Understanding Antiviral Drugs

Like all other medicinal products, antivirals bring beneficial effects in the management of the disease condition, however, they may also cause side effects in certain patients.

Given the current H1N1 pandemic with its associated increase in the use of antivirals, including oseltamivir (Tamiflu®) and zanamivir (Relenza®) to treat patients at risk of developing serious complications of influenza, the Health Sciences Authority (HSA) is providing a list of Frequently Asked Questions to address some common concerns associated with the use and effectiveness of these medicines.

Antiviral Drugs – What are They?

Q1. What are the antiviral drugs used for the treatment of the flu?

Locally, there are three antiviral medicines licensed by HSA for the treatment or the prevention of infections caused by influenza viruses, including the current Influenza A (H1N1–2009) virus. These medicines are oseltamivir (Tamiflu®), zanamivir (Relenza®) and amantadine (Symmetrel®, PMS-Amantadine®).

Q2. Are these antiviral drugs effective against the recent worrying H1N1 virus?

While these antiviral medicines have been previously shown to be effective in treating the flu that is caused by most influenza viruses, the recent H1N1 flu, which is caused by the Influenza A (H1N1–2009) virus, was found to be resistant to older antiviral medicines such as amantadine. From data available to date, newer antivirals such as oseltamivir (Tamiflu®) and zanamivir (Relenza®) are effective in treating infections caused by the H1N1 influenza virus.

The Ministry of Health (MOH), Singapore currently recommends the use of oseltamivir or zanamivir for the treatment and/or prevention of infections caused by the H1N1 virus. Doctors are advised to exercise clinical judgement when prescribing these antivirals for their patients, taking into account the risks versus the benefits of these drugs for the individual patient.

Q3. What are Tamiflu® and Relenza® approved for and available as?

Tamiflu® contains the antiviral drug, oseltamivir, supplied as an oral capsule or oral solution. It
is approved for use in adults and children aged one year and above for the treatment and prevention of influenza. For children under one year of age, MOH has developed guidelines for doctors on the appropriate dosing for these patients.

Relenza® contains the antiviral drug, zanamivir, supplied as an oral inhalation powder. It is approved for use in adults and children aged five years and above for the treatment of influenza. Relenza® is also approved for the prevention of influenza in adults and adolescents aged over 12 years.

Both Tamiflu® and Relenza® are regulated as Prescription-Only-Medicines (POM) in Singapore and are only available with a doctor's prescription, which will be issued when the doctor has assessed that the antiviral medicine is suitable for the patient. Both antiviral medicines should be used under a doctor's supervision.

Q4. How do Tamiflu® and Relenza® work?

Tamiflu® and Relenza® contain antiviral medicines that will interfere with the influenza virus’s entry into uninfected cells. In addition, both Tamiflu® and Relenza® disrupt the release of newly formed influenza virus from infected cells. Both these actions prevent the H1N1 virus from spreading to uninfected cells.

When taken within 2 days of the initial flu symptoms, both Tamiflu® and Ralenza® may ease and shorten the duration of flu symptoms and may help prevent serious influenza complications.

Antiviral Drugs – How to Use Them?

Q5. Will taking antiviral medicine such as Tamiflu® early (e.g. before going overseas) protect me from the H1N1 flu even though I do not have flu symptoms?

Antivirals such as Tamiflu® and Relenza® are not vaccines and are NOT advised to be given for pre-exposure prophylaxis. Post-exposure prophylaxis could however be considered for contacts of confirmed cases who are at higher risk for influenza-related complications or other circumstances where the doctor feels that it is clinically appropriate.

Antiviral medicines are intended as a treatment for those showing early flu-like symptoms, especially within 48 hours upon contracting the virus. Antiviral medicines help our body to fight a viral infection but do not train our body's immune system to fight viruses.
HSA would like to highlight and emphasize that taking antivirals indiscriminately or inappropriately may end up limiting their effectiveness in the future, as this may increase the risk of the influenza virus developing resistance to the antiviral medicines.

Q6. What should I do if I miss a dose?

If a dose of the antiviral medicine has been missed, you should not double the next dose. Instead, you should take the missed dose as usual as soon as you remember to do so.

However, if it is near the time for the next dose of antiviral medicine, skip the missed dose altogether. A double dose of antiviral medicine should not be taken because this may increase the risk of adverse or unwanted effects.

Q7. What is the advice for pregnant women and/or mothers who are breast-feeding?

The decision to treat pregnant and/or breast-feeding mothers with Tamiflu® or Relenza® will be determined by their doctors. Antiviral medicines are used only when the potential benefits to the mother justifies the potential risk to the foetus or child.

Q8. How should Tamiflu® and Relenza® be stored?

Tamiflu® capsules should be stored in a cool, dry place, preferably at temperatures below 25°C.

Tamiflu® oral suspension 12mg/ml which has been reconstituted into a solution should be stored in a refrigerator at temperatures from 2°C to 8°C. Do NOT freeze the oral Tamiflu® solution.

Relenza® rotadisks should be stored at temperatures below 30°C.

As with all medicines, Tamiflu® and Relenza® should be kept out of the reach of children.

Q9. The Tamiflu® capsules that my doctor prescribed to me have expired, however, there is a MOH sticker on the box that says the shelf life of the capsules has been extended. Should I still take it?

Antiviral Drugs: Concerns about Expiry Dates
In June 2009, HSA approved the extension of Tamiflu®’s shelf life for another two years from the date of expiry. For instance, if the label on the Tamiflu® box indicates that the expiry date is January 2008, then the extended shelf life is January 2010.

The approval by HSA for shelf life extension of Tamiflu® was based on scientific data such as stability studies provided by the manufacturer of Tamiflu® to support that the potency of the medicine continues to be within the international standards of quality as stipulated by international regulatory agencies.

The extension of the shelf life of a medicine is not unique to Tamiflu® and has been done for other medicines. Pharmaceutical companies may apply for product shelf life extensions to HSA with supporting scientific evidence. The extension of the shelf life of Tamiflu® has also been approved in other countries such as the US, Australia and Canada.

Q10. The Relenza® rotadisk which my doctor prescribed to me has expired. Should I still use it?

In May 2009, HSA approved the extension of Relenza®’s shelf life for another two years from the date of expiry. For instance, if the label on the Relenza® box indicates that the expiry date is January 2008, then the extended shelf life is January 2010.

The approval by HSA for shelf life extension of Relenza® was based on scientific data such as stability studies provided by the manufacturer of Relenza® to support that the potency of the medicine continues to be within the international standards of quality as stipulated by international regulatory agencies.

The extension of the shelf life of a medicine is not unique to Relenza® and has been done for other medicines. Pharmaceutical companies may apply for product shelf life extensions to HSA with supporting scientific evidence. The extension of the shelf life of Relenza® has also been approved in other countries such as the US, Australia and the European countries.

Antiviral Drugs: Concerns about Adverse Effects

Q11. What are the common adverse or unwanted effects of Tamiflu® and Relenza® and what should I do to avoid these adverse effects?
The most common unwanted or adverse effects of these antiviral medicines are nausea, vomiting, dizziness, stomachache, diarrhoea and headache.

You are advised to consume Tamiflu® with food to reduce the occurrence of these adverse effects. You should consult your doctors if you experience these adverse effects persistently or any other bothersome adverse effects.

Q12. a) What are the neuropsychiatric events suspected to be associated with Tamiflu® as reported in the news media?
b) Are these also suspected to be associated with Relenza®?

Neuropsychiatric events have been reported rarely with both Tamiflu® and Relenza®. It is important to note that the neuropsychiatric events are very rare, given the large number of patients who have taken the medicines without experiencing similar problems.

a) On Tamiflu®:
There have been reports of neuropsychiatric adverse events including delirium with abnormal behaviour, thoughts of suicide, panic attacks, hallucination, convulsions, lower levels of consciousness and loss of consciousness suspected to be associated with the use of Tamiflu®.

[Delirium is a reversible mental disorder whereby the patient may not respond to another person and is disorganised in thinking. He or she may be rambling and not making sense in what he says. Some delirious patients also have a lower level of consciousness, are disorientated, suffer from sleep disturbances and memory impairment.]

These neuropsychiatric adