European Medicines Agency

London, 7 May 2009
EMEA/CHMP/287662/2009

CHMP ASSESSMENT REPORT

ON

Novel Influenza (H1N1) outbreak
Tamiflu (oseltamivir)
Relenza (zanamivir)

EMEA/H/A-5.3/1172

Procedure under Article 5(3) of Regulation (EC) No 726/2004

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1 BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Article 5(3) of Regulation (EC) No 726/2004

In view of the novel Influenza A (H1N1) outbreak, 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.

The CHMP opinion was sought on the following:

(1) The potential usability of Tamiflu (oseltamivir) capsules already on the market in the EU for which the expiry date is about to expire or has already passed, taking into account (a) the outcome of the ongoing variation procedure to extend the shelf-life from 5 to 7 years, and (b) the exceptional potential health implications that may result from a shortage of oseltamivir available in the EU. The recommendation should also elaborate on the conditions to be fulfilled, e.g. in terms of the storage conditions to be adhered to. The CHMP should also consider whether it is in a position to provide a recommendation regarding the usability of oseltamivir bulk over the extended period.

(2) The appropriateness of administering oseltamivir to children younger than 1 year of age to treat or prevent the novel Influenza A (H1N1) in case of a pandemic. If appropriate, the CHMP should make dosing recommendations.

(3) The use of oseltamivir during pregnancy and lactation to treat or prevent the novel Influenza A (H1N1) in case of a pandemic.

(4) The use of Relenza (zanamivir) during pregnancy and lactation to treat or prevent the novel Influenza A (H1N1) in case of a pandemic.

1.2 Steps taken for the procedure

At the request of the Executive Director, the following was agreed on April 30 2009:

- The Rapporteur for Tamiflu, Dr. Outi Lapatto-Reiniluotto, was appointed for the review procedure under Article 5(3).
- The Rapporteur for Relenza, Dr Bengt Ljungberg was appointed for the review procedure under Article 5(3),
- Experts from the Paediatric Committee (PDCO) were identified for the review procedure. There were the following: Dr. Marta Granstrom, Dr. Ann Marie Kaukonen, Dr. Irja Lutsar, Dr. Gerard Pons, Dr. Francesca Rocchi, Dr. Paolo Rossi, Dr. Siri Wang.
- Other experts were also identified for the review procedure: Dr. Ingrid Uhnoo, Dr. Regine Lehnert and Dr. Elisabeth Elefant.
- An eight day time frame for the procedure was set.
- The procedure was initiated on 30 April 2009.
- The Marketing Authorisation Holders (MAHs) for Tamiflu and Relenza, respectively Roche Registration Limited (Roche) and GlaxoSmithKline (GSK), were informed of the start of this procedure on the 1st of May 2009.
- Roche provided additional information on Tamiflu on the 1st of May 2009.
- The PDCO experts' assessment report on the appropriateness of administering oseltamivir to children younger than 1 year of age to treat or prevent the novel Influenza A (H1N1) in case of a pandemic was circulated on 4 May 2009.
- The Rapporteur's overall assessment report was circulated on 4 May 2009.
- The assessment report on the use of Relenza was circulated on 5 May 2009.
- The Rapporteur's final assessment report was circulated on 6 May 2009.
- On 7 May 2009 the CHMP adopted an Opinion via written procedure.

2 SCIENTIFIC DISCUSSION

2.1 Background

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 Infuenza 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 viruses detected in humans in Mexico and USA were found to be resistant to amantadine and rimantadine. Laboratory testing however indicated that these viruses may be susceptible to oseltamivir (Tamiflu) and zanamivir (Relenza).

Oseltamivir is a centrally authorised product with a marketing authorisation valid since 20 June 2002. Zamivir is authorised via the mutual recognition procedure since June 1999.

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

Zanamivir is indicated for treatment of influenza in patients above 5 years of age who present with symptoms typical of influenza when influenza is circulating in the community. Zanamivir is also indicated for post-exposure prevention in individuals 5 years of age or older. Zanamivir is approved as oral inhalation powder administered through a Diskhaler device.

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 and pregnant and breastfeeding women for both oseltamivir and zanamivir should be investigated.

On 27 April 2009 the MAH for Tamiflu submitted a variation (EMEA/H/C/402/II/65) to extend the shelf-life of Tamiflu 75 mg, 45 mg and 30 mg hard capsules from 5 to 7 years. A positive opinion was issued by the CHMP on 6 May 2009.
Considering the data presented and the potential health implications of a shortage of oseltamivir in the EU, the EMEA requested that recommendations be given on the use of oseltamivir (finished product and bulk) manufactured since May 2002 onwards (for which stability has or will shortly expire).

The following information was submitted by the MAH for oseltamivir on 1st May 2009 and assessed by the CHMP to form the basis of this assessment report:

- 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

- 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).

This assessment report also takes into consideration the Completed NIH Chart Review - CASG 113 FSR submitted by the MAH in June 2007.

