IRISH MEDICINES BOARD

Drug Safety NEWSLETTER

SPECIAL EDITION

IRISH MEDICINES BOARD UPDATE ON OSELTAMIVIR (TAMIFLU) AND ZANAMIVIR (RELENZA) FOR PANDEMIC H1N1 (2009)

Regulatory activities concerning antiviral medicines for the pandemic

- Antiviral medicines are available for clinical management of pandemic swine influenza. Among the antiviral medicines that are authorised in the EU for use in an influenza outbreak, the neuraminidase inhibitors Tamiflu (oseltamivir) and Relenza (zanamivir) are two to which the A/H1N1 virus has shown susceptibility.

- The European Medicines Agency (EMEA) has recently advised that **Tamiflu can be used in children under one year during the influenza pandemic.** The dose recommendation is 3mg/kg for treatment of children aged between 6 and 12 months during the influenza pandemic.

  As the available data for children aged between 0 to 6 months of age remain very limited, a precise dose could not be recommended for this age group and the EMEA recommendation is to use 2-3mg/kg for this population.

- The EMEA has also issued guidance on the use of Tamiflu and Relenza in pregnant and breastfeeding women. The recommendation is that, due to the potentially serious risks of H1N1 swine influenza in pregnancy, the benefits of using Relenza and Tamiflu in treating influenza in pregnant or breastfeeding women outweigh any known risks.

- In addition, the EMEA also recommended in May that the shelf life of Tamiflu be extended from 5 to 7 years. A similar extension was approved for Relenza at the end of May.

- Further information is available at **http://www.imb.ie/EN/Medicines/Pandemic H1N1-2009.aspx** and on the EMEA website **http://www.emea.europa.eu**.

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Tamiflu (Oseltamivir) 30mg/45mg/75mg Capsule

Formulation and posology: Tamiflu is given orally. The product information for the capsules includes guidance on how to administer the appropriate dose to children from the commercially manufactured Tamiflu® capsules. This advice and information on dose is included in the product information (SmPC and package leaflet) which is available at http://www.imb.ie/EN/Medicines/Swine-Flu-Medication.aspx.

Indication: Tamiflu is approved for the following indication:
'*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. Efficacy has been demonstrated when treatment is initiated within two days of first onset of symptoms. This indication is based on clinical studies of naturally occurring influenza in which the predominant infection was influenza A.

Tamiflu is indicated for the treatment of children 6 to 12 months of age during a pandemic influenza outbreak.
Prevention of influenza – Post-exposure prevention in individuals one year of age or older following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community. The appropriate use of Tamiflu for prevention of influenza should be determined on a case by case basis by the circumstances and the population requiring protection. In exceptional situations (e.g., in case of a mismatch between the circulating and vaccine virus strains, and a pandemic situation) seasonal prevention could be considered in individuals one year of age or older.

Tamiflu is not a substitute for influenza vaccination. The use of antivirals for the treatment and prevention of influenza should be determined on the basis of official recommendations. Decisions regarding the use of antivirals for treatment and prophylaxis should take into consideration what is known about the characteristics of the circulating influenza viruses and the impact of the disease in different geographical areas and patient populations.

Based on limited pharmacokinetic and safety data, Tamiflu can be used in children 6 to 12 months of age for treatment during a pandemic influenza outbreak. The treating physician should take into account the pathogenicity of the circulating strain and the underlying condition of the patient to ensure there is a potential benefit to the child.'

Safety Profile: A list of the known possible side effects can be found in the Summary of Product Characteristics **(SmPC) http://www.imb.ie/EN/Medicines/Swine-Flu-Medication.aspx**. Tamiflu is well tolerated by most individuals both in short and in long-term administration. As with all medicines, side-effects may occur and are listed in the product information, which is reviewed on a continuous basis as new safety data emerges:

Nausea and Vomiting: Nausea and vomiting are common but will rarely lead to the discontinuation of the treatment.

Neuropsychiatric adverse events: Neuropsychiatric adverse effects, including convulsions and delirium (with symptoms such as confusion, abnormal behaviour, hallucinations, agitation, anxiety and nightmares) are listed as possible side effects in the Tamiflu product information. However, influenza infection itself can be associated with a variety of neurological and behavioural symptoms including the above, sometimes without obvious signs of a severe infection. Some studies have found that these types of events are no more frequent in influenza patients who have taken Tamiflu when compared to those who have not taken the drug. It therefore remains unclear whether these neuropsychiatric events may be a true side effect of Tamiflu or whether they are due to underlying infection (or a combination of both). Reported cases will remain under close review by the IMB but those reported so far do not raise any new safety concerns. Nonetheless, patients should remain vigilant to the possibility of such events and discuss any serious concerns with their healthcare provider.

Serious skin reactions: Serious skin disorders such as Toxic Epidermal Necrolysis (TEN), Stevens-Johnson Syndrome (SJS) and erythema multiforme are listed as possible side effects in the Tamiflu product information on the basis that some cases have occurred in patients following Tamiflu therapy. Such conditions may also be caused by various infections including influenza. In patients being treated with Tamiflu for influenza, it therefore remains unclear whether reported cases of severe skin disorders are due to the drug or to the underlying infection and illness.

Hepato-biliary system disorders: There have been post-marketing reports of hepato-biliary system disorders in patients treated with Tamiflu. While these have included reports of hepatitis and elevated liver enzymes in patients with influenza-like illness, there have also been very rare reports of fatal fulminant hepatitis/hepatic failure in patients taking Tamiflu. As a causal relationship between Tamiflu and severe hepatic disorder including fatal fulminant hepatitis/hepatic failure could not be excluded, especially in patients with a pre-existing liver disease, the product information lists fulminant hepatitis/hepatic failure as a possible side-effect of Tamiflu.

Drug interactions: Clinically important drug interactions with Tamiflu are unlikely, including those involving competition for renal tubular secretion. However, care should be taken when prescribing Tamiflu for patients who are taking co-excreted medicines with a narrow therapeutic margin (eg, chlorpropamide or methotrexate). No dose adjustment is required when coadministering with probenecid in patients with normal renal function. Coadministration of probenecid, a potent inhibitor of the anionic pathway of renal tubular secretion, results in an approximate two-fold increase in exposure to the active metabolite of oseltamivir.

There have been reports in other countries suggestive of a possible drug interaction between Tamiflu and warfarin leading to prolonged blood clotting time. The available evidence is currently insufficient to establish whether such cases are a true drug interaction between Tamiflu and warfarin or whether blood clotting control in these patients may have been affected by underlying infection and associated illness. As with any drug prescribed to patients taking warfarin, more frequent monitoring of INRs (with appropriate warfarin dosage adjustment as necessary) may be prudent when oseltamivir is prescribed concurrently with warfarin.

Renal impairment: Dose adjustment is recommended for adults with severe renal insufficiency (i.e. ≤30 mL/min). Tamiflu is not recommended for patients with a creatinine clearance of ≤10 mL/min or in those undergoing dialysis. The IMB will continue to monitor experience of use in patients with renal impairment.

Postmarketing safety data: To date, the IMB has received five adverse reaction reports associated with the use of Tamiflu. The suspected adverse reactions reported to date in association with the use of Tamiflu during the current pandemic were abdominal pain and nausea, vomiting, agitation and insomnia, pruritus and rash. These suspected adverse reactions are consistent with the known safety profile of the active substance.

Relenza 5mg/dose, inhalation powder, pre-dispensed.

Formulation and posology: Relenza is delivered by inhalation. The recommended doses are provided in the product information **http://www.imb.ie/EN/Medicines/Swine-Flu-Medication.aspx.**

Indication: Relenza is approved for the following indication:
'*Treatment of influenza*
Relenza is indicated for treatment of both influenza A and B in adults and children (>5 years) who present with symptoms typical of influenza when influenza is circulating in the community.
Prevention of influenza
Relenza is indicated for post-exposure prophylaxis

of influenza A and B in adults and children (≥ 5 years) following contact with a clinically diagnosed case in a household (see section 5.1 for children aged 5-11 years). In exceptional circumstances, Relenza may be considered for seasonal prophylaxis of influenza A and B during a community outbreak (e.g. in case of a mismatch between circulating and vaccine strains and a pandemic situation).

Relenza is not a substitute for influenza vaccination. The appropriate use of Relenza for prevention of influenza should be determined on a case-by-case basis depending on the circumstances and the population requiring protection.

The use of antivirals for the treatment and prevention of influenza should take into consideration official recommendations, the variability of epidemiology, and the impact of the disease in different geographical areas and patient populations.'

Safety Profile: Recognised side effects to Relenza are very rare and include:

Hypersensitivity reactions: Allergic-type reactions such as swelling of the face, mouth, or throat; skin rash; or hives.

Respiratory events: Acute bronchospasm or serious decline in respiratory function (or both) have been seen in patients with a history of asthma or chronic obstructive pulmonary disease (COPD), and in those without a history of respiratory disease (see below).

Neuropsychiatric events: The product information for Relenza also lists neuropsychiatric disorders as a possible side effect of the medicine. As with Tamiflu, a causal association with Relenza is uncertain.

Drug interactions: Clinically significant drug interactions with Relenza are unlikely. Relenza is not protein bound and not hepatically metabolised or modified. Relenza, when given for 28 days, did not impair the immune response to influenza vaccine.

Patients with asthma or COPD: Patients with severe asthma should not receive Relenza unless close medical monitoring and appropriate clinical facilities are available, in case of bronchoconstriction. In patients with persistent asthma or severe COPD, management of the underlying disease should be optimised during Relenza treatment. If Relenza is considered appropriate for any patient with asthma or COPD, the patient should be informed of the potential risk of bronchospasm and should have a fast-acting bronchodilator available. Patients on maintenance inhaled bronchodilating therapy should be advised to use their bronchodilators before taking Relenza.

Postmarketing safety data

To date, the IMB has received six reports of suspected adverse reactions associated with Relenza. The reports pre-date the current pandemic. The reported adverse reactions were nausea and vomiting, headache, convulsion, anaphylactic reaction, bronchospasm, erythema multiforme and urticaria.

Use of Antivirals in Pregnancy and Lactation

Tamiflu (oseltamivir)

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has adopted recommendations to update the product information for Tamiflu with more information on the medicine's use in pregnant and breast-feeding women.

The product information for Tamiflu is being updated to include the following text in Section 4.6:

> '***Pregnancy and Lactation***
> While no controlled clinical trials have been conducted on the use of oseltamivir in pregnant women, there is limited data available from post-marketing and retrospective observational surveillance reports. These data in conjunction

with animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal or postnatal development (see section 5.3). Pregnant women may receive Tamiflu, after considering the available safety information, the pathogenicity of the circulating influenza virus strain and the underlying condition of the pregnant woman.

In lactating rats, oseltamivir and the active metabolite are excreted in milk. Very limited information is available on children breast-fed by mothers taking oseltamivir and on excretion of oseltamivir in breast milk. Limited data demonstrated that oseltamivir and the active metabolite were detected in breast milk, however the levels were low, which would result in a subtherapeutic dose to the infant. Considering this information, the pathogenicity of the circulating influenza virus strain and the underlying condition of the lactating woman, administration of oseltamivir may be considered, where there are clear potential benefits to lactating mothers.'

A recent European review evaluated use of Tamiflu in pregnancy by assessing the company's oseltamivir safety database. The available data was considered in the context of the available information on the effect of influenza on pregnancy, impact of high fever on pregnancy, relevant background rates and available pre-clinical data. 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.

The review of the safety database revealed a total of 232 cases with maternal exposure to oseltamivir. This included all cases reported in the literature as well as study cases. The most common indication for oseltamivir was treatment of influenza (rather than prophylaxis). 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 suggests that no new safety risks to the foetus are connected to the use of Tamiflu in pregnant women. The overall data suggest that the benefit of using Tamiflu in pregnant or breastfeeding women outweighs the risk in the context of the pandemic situation as reflected in the updated product information.

More information about Tamiflu is available in the European Public Assessment Report for Tamiflu: **http://www.emea.europa.eu/humandocs/Humans/EPAR/tamiflu/tamiflu.htm**.

Relenza (zanamivir)

The current product information for Relenza includes the following text in Section 4.6

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.*

Relenza is delivered by inhalation. Clinical experience with the use of Relenza during pregnancy and lactation is very limited. However, the systemic exposure to zanamivir is reduced because of the route of administration. 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 gas-

tro intestinal tract and is excreted in faeces.

No new safety risks to foetuses were identified in the recent European review of Relenza use during pregnancy. Overall, non-clinical data do not raise any relevant concerns for the safe use of zanamivir inhalation powder during pregnancy and lactation. 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.

Overall conclusion on use of antiviral medicines during pregnancy

The review of available evidence by European regulatory authorities led to a recommendation that, due to the potentially serious risks of H1N1 swine influenza in pregnancy, the benefits of using Relenza and Tamiflu in treating influenza in pregnant or breastfeeding women outweigh any known risks.

Further information is available on the EMEA website **http://www.emea.europa.eu/htms/human/pandemicinfluenza/novelflu.htm**

Reporting of suspected adverse reactions to antiviral medicines

Increased exposure during the pandemic may reveal rare adverse reactions that have not been previously observed and as such, the IMB is requesting that all suspected adverse reactions are promptly reported. We have a special web-based system for reporting suspected adverse reactions (ARs) to Tamiflu and Relenza. This on-line reporting system is accessible via the Pandemic webpage on the IMB homepage (**http://www.imb.ie**).

- Please report all suspected ARs to Tamiflu and Relenza via the Pandemic AR On-line reporting system at **http://www.imb.ie/EN/ Medicines/Pandemic-H1N1-2009.aspx**.

- It is of particular importance that serious adverse reactions should be notified promptly including cases where an antiviral medicine is thought to have been ineffective.

- Please remember to include the following important information in your report:
  - Patient age
  - Indication (prophylaxis or treatment)
  - Outcome of the Adverse Reaction
  - Information on any underlying risk factors for the Adverse Reaction or for influenza complications; or state if there are no known risk factors
  - Any other information about the patient or additional clinical details that will help us in our assessment of the case

- During the pandemic, the IMB recommends that healthcare professionals should, where feasible report using the on-line reporting system. However, the Yellow Card system will remain in use and a downloadable report form can also be printed from the IMB website.

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