Enrollment Sequence	Anticipated Sample Size	Anticipated Starting Dose
I	12-23 Months	May be enrolled at any time during the study.	12	30 mg bid
II	9-11 Months	Will be enrolled at the beginning of the study and simultaneously with Cohort III.	9-24	3 mg/kg bid
III	6-8 Months	Will be enrolled at the beginning of the study and simultaneously with Cohort II.	9-24	3 mg/kg bid
IV	3-5 Months	Sequential: will be enrolled after Cohorts II-III are enrolled.	9-24	3 mg/kg bid or dose determined by previous cohort
V	0-2 Months	Sequential: will be enrolled after cohort IV is enrolled.	9-24	3 mg/kg bid or dose determined by previous cohort

At study onset, Cohort II and III are enrolled simultaneously. Cohorts IV and V are enrolled sequentially by decreasing age groups, predicated upon the pharmacokinetic and safety data from the preceding cohort. The oldest cohort (Cohort I), which falls under the marketed indication for oseltamivir treatment, is enrolled at any time during the study.
The scientific discussion linked to this procedure can be found on the EMEA website at: http://www.emea.europa.eu/humandocs/PDFs/EPAR/tamiflu/tamiflu-H-402-II-68-AR.pdf

To support this type II variation II/70, the MAH provided interim pharmacokinetic data on children aged 0 to 6 months from the NIH study CASG 114, which are the basis on this assessment.

- Results and Discussion

CASG 114 is an AUC (Area Under Curve)-targeted, age de-escalation study to determine the appropriate dose of oseltamivir (OST) in paediatric patients with confirmed influenza infection. Oseltamivir is converted to a carboxylate metabolite which is the active substance against influenza.

The AUC target was defined as follows:
The estimated mean AUC_{12} of oseltamivir carboxylate (CBX) is 3800 ng.h/mL in older children. Assuming a 30% coefficient of variation, the standard deviation is 1140 ng.h/mL. The lower target limit for the CBX AUC_{12} target is 2660 ng.h/mL (3800 ng.h/mL minus 1 standard deviation) for

Cohorts II-V. The target upper limit for the CBX AUC_{12} is 7,700 ng.h/mL (2 standard deviations above the mean exposure following a regimen of 150 mg bid). Cohorts II-V began dosing at 3.0 mg/kg bid (not to exceed 30 mg bid). OST and CBX concentrations for intensive pharmacokinetic analysis are obtained at steady-state on Day 3 of treatment at 0 hr (baseline), 1 hr, 2-3 hr, 5-7 hr, and 10-12 hr.

OST and CBX concentration-time results were analyzed in real-time using non-compartmental methods. Modification of this dose is predicated upon data from the first 3 to 9 subjects enrolled in each of these cohorts. All dose adjustments are made in a linear fashion. In addition, they are examining the $AUC_{metabolite}$:AUC_{parent} ratio for C_{max} and AUC_{12} across each cohort.

The cohorts with any subjects enrolled to date and the dose administered are summarized below. Because this study is adaptive by design, a second dosage is being evaluated in the 9-11 months age group.

Cohort	**Age (months)**	**Dose Administered**
1	12-23	30 mg bid
2	9-11	3.0 mg/kg bid
2B	9-11	3.5 mg/kg bid
3	6-8	3.0 mg/kg bid
4	3-5	3.0 mg/kg bid
5	0-2	3.0 mg/kg bid

As already discussed in the frame of the type II variation II/68 for the children 6-12 months of age these new interim data show that the 3mg/kg twice daily dose will lead to a higher mean exposure to oseltamivir in children as compared to adults with 75mg x 2. The reason to have this higher mean exposure has been that children need a higher exposure since they have a higher viral load and viral shedding of longer duration. This could also help avoiding the emergence of resistance to the drug by under dosing, which supports what has been described in Japan where high incidence of resistant influenza strains seems to concur with low oseltamivir doses. Taking all these data into consideration the CHMP confirmed the dose to be 3 mg/kg for the treatment of children 6-12 months of age as adopted in the July 2009 CHMP (Type II variation II/68).

Additionally according to a recent publication[1], the liver enzyme needed to metabolize oseltamivir are present at birth and are maturing with time and that the liver function in the lower age groups is sufficiently developed to metabolize oseltamivir, but excretion of the metabolite via kidneys is lower than in the older age groups. This would correlate well with the fact that the estimated Glomerular Filtration Rate (GFR) of the neonates 0-1 month of age is less than half of that of the infants 6-12 months of age according to the Schwartz formula[2]. The GFR increases significantly during the first 6 months of age.

The current data on children 0-6 months of age is very limited. The exposure to the active metabolite concentration seems to increase especially in the youngest age group (0-2 months). The median values of exposure are higher than the target concentration of 3800 ng.h/ml, although it is still within the target range defined by the study protocol. The current protocol of CASG 114 does provide an option to reduce the dose in case the AUC of the metabolite is above 7700 ng.h/ml in 3 or more patients out of 9. As this limit has not been reached in the lower age groups, no exposure data is available on lower doses.

[1] Yang D, Pearce RE, Wang X, Gaedigk R, Wan YJY, Yan B, Human carboxylesterases hce1 and HCE2: *Ontogenic expression, interindividual variability and differential hydrolysis of oseltamivir, aspirin, deltamethrin and permethrin*, Biochemical Pharmacology (2008), doi:10.1016/j.bcp.2008.10.005

[2] Schwartz formula = Estimate creatinine clearance from a serum creatinine, the patient's height, and a proportionality constant using the Schwartz method (CrCl = (k.Ht)/Cr).

Since the exposure of the metabolite clearly increases in the youngest age groups and no safety data has been provided the CHMP could not agree with the initial suggestion of the MAH that the dose would be 3 mg/kg for children between 1 and 6 months of age. At least in the youngest age group (0-3 months of age) a lower than 3 mg/kg dosing should be considered. The MAH was therefore requested to carry out a modeling of the exposure with a lower dose than 3 mg/kg for this age group.

During the Oral explanation, which took place on 22 September 2009, the MAH presented a pharmacokinetic model to simulate different doses and dosing schedules in an attempt to derive relationships between drug exposure and response to treatment.
The model proposed by the MAH was developed using NONMEM, a non linear mix effect program. Data were available from 1 month of age. A sample of 100 subjects was taken from a model of 1000 profiles to produce box-whisker plots.
The aim was to compare a predicted OC (Oseltamivir Carboxylate) exposure in children less than 3 months of age with different doses with the OC exposure in adults dosed at 75 mg. The modelling data presented by the MAH supports the use of a dose between 2 and 3 mg for children less than 1 year of age as recommended by the CHMP in May 2009.

For children aged 1-3 months, it was shown that a dose of 2,5mg/kg provides the same exposure than in the older cohorts and a higher exposure than in adults dosed at 75 mg, which should suppress the higher viral load in children than in adults. The lower dose 2 mg/kg for this age range would give a lower exposure than the exposure in adult at a dose of 75 mg.

For children less than 1 month of age, the MAH did not provide any additional pharmacokinetic data or safety data at the time of the submission of this type II variation II/70. No modeling data for this age range was presented by the MAH during the oral explanation. However the CHMP discussed the urgent need for instructions to be given to health care professional in order to treat children younger than 1 month of age to face this current pandemic situation. Due to the non maturity of the renal system leading to a lower clearance than older children, one could assume that the exposure to OC in children younger than 1 month of age dosed with 2 mg/kg should be higher than the exposure in children aged 1-3 months dosed with 2 mg/kg and therefore slightly higher than the OC exposure in adults dosed at 75 mg. Therefore, in the light of the very limited data provided so far for this very young population and balancing the urgency of the current situation with a prudent approach, the CHMP concluded that a lower dose of 2 mg/kg should be recommended to treat children less than 1 month of age in the context of an pandemic influenza only.

The CHMP also concluded that the MAH should submit any updated data/information they receive concerning this ongoing NIH study CASG 114.

The safety data recently provided in connection with the Drug Safety Report (DSR) No.1034695 focusing on the safety of oseltamivir in children less than one year of age included only data from children 6-8 months of age or older from this study. These data including pharmacological, toxicological and clinical data available in children less than 1 year old were presented in this DSR submitted in August 2009. In September 2009 the CHMP concluded the following:

- Overall clinical data in 4565 children less than one year of age were presented from the following sources: In the Japanese prospective Interventional Study, among the study subjects, who experienced ADRs, one third of patients experienced neuropsychiatric events. And in many cases, causal association with oseltamivir cannot be ruled out. This is a major concern and evaluating and diagnosing neuropsychiatric events in infants is a challenge for especially parents or guardians and also for HCPs in clinical settings. In most situation, the ADRs mostly expressed as crying/screaming by infants, cannot be interpreted correctly.
- In the Japanese prospective surveillance study, subjects in the Tamiflu arm tended to have higher incidence of ADRs compared to other treatment and non treatment groups. Among the age groups, 3-6 months old age children frequently experienced ADRs (10.24%).The children below 6 months old may be vulnerable to the side effects and risk management should be focussed in this age group of children.

- German retrospective study in hospitalised infants is the only European study available so far in infants. In this study, more than half of the patients (96/157) experienced GI events such as vomiting and diarrhoea. The number of infants experienced other ADRs was not presented.
- The CASG114 study was designed for sequential enrolment. The efficacy and safety, mainly efficacy may vary since the virulence of influenza strains may change with season. No new safety concerns were identified based on the data presented for the children older than 6 months old. No nervous SOC ADRs have been reported. Only one psychiatric ADR, 'Staring' was reported in cohort III. Safety results from children less than 6 months old are to be submitted when available.
- In the USA claims data base, no significant increase in ADRs in the oseltamivir arm was reported. No ADRs related to neuropsychiatric disorders was presented in the report. This data base used ICD 9 codes, which may slightly differ from the MeDRA code in some situations. Extrapolation to whole population is restricted since this data included only insured patients.

Based on the safety data presented by Roche in this report, children less than one year appeared to tolerate oseltamivir at the doses used between 3.0-4.3 mg/kg/day.
Until the cut off date of 29 April 2009, 78 cases including 118 events were retrieved from the MAH's safety database. Of the reported events, a 59/118 were unexpected and 50/118 events were serious. One (1) fatal case was reported. Based on the information available, there seems to be no causal relationship of oseltamivir in this fatal case. Emergence of viral resistance was not reported. Convulsion was frequently reported in infants and is a listed event in the PI. Among unexpected events, hypothermia was frequently reported. One (1) serious and 5 non serious events of hypothermia were retrieved. In the above unexpected cases, due to the temporal relationship the causal relationship of oseltamivir cannot be completely excluded. The unexpected events such as hypothermia, encephalitis/encephalopathy, cardiac arrest, respiratory failure, and liver disorder should be kept under close surveillance in infants as well as in children and adults. The MAH should also closely monitor convulsion in infants.
Based on the data presented in this DSR, no new safety signal was identified in this population. Although most of the ADRs from the ADVENT data base appeared to be unexpected in an infant, however, overall, ADR pattern was consistent with the established safety profile in children aged >1 year age.
Prior to the CHMP September 2009 plenary meeting, the MAH provided some additional safety information on the children 0-2 months of age: out of 6 neonates 3 had diarrhea, there was one report on irritability, one of insomnia and one report on rash. These adverse events are in the known safety profile of Tamiflu.
Based on the data presented there is no safety restriction in the use of oseltamivir in infants during the pandemic situation.

- CHMP conclusion

Considering all the data submitted and assessed so far for children below 6 months of age, the CHMP concluded that the following should apply during an influenza pandemic outbreak:
- A dose of 3mg/kg should be given bid during 5 days to treat children between 3 and 6 months of age,
- A dose of 2,5mg/kg should be given bid during 5 days to treat children between 1 and 3 months of age,
- A dose of 2mg/kg should be given bid during 5 days to treat children less than 1 month of age.

The CHMP also concluded that the MAH should submit regular updated data from this ongoing NIH study CASG 114.

It should be noted that the MAH submitted the protocol of the study WP22849 currently titled: "*An open label, prospective, pharmacokinetic/pharmacodynamic and safety evaluation of oseltamivir (Tamiflu) in the treatment of infants up to 12 months of age with laboratory confirmed influenza infection*", which we refer as "EU PK study was submitted to CHMP and PDCO and the assessment was performed in August 2009. This protocol proposed the use of a 3mg/kg for all children below 1 year of age, however in the light of the dosing recommendations adopted by the CHMP through this

type II variation II/70, the MAH will update the protocol and submit very rapidly the CTAs (Clinical Trials Authorisations) to the selected EU countries. This EU PK study in planned to start in November 2009. The MAH should commit to submit regular update on the progress of this study.

- **Extension of the therapeutic indication to include post-exposure prophylaxis for children less than 1 year of age in case of pandemic influenza**

Throughout the approved age range for Tamiflu, effective prophylaxis against clinical influenza has been shown to be achieved using a single dose equivalent to one of the two doses administered for *bid* treatment regimen during 10 days instead of 5 days for the treatment.
Protection is then maintained as long as the drug is administered, but ceases as soon as prophylaxis is stopped.
There is currently no scientific rationale to suggest that the validity of this approach in 1 year old and older that have been in contact with a circulating influenza strain should be different in neonates and infants.

Therefore, in line with this approach and with the extension of indication to include treatment less than 1 year old children, the CHMP is of the view that for post-exposure prophylaxis during an influenza pandemic outbreak:
- A dose of 3mg/kg should be given once a day during 10 days to children between 3 and 6 months of age,
- A dose of 2,5mg/kg should be given once a day during 10 days to children between 1 and 3 months of age,
- A dose of 2mg/kg should be given once a day during 10 days to children less than 1 month of age.

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) in line with this extension of indication. The CHMP agreed that this updated RMP would be submitted at a later stage for assessment.

2.3. Conclusions and Benefit / Risk Assessment

The CHMP concluded that overall data suggest that the benefit of using Tamiflu for the treatment and post exposure prophylaxis of children between 0 and 6 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 0 and 6 months of age in the context of a pandemic influenza and recommendations of dose in case of an exposure to a circulating pandemic influenza strain for children less than 1 year of age.

2.4. Changes to the Product Information

- *Sections 4.1 SPC has been updated to include* treatment of children between 0 and 6 months of age and prophylaxis for children less than 1 year of age in case of a pandemic influenza

- Consequently section 4.2 of the SPC has been updated to include the dosing recommended as follows:

> During an influenza pandemic outbreak:
> - A dose of 3mg/kg should be given bid during 5 days to treat children between 3 and 6 months of age,
> - A dose of 2,5mg/kg should be given bid during 5 days to treat children between 1 and 3 months of age,
> - A dose of 2mg/kg should be given bid during 5 days to treat children less than 1 month of age.
>
> For post-exposure prophylaxis during an influenza pandemic outbreak:

- A dose of 3mg/kg should be given once a day during 10 days to children between 3 and 6 months of age,
- A dose of 2,5mg/kg should be given once a day during 10 days to children between 1 and 3 months of age,
- A dose of 2mg/kg should be given once a day during 10 days to children less than 1 month of age.

- Section 5.2 has been updated with new PK information for children less than 1 year of age.

- The PL has been modified accordingly.

Detailed changes in the PI can be found in Attachment 1. "SPC and Package Leaflet (changes highlighted) as adopted by the CHMP on 24 September 2009"

It should be noted that a type II variation II/71 has been adopted in parallel to update the PI with information on preparation of an extemporaneous formulation and dosing recommendations for children less than 1 year of age.

3. Conclusion

On 24 September 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 and Package Leaflet.