For zanamivir, the present assessment is based on data available from the recent renewal, periodic safety assessment reports (PSUR) and data from the initial marketing authorisation (non-clinical reproduction toxicity studies). No updates on the use of Relenza during pregnancy and lactation were received from the MAH of zanamivir in the framework of this Article 5(3) procedure.

2.2 Question 1

The potential usability of Tamiflu (oseltamivir) capsules already on the market in the EU for which the expiry date is about to expire or has already passed, taking into account (a) the outcome of the ongoing variation procedure to extend the shelf-life from 5 to 7 years, and (b) the exceptional potential health implications that may result from a shortage of oseltamivir available in the EU. The recommendation should also elaborate on the conditions to be fulfilled, e.g. in terms of the storage conditions to be adhered to. The CHMP should also consider whether it is in a position to provide a recommendation regarding the usability of oseltamivir bulk over the extended period.

On 27 April 2009 the MAH for Tamiflu submitted a variation (EMEA/H/C/402/II/65) to extend the shelf-life of Tamiflu 75 mg, 45 mg and 30 mg hard capsules from 5 to 7 years. A positive opinion was issued by the CHMP on 6 May 2009.

It should be noted that this extension of shelf life to 7 years does not apply to the paediatric suspension of Tamiflu.

Due to the public health emergency linked to the current risk of pandemic influenza, and based on data made available regarding the stability of Tamiflu (Oseltamivir) 30mg, 45mg and 75mg capsules for an additional period of 2 years, the CHMP recommends that boxes of Tamiflu capsules should not be discarded where the expiry date has already passed. For these batches an updated expiry date should be determined by adding a further period of 2 years to the stated expiry date.
The conditions of storage play a role in the stability of medicinal products. It is of great importance that these boxes have always been kept and remains stored below 25^{o}C.

More detailed instructions concerning the use of capsules for which the expiry date has passed will be available in case a pandemic influenza is declared by the WHO in the context of the Novel influenza A (H1N1) outbreak.

With regard to bulk of active substance as stockpiled by some Member States, no specific data have been provided in the framework of this Article 5(3) procedure, and therefore assessed by the CHMP. The decision to stockpile and use this specific form is the prerogative of the individual Member States in accordance with the stability data provided by the MAH.

2.3 Question 2

The appropriateness of administering oseltamivir to children younger than 1 year of age to treat or prevent the novel Influenza A (H1N1) in case of a pandemic. If appropriate, the CHMP should make dosing recommendations.

Amongst the set of data submitted by Roche in the framework of this Article 5(3) procedure, 2 documents have been assessed: the drug safety report 1032998 which evaluates literature, preclinical data and cases of maternal exposure recorded in the Roche oseltamivir safety database, and the poster presentation describing German retrospective survey.

- *Data from the 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)" was assessed by the CHMP.*

This study 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. At study onset, Cohort II and III will be enrolled simultaneously. Cohorts IV and V will be 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, may be enrolled at any time during the study.

The table 1 below summarises the 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

Summary of Trial to Date (April 2009):
Cohort I – N=11 (enrolled)
Cohort IIA – N=7 (closed)
Cohort IIB – N=3 (enrolled)
Cohort III – N=15 (closed)
Cohort IV – N=4
Cohort V - (not open)

Forty (40) subjects have been enrolled on the study as of 23 April 2009. It should be noted that this study is still ongoing and only a very short interim report is available. No children between 0 and 3 months of age are yet included. Furthermore the pharmacokinetic analysis of the data is still premature. However some interim information can be used here.

Demographic Assessments

Sixty-three (63) percent (25 of 40) are male, and fifty-eight (58) percent (23 of 40) are Caucasian. The median symptom duration (confirmed diagnosis of influenza) prior to enrolment ranged from 2 days to 4 days.

Two (2) patients have withdrawn from the study prior to completion. One (1) withdrew after the second dose of oseltamivir due to hypersensitivity reaction. The other stopped medication and the parents withdrew consent on Day 4 of dosing.

Six (6) patients have reported serious adverse events (AEs) during their study participation. These events included: influenza (in 2 patients), hypersensitivity with rash and difficulty breathing, pneumonia, pyrexia, and decreased oxygen saturation (in 1 each). The event of hypersensitivity was considered to be related to study drug; all other serious adverse events (SAEs) were considered not related. Most were thought to be consistent with the underlying influenza infection.

A total of 57 AEs have been reported among 26 patients. One (1) patient experienced neutropenia (Grade 4 absolute neutrophil count (ANC) not accompanied by other clinical symptoms) which resolved spontaneously without interruption of study drug. Five (5) patients were diagnosed with otitis media (OM) (4 in Cohort III and one in Cohort II A). The most common AEs reported were gastrointestinal events; 8 patients reported vomiting, 3 reported diarrhoea, and one each reported flatulence and teething. One (1) patient experienced urticaria but 11 reported less severe skin disorders. Three (3) of the gastrointestinal AEs were considered related to study drug but all other events were considered not related.

- *Poster presentation describing German retrospective study: 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-Straße 81, D-67550 Worms*

This poster presentation described a retrospective analysis of data from 157 infants < 1 year of age who received oseltamivir 2 mg/kg BID during the flu seasons of 2003-2007. This survey identified all infants presenting with fever > 38.0^{o} C and at least 3 influenza like symptoms such as rhinitis, pharyngitis, cough, general ill appearance, and sudden onset of symptoms. Patients positive in rapid influenza testing were hospitalised and treated with oseltamivir 2 mg/kg BID. Duration of fever after therapy start was used as the primary criterion for analysis of oseltamivir efficacy.

As noted, 157 infants were included in the study: 45% male, mean age 6.2 months (+/- 3.2 months). Of the patients who had siblings at home, 34/90 (37%) siblings reported influenza symptoms within one week of the patient's admission. Most infants did not report underlying medical conditions: 7 had pre-existing cardiovascular disease, 6 had pre-existing pulmonary disease, and 2 had pre-existing dermatologic disease. Eight (8) infants were diagnosed with concomitant pneumonia, 7 had concomitant seizures, 2 had concomitant RSV infection, 1 had meningococcal meningitis, and 1 had enteritis due to salmonella. Overall, 10 infants had secondary infections requiring antibiotic treatment. It was not clear from the report submitted if the "concomitant" conditions represent conditions diagnosed at baseline or if they developed during treatment.

The most common presenting symptoms in this cohort of infants were: rhinitis (85%), pharyngitis (84%), cough (66%), feeding difficulties (40%), otitis (24%), conjunctivitis (18%), and vomiting (16%). Wheezing, sepsis-like illness, enteritis, tonsillitis, febrile seizure, and stridor were each reported in < 10% of patients. Resolution of fever to < 37^{o} C occurred in 128/157 (82%) within 36 hours of beginning oseltamivir treatment and in 136 (87%) within 48 hours. Oseltamivir was reported to be well-tolerated although vomiting during treatment was reported in 62 infants and

diarrhoea was reported in 34 infants. These events were reported to be mild and did not require intervention.

The authors concluded that "Oseltamivir carboxylate in infants proved to be as effective and safe as in older children….Since infants are particularly vulnerable to influenza the approval of oseltamivir for this age group health authorities is desirable."

Two (2) other studies had already been assessed previously by the CHMP and therefore have not been evaluated in this assessment report although the previous conclusions were revisited and considered for the purpose of this review.

These 2 studies are the following:

- *The Japanese Retrospective Surveillance in Children Less than 1 Year of Age*

Substantial use of oseltamivir in young children below the age of 1 year has been reported in Japan.
As a result, a retrospective surveillance study was conducted in young infants who were administered oseltamivir during the influenza season of 2003-2004. Of the 834 cases collected under the surveillance, 771 of them were found eligible for safety analysis. Diarrhoea was the most frequently reported event. No serious adverse drug reactions were recorded.
A prospective survey of the use of oseltamivir in children aged <1 year of age was also undertaken in the 2004-2005 influenza season in Japan. A total of 1771 cases were collected under the surveillance, and 1674 of them were found eligible for safety analysis. Eighty-two percent (82%) of these children were aged 6-12 months. The most frequently reported adverse events in the oseltamivir group were diarrhoea, upper respiratory tract inflammation, vomiting and rash. Data from these retrospective and prospective analyses indicate that no new safety signals are emerging associated with the use of oseltamivir in children <1 year of age. However, further studies are warranted to confirm the safety of oseltamivir in children <1 year of age. A prospective study evaluating the pharmacokinetics, pharmacodynamics and safety of oseltamivir in children 0-24 months of age is planned.
In May 2007, in the framework of the first renewal of the Marketing Authorisation, the CHMP concluded that the data submitted did not suggest that the use of oseltamivir increases the incidence of adverse events, serious adverse events, or adverse events related to the central nervous system in children younger than 1 year of age, and therefore no new major concerns about the safety of oseltamivir in infants younger than 1 year of age had emerged. However, the data were then insufficient to rule out serious but infrequently occurring adverse events.

- *The Completed NIH Chart Review - CASG 113 FSR submitted by the MAH in June 2007.*

In 2007, the MAH submitted a retrospective chart review (Study CASG 113) designed to assess the safety of oseltamivir as a treatment for influenza in children less than 12 months of age in the US. From 15 medical centers, 180 patients were enrolled.

The primary study objective was to evaluate the frequency of neurological adverse events among children less than 12 months of age who received antiviral therapy as a treatment for suspected or laboratory diagnosed influenza (oseltamivir versus amantadine or rimantadine). The most frequently reported adverse event was"irritability". During treatment with oseltamivir, 13 infants reported a new symptom of "irritable" than at baseline (n = 21). No other significant neurological disorders were observed.
The secondary objective of the review was to describe the frequency of all adverse events among children less than 12 months who were administered oseltamivir, amantadine or rimantadine and to compare the frequency of adverse events at various doses of oseltamivir when administered to children less than 12 months. There was a notable increase of "gastro-intestinal disorders", such as vomiting. At baseline, 14 infants reported to have vomiting, whereas a new symptom of vomiting during treatment with oseltamivir was reported in 9 infants. Vomiting is a known and labelled side effect of oseltamivir. One subject with a history of failure to thrive died within 30 days of initiating the antiviral medication.

In summary, the proportion of babies with any neurologic event was not statistically different between the treatment groups (p=0.13). Review of the adverse events observed in other system organ classes indicated a favourable safety profile with the antivirals used in this paediatric population.

In February 2008, the CHMP concluded that the most common adverse events, probably related to medication, were irritability and vomiting. Neurologic adverse events during treatment reported were irritability (n=13), agitation (n=1), hypertonia (n=1), hypotonia (n=2), seizures (n=1). Neurologic adverse events were rare and not statistically significant between treatment groups. From the report, it could be concluded that oseltamivir did not cause unknown safety problems in children below 12 months of age.

Two (2) safety studies (the German poster and the Japanese retrospective study) have used a dose of 2 mg/kg in children below 1 year of age and showed that oseltamivir was well tolerated.

It is acknowledged that limited data are available supporting the use of Tamiflu in children below 1 year of age. However considering the urgent need for recommendations to treat this population **in case of a pandemic influenza is declared by the WHO in the context of the Novel influenza A (H1N1) outbreak**, the CHMP recommends:

1. To treat children below 1 year of age with Tamiflu ..
2. The appropriate dosage to treat children below 1 year of age is 2-3mg/kg twice daily during 5 days.
3. The post-exposure prophylaxis of children below 1 year of age should be very carefully considered by prescribers. If it is decided to prescribe Tamiflu to prevent influenza for children below 1 year of age who have been exposed to the virus, the appropriate dose should be 2-3mg/kg once a day during 10 days.
4. The paediatric suspension or dilution of the capsules of tamiflu can be used to prepare the dose in children below 1 year of age.
5. Children below 1 year of age should be treated under medical supervision. However in case of pandemic influenza, this recommendation could potentially place huge burden on hospital resources and therefore, the CHMP strongly recommends that at least children below 3 months of age are treated under medical supervision in hospital.

2.4 Question 3

The use of oseltamivir during pregnancy and lactation to treat or prevent the novel Influenza A (H1N1) in case of a pandemic

The current product information includes the following text in **Section 4.6** *Pregnancy and Lactation*

There are no adequate data from the use of oseltamivir in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal or postnatal development (see section 5.3). Oseltamivir should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the foetus.

In lactating rats, oseltamivir and the active metabolite are excreted in the milk. It is not known whether oseltamivir or the active metabolite are excreted in human milk. Oseltamivir should be used during breast-feeding only if the potential benefit for the mother justifies the potential risk for the breast-fed infant.

This reflects that oseltamivir should not be used during pregnancy or breast-feeding unless the potential benefit to the mother justifies the potential risk to the foetus or breast-fed infant.
It is noted that data are available from animal studies, which do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal or postnatal development. In animal reproductive studies in rats and rabbits, no teratogenic effect was observed. Fertility and reproductive toxicity studies have been conducted in rats. There was no evidence of an effect on fertility at any dose of oseltamivir studied. Foetal exposure in rats and rabbits was approximately 15-20% of that of the mother.

Data in lactating rats indicates that oseltamivir and the active metabolite are excreted in the milk. It is not known whether oseltamivir or the active moiety (Oseltamivir carboxylate) is excreted in human milk.

In the framework of this Article 5(3) procedure, the MAH submitted an overview of 232 cases with maternal exposure to oseltamivir, including 12 cases with a foetal outcome of birth defect/other disorder

- *Description of the data*

The age was unknown for 81/232 pregnancy cases and 3/12 birth defects/other disorder cases. The distribution by age for the pregnancy cases was similar to what would be expected for the general population: women in the 16 to 25 age group (32/232 cases) and 26 to 35 (101/232 cases) outnumbered women in the 36 to 45 age group (18/232 cases). There was one case of birth defect in the 36 to 45 age group compared to 4 each in the 16-25 and 26-35 age group (see table 2 below]

Table 2 Maternal Cases – Overview

Parameter		All Cases (N=232) n (%)	Birth defect/other disorder (N=12) n (%)
Country	USA	25 (11.0)	1 (8.3)
	EU[1]	27 (11.6)	
	Japan	169 (73.0)	9 (75.0)
	ROW	11 (4.8)	2 (16.6)
Reporter	Literature	2 (0.86)	2 (17.0)
	Spontaneous	153 (66.0)	4 (33.0)
	Study	77 (33.0)	6 (50.0)
Age (years)	16 – 25	32 (14.0)	4 (33.0)
	26 – 35	101 (44.0)	4 (33.0)
	36 – 45	18 (7.8)	1 (8.3)
	Unknown	81 (35.0)	3 (25.0)

[1] Includes – Denmark (1), France (11), Germany (6), Greece (2), Ireland (1), Netherlands (2), Norway (1), Switzerland (1), United Kingdom(2)

The indications for which oseltamivir was used in these pregnancies were categorised as influenza (treatment), prophylaxis (of influenza), miscellaneous and unknown indication. The distribution of cases by category of indication is shown in the table 3 below.

Table 3 Distribution of Cases by Oseltamivir Indication Category

Indication category[1]	All Cases (n=232) n (%)	Birth defect/other disorder (n=12) n (%)
Influenza	158 (68.29)	10 (83.3)
Prophylaxis	10 (4.26)	
Miscellaneous[2]	5 (2.15)	
Drug Use For Unknown Indication	59 (25.0)	2 (17.0)

[1] A detailed distribution of cases by indication is provided in Appendix 3.

[2]Includes one case each of bronchitis, febrile infection, influenza like illness, medication error and unevaluable infection. The case of 'medication error' occurred in a patient (MCN #267026) of unknown age who took oseltamivir in place of an analgesic, at two months of gestation. She had no adverse events; her pregnancy outcome and foetal outcome are unknown

- *Results*

There were a total of 416 adverse events in 232 cases with maternal exposure (see the table 4 below for the cumulative cases). The adverse events presented here comprise both medical adverse events and events consistent with the normal course of pregnancy. The latter were the majority and comprised terms such as pregnancy (119 events), normal newborn (82 events), 'no adverse reaction' (169 events) and live birth (2 events).

Cumulative Adverse Events in Maternal Exposure Cases

Preferred term	Number of events (n=416)[1]
No adverse event	169
Pregnancy	119
Normal newborn	82
Abortion induced	11
Abortion spontaneous	3
Abortion missed	2
Live birth	2
Premature baby	2
Ventricular septal defect	2
Abortion	1
Acute respiratory distress syndrome	1
Anaemia	1
Anencephaly	1
Anophthalmos	1
Apnoea	1
Aspartate aminotransferase increased	1
Blood creatine phosphokinase increased	1
Blood creatine phosphokinase mb increased	1
Blood lactate dehydrogenase increased	1
Bradycardia	1
Cleft lip and palate	1
Cytogenetic abnormality	1
Delivery	1
Disseminated intravascular coagulation in newborn	1
Hydrocele	1
Hydrops foetalis	1
Intra-uterine death	1
Melanocytic naevus	1
Respiratory distress	1
Respiratory failure	1
Retinopathy	1
Stillbirth	1
Trisomy 21	1
Total	**416**

Most of the medical adverse events occurred in patients with adverse pregnancy (spontaneous or therapeutic abortions) or foetal outcomes (birth defect or other disorder). The events of apnoea, bradycardia, anaemia, retinopathy and respiratory distress were seen in a premature baby with a congenital hydrocele. The events of respiratory failure, acute respiratory distress syndrome, blood creatinine phosphokinase-MB increased, blood creatinine phosphokinase increased, blood lactate dehydrogenase increased, aspartate aminotransferase increased were seen in one patient with avian influenza who had a pregnancy outcome of spontaneous abortion and a foetal outcome of other disorder.
The 416 adverse events included 32 serious adverse events seen in 18 cases. Of these, 31 events were from 17 cases that had an adverse pregnancy or foetal outcome.

Adverse events in cases with a foetal outcome of birth defect/other disorder
Twenty seven (27) events occurred in 12 cases with a foetal outcome of birth defect or other disorder. All adverse events that were considered as anatomic birth defects in the cases with birth defect or

other disorder are shown in the table 5 below. Thus adverse events such as abortion induced, acute respiratory distress syndrome and laboratory related adverse events are excluded from the table.

Table 5 Cumulative Adverse Events in Cases with a Foetal Outcome of Birth Defect/Other Disorder

Preferred term	Number of events (n=27)[1]
Anencephaly	1
Anophthalmos	1
Cleft lip and palate	1
Cytogenetic abnormality	1
Hydrocele	1
Hydrops foetalis[2]	1
Melanocytic naevus	1
Trisomy 21	1
Ventricular septal defect	2

[1] A complete table with all 27 adverse events classified under various SOCs is provided in Appendix 8.

[2] The PTs Hydrops foetalis and cytogenetic abnormality originate from the same case

Overall, 10 birth defects were described in 10 offspring; ventricular septal defect was reported twice, all other birth defects only once.

The overall reporting rates (based on known pregnancy outcomes captured in the safety database) for foetal loss (7%) and spontaneous abortions (6.1%) were not higher than the background rates observed in literature of 16% and 14.3% respectively. There are, however, some limitations to this comparison.

There were a total of 13 of 232 cases with therapeutic abortion. There were 13/115 (11.3%) therapeutic abortions among all cases with a known pregnancy outcome. There were 8 cases of therapeutic abortion among the 44 cases with first trimester exposure to oseltamivir for a reporting rate of 18.2%. These rates were not higher than the background rate (19.1%). No association between therapeutic abortion and use of oseltamivir was identified.

Of the 232 maternal exposure cases, there were 95 with a pregnancy outcome of delivery. In one of these cases, there was a still birth. There were therefore 94 live births, with 2 premature deliveries (2/94 or 2.12%). The background rate for preterm deliveries is 1 in 8 live births or 12.5%. The reporting rate for premature deliveries was not greater than the background rate. Most causes of preterm delivery are related to medical and obstetric complications or lifestyle factors. Drugs such as ergotamine can cause preterm delivery by a direct pharmacologic effect. Oseltamivir is not known to have any such effect. In preclinical studies in mice at doses several fold higher than humans, oseltamivir caused a prolongation in parturition.

As the background rate for birth defects is low, no attempt was made to compute reporting rates for individual and overall birth defects in the MAH's oseltamivir safety database with background rates. Instead, each case was reviewed individually to determine if the timing for the birth defect was associated with use of oseltamivir and if there was a pattern of birth defects across cases. A single case analysis was performed for 10 cases with a birth defect. There were 3 cases (2 cases with ventricular septal defect, 1 case with anophthalmos) where exposure to oseltamivir occurred during the critical period for the birth defect. Ventricular septal defect is a common birth defect with a high background rate. Anophthalmos/ microphthalmos are birth defects that are not uncommon in the general population.
Furthermore, microphthalmos is associated with fever irrespective of influenza. In all 3 cases, the patient was exposed to therapeutic doses of oseltamivir. At therapeutic doses, oseltamivir has not been detected in the foetal compartment in *ex vivo* human placental models. Thus, the birth defects did not appear to be related to the use of oseltamivir.

There were no adverse events suggestive of other (foetal) disorders such as low birth weight, small for gestational age or intrauterine growth retardation. Other adverse events in the foetus/newborn were consistent with preterm labour (the rates for which were not higher than the background rates).

- *Discussion on the results of this safety report*

A review of the literature indicates that physiological changes caused by pregnancy may increase the risk for influenza complications. There is some evidence to suggest that there may be an increased risk of foetal loss on exposure to influenza itself in the first trimester. There is the possibility therefore, that a treating physician may want to use oseltamivir to treat influenza during pregnancy. Oseltamivir phosphate (OP) is a pro-drug of the active moiety Oseltamivir carboxylate (OC). Theoretically, direct toxicity to the foetus may potentially result if either of these substances crosses the placental barrier. OP and OC are, respectively, substrates for the active exporters P-glycoprotein (P-gP) and the multidrug resistance protein 4 (MRP 4) in the placenta. It is thus unlikely that significant amounts of either drug reach the foetus at therapeutic doses. However, if genetic polymorphisms or specific inhibitors that decrease the activity of these transporters are present, an increase in the concentrations of OP and/or OC in the foetus can be expected. However, the clinical relevance of potentially increased drug concentrations is unclear. In preclinical studies, no teratogenicity was observed in rats and rabbits at doses of 1,500 and 500 mg/kg/day, respectively, despite an estimated foetal exposure in these species of about 20% of maternal plasma. Based on experimental animal studies, oseltamivir therapy during pregnancy is not expected to increase the risk of congenital anomalies.

The risk from exposure in humans was evaluated by reviewing the MAH's oseltamivir safety database. The data was put into context with information on the effect of influenza on pregnancy, the background rates for abortions in the general population, impact of high fever on pregnancy and available pre-clinical data. The cumulative review of the safety database revealed a total of 232 cases with maternal exposure to oseltamivir (with 416 adverse events) with 12 foetal disorders. This included all cases reported in literature as well as study cases. The most common indication for oseltamivir was treatment of influenza. The evaluation of the information does not suggest restrictions of the use of oseltamivir in pregnant women. Based on the data presented, the birth defects found in this review could not be directly related to oseltamivir.

Overall, there did not appear to be any evidence to suggest that maternal exposure to oseltamivir was associated with adverse pregnancy or foetal outcomes.

This review seems to show that no new safety risks to foetus are connected to the use of Tamiflu in pregnant women. At the moment the statement in section 4.6. of the SPC "*Oseltamivir should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the foetus*." remains valid for **seasonal influenza** epidemics.

However, the overall data suggest that the benefit of using Tamiflu in pregnant or breastfeeding women outweighs the risk in the context of a **novel influenza (H1N1) in a <u>pandemic</u> situation.**

2.5 Question 4

The use of Relenza (zanamivir) during pregnancy and lactation to treat or prevent the novel Influenza A (H1N1) in case of a pandemic

The current product information includes the following text in **<u>Section 4.6</u>** *Pregnancy and Lactation*

Pregnancy*: The safe use of Relenza during pregnancy has not been established.*
In rats and rabbits zanamivir has been shown to cross the placenta. High doses of zanamivir were not associated with malformations in rats or rabbits and only minor alterations were reported. The potential risk for humans is unknown. Relenza should not be used in pregnancy unless the expected benefit to the mother is thought to outweigh any possible risk to the foetus.
Lactation*: In rats zanamivir has been shown to be secreted into milk. There is no information on secretion into breast milk in humans.*
The use of zanamivir is not recommended in mothers who are breast feeding.

- *Non-clinical aspects*

Zanamivir is not metabolised and approximately 20% of an oral inhaled dose of zanamivir can be accounted for in urine as unchanged parent drug. The remaining portion of the oral inhaled dose (approximately 80%) is unchanged material unabsorbed from the gastro intestinal tract and is excreted in faeces. At a dose of 10 mg bid in humans, AUC levels in the range of 0.5 μg.h/ml have been recorded with maximum plasma levels ranging from 0.03 to 0.1 μg/ml.

Standard reproduction toxicology studies are available. These were conducted in relation to the first marketing authorisation in 1999 and included studies in rat and rabbits using the intravenous administration route, see table 6 below.

Table 6

Study Type/Study ID	**Species, No./sex/group**	**Dose/Route/Duration**	**Major Findings**
Preliminary Segment II (WPT/93/013)	Rat (10 ♀)	0, 1, 9, 90 mg/kg, IV day 6-day 15 of pregnancy	No effects on F0 or F1 generation. Preimplantation loss ↑, not stat. sign.
Segment II (WPT/93/047)	Rat (28 ♀)	0, 1, 9, 90 mg/kg, IV day 6-day 15 of pregnancy	No effects on F0 or F1. Implantations, live foetuses, foetal weights unaffected.
Segment II (WPT/93/095)	Rabbit (17-18 ♀)	0, 1, 9, 90 mg/kg, IV day 7-day 19 of pregnancy	Post-implantation loss ↑ (MD-HD). Mean foetal bw. ↓ (HD)

Pharmacokinetic studies did not indicate any differences in the disposition of the drug in pregnant and non-pregnant rat. In rats, low amounts of radiolabelled material appeared to cross the placenta. In rabbits, drug-related material crossed the placenta and was widely distributed in foetuses. Zanamivir was excreted into milk of lactating rats and levels in milk were higher than in plasma.

Maximum plasma levels of up to 2000-3000 times the clinical level were achieved in these studies. However, levels of zanamivir rapidly decline in plasma indicative of possible treatment interruption occurring during critical periods of organogenesis. A sustained exposure was achieved in rabbits while rats seemed to have been exposed only during a few hours per day. Systemic exposure data from these studies are not available, but data from other rat studies at an intravenous dose of 90 mg/kg/day indicated levels approximately x300 the estimated human dose.

The compound at doses of up to 90 mg/kg intravenously was devoid of any effects on fertility parameters.

There were no findings in Segment II studies considered related to zanamivir treatment. A dose-related increase in the mean % foetuses/litter with visceral anomalies was noted, but the differences in incidences were not statistically significant. In rabbits, post-implantation loss was increased at the mid- and high dose, but again a statistical significance was not evident and the apparent increase may have reflected the lower number of control animals. Foetal body weights appeared lower. In one high dose animal study indicated minor skeletal changes and variants were reported, but the increase was not significantly different from controls. Overall, considering historical control data, the pattern, frequency and distribution of malformations and anomalies among foetuses and litters in different groups, no effects related to zanamivir treatment were evident.

Overall, non-clinical data do not indicate any relevant concerns for the safe use of zanamivir inhalation powder during pregnancy and lactation. Although excretion into breast milk seems to occur, maternal systemic exposure levels are low after inhalation of zanamivir and there would be only very low amount of systemic zanamivir available for excretion into breast milk. Further, animal studies have shown that zanamivir has a low potential for toxicity by the oral route.

- *Clinical data*

In the data covering the period from 1 August 2003 to 31 January 2008 there was a total of 16 adverse events reported, 2 of which were serious unlisted (premature baby=2) and 14 were non-serious, unlisted including delivery.
In the data covering the period from 1 February 2008 to July 2008 13 cases possibly related to administration of zanamivir were observed.

In the PSUR covering the reporting period 01 August 2008 to 31 January 2009 were 97 cases reported possibly related to administration during pregnancy (n=52) or lactation (n=45). Pregnancy outcomes for the current reporting period and cumulative totals are summarised in the table (below). No serious unlisted or listed adverse events were identified (see table 7 below).

Table 7 Pregnancy Outcomes

Outcome[1, 2]	**In Period (n=52)**	**Cumulative (n=133)**
Live infant, no apparent congenital anomaly[3]	1	43[4,5,6]
Live infant with congenital anomaly		
Elective termination, no apparent congenital anomaly[3]		2
Elective termination with congenital anomaly		
Spontaneous abortion, no apparent congenital anomaly[3]		4
Spontaneous abortion with congenital anomaly		
Stillbirth, no apparent congenital anomaly3		
Stillbirth with congenital anomaly		
Ectopic pregnancy		1
Molar pregnancy		
Pregnancy ongoing, lost to follow-up or unknown	51	83
Total	**52**	**133**

1. The number of pregnancy outcomes may not match the number of cases in Appendix 5E due to the nature of the search strategy used for the narratives;
2. Changes in the numbers of the cumulative outcomes since the previous safety update reflect not only the addition of new cases but also follow-up obtained on previously received cases;
3. Pregnancy outcome categories stating 'no apparent congenital anomaly' include outcomes where it is unknown whether a congenital anomaly occurred.
4. The baby's first exposure to zanamivir was in utero, in the third trimester, 5 days prior to delivery. Three days after the birth, the baby developed convulsions which were considered possibly related to Zanamivir by the reporting physician. The event resolved following treatment with phenobarbital.
5. In one case the infant exhibited decreased motion and strength of upper extremities.
6. A sick infant was born through emergency caesarean section. The patient eventually died (approximately 17 weeks after birth) and the cause of death was chronic lung disease and influenzae A pneumonia.

No new important safety information regarding use in pregnancy has been identified. No serious unlisted or listed adverse events were reported.

Concerning lactation, while zanamivir may be excreted in breast milk the systemic levels after inhalation would be low and the low oral toxicity would suggest that exposure of infants via the gastrointestinal tract should not prevent the use of Relenza during lactation.

Clinical experience with the use of Relenza during pregnancy and lactation is very limited. Zanamivir should not be used in pregnancy unless the expected benefit to the mother is thought to outweigh any possible risk to the foetus. Pregnant women were excluded from the clinical studies and use of zanamivir in this group has not been established. Since the systemic exposure to zanamivir is very limited, it might be the preferred choice for treatment/ prophylaxis of influenza during pregnancy. However, in cases of suspected systemic virus infection oseltamivir might be preferred choice due to its systemic activity.

No new safety risks to foetuses were identified in the current review.

A benefit-risk analysis should also take into consideration that influenza in itself in pregnant women during the first trimester has been reported to include adverse effects such as hyperthermia that may double the risk for neural tube defects and may be related to birth defect.

At the moment the statement in section 4.6. of the SPC "*Relenza should not be used in pregnancy unless the expected benefit to the mother is thought to outweigh any possible risk to the foetus*." remains valid for **seasonal influenza** epidemics.

Zanamivir has in animal studies been shown to cross the placenta and to be secreted in breast milk. The non-clinical data are not indicative of any relevant cause for concerns regarding the safe use of Relenza at recommended doses.

Taken together the overall data suggest that the benefit of using Relenza in pregnant or breastfeeding women outweighs the risk in the context of a **novel influenza (H1N1) in a pandemic situation.**

3 OVERALL RECOMMENDATIONS

Due to the public health emergency linked to the current risk of pandemic influenza, and based on data made available regarding the stability of Tamiflu (Oseltamivir) 30mg, 45mg and 75mg capsules for an additional period of 2 years, the CHMP recommends that boxes of Tamiflu capsules should not be discarded where the expiry date has already passed. For these batches an updated expiry date should be determined by adding a further period of 2 years to the stated expiry date.
The conditions of storage play a role in the stability of medicinal products. It is of great importance that these boxes have always been kept and remains stored below 25°C.

It is acknowledged that limited data are available supporting the use of Tamiflu in children below 1 year of age. However considering the urgent need for recommendations to treat this population **in case of a pandemic influenza is declared by the WHO in the context of the Novel influenza A (H1N1) outbreak**, the CHMP recommends:
1. To treat children below 1 year of age with Tamiflu.
2. The appropriate dosage to treat children below 1 year of age is 2-3mg/kg twice daily during 5 days.
3. The post-exposure prophylaxis of children below 1 year of age should be very carefully considered by prescribers. If it is decided to prescribe Tamiflu to prevent influenza for children below 1 year of age who have been exposed to the virus, the appropriate dose should be 2-3mg/kg once a day during 10 days.
4. The paediatric suspension or dilution of the capsules of tamiflu can be used to prepare the dose in children below 1 year of age.
5. Children below 1 year of age should be treated under medical supervision. However in case of pandemic influenza, this recommendation could potentially place huge burden on hospital resources

and therefore, the CHMP strongly recommends that at least children below 3 months of age are treated under medical supervision in hospital.

This review seems to show that no new safety risks to foetus are connected to the use of Tamiflu in pregnant women. At the moment the statement in section 4.6. of the SPC "*Oseltamivir should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the foetus*." remains valid for **seasonal influenza** epidemics.

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Zanamivir has in animal studies been shown to cross the placenta and to be secreted in breast milk. The non-clinical data are not indicative of any relevant cause for concerns regarding the safe use of Relenza at recommended doses.

Taken together the overall data suggest that the benefit of using Relenza in pregnant or breastfeeding women outweighs the risk in the context of a **novel influenza (H1N1) in a pandemic situation.**