European Medicines Agency

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FOLLOW-UP RECOMMENDATIONS FROM CHMP

ON

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

EMEA/H/A-5.3/1172
Article 5(3) of Regulation (EC) No 726/2004

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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).

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.

The procedure started on 30 April 2009 and was finalised on 7 May 2009.

2 OVERALL RECOMMENDATIONS ADOPTED ON 7 MAY 2009

On 7 May 2009, the CHMP, having considered the matter, reviewed the available evidence and came to the conclusion that:

(1) 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.

(2) 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.

(3) 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 pandemic situation.**
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.

(4) 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 FOLLOW-UP RECOMMENDATIONS ADOPTED ON 29 MAY 2009

During its plenary meeting in May 2009, the CHMP discussed the following concerns as follow-up of the Article 5(3) of Regulation (EC) No 726/2004 adopted on 7 May 2009:

(1) Practical guidance to prepare the solution for children < 1 year of age from a capsule of Tamiflu should be defined and agreed.
(2) The long term prophylaxis for children < 1 year of age should be discussed.
(3) The hospitalization of children less than 1 year of age should be considered in the context of a pandemia.
(4) The apparent non severity of the current Influenza A (H1N1) should be considered in the view of revising or not the CHMP recommendations.

(1) Practical guidance to prepare the solution for children < 1 year of age from a capsule of Tamiflu should be defined and agreed.

In January 2009, the European Commission granted a Commission Decision to a type II variation (II/61) to update of section 4.2 of the SPC to provide instructions on the extemporaneous preparation of liquid formulations of Tamiflu using the contents of the 30mg, 45mg and 75mg capsules. The rational for this extemporaneous solution is that Tamiflu powder for oral suspension was developed and is approved and commercialised in the EU for children above 1 year of age and adults who cannot swallow capsules. This formulation has a shelf life of 24 months and it is anticipated that limited availability of this formulation may occur specifically in emergency situations such as an influenza pandemic or more simply when supplies of the oral suspension are not available. Development activities were undertaken to explore the feasibility of preparing extemporaneous formulations at home by the patient, parent or guardian using readily available sweetened food products to mask the bitter taste of the capsule content. This type II variation (II/61) was submitted to provide instructions in the SPC and the PL on how this liquid extemporaneous preparation should be made using the 30 mg, 45 mg and 75 mg capsules of Tamiflu.

The CHMP is now working in close collaboration with the MAH (Roche) to give practical guidance on how Tamiflu can be dosed from this extemporaneous solution to be given to children less than 1 year of age. **This practical guidance should soon be agreed and released**.

(2) The long term prophylaxis for children < 1 year of age should be discussed.

The data of use of Tamiflu in children under 1 year of age are very limited. At the moment the CHMP has given a recommendation to treat children below 1 year of age only during a possible pandemia and the use of prophylaxis is restricted to the pandemic era too. The limited information of prophylaxis are only for 10 days concerning the situations where a possible contamination has happened. No data concerning a long-term prophylaxis for children less than 1 year of age are available. **Therefore and for the time being, the CHMP is of the view that the prophylaxis for children less than 1 year of age should not exceed 10 days.**

(3) The hospitalization of children less than 1 year of age should be considered in the context of a pandemia.

During its plenary session in May 2009, the CHMP agreed that 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 recommends that at least children below 3 months of age are preferably treated under medical supervision in hospital.

However hospitalisation of children below 1 year of age, including the children below 3 months of age, should follow recommendations from Member States depending on the local situation.

(4)	The apparent non severity of the current Novel Influenza A (H1N1) should be considered in the view of revising or not the CHMP recommendations.

The recommendations adopted on 7 May 2009 by the CHMP were made in the context of a pandemic influenza, meaning a phase 6 declared by the WHO. Further to a discussion during its plenary, **the CHMP is of the view that the previously adopted recommendations remain valid in the context of a pandemia occurring with the current Novel Influenza A (H1N1) virus.** These recommendations can always be updated should a phase 6 be declared by WHO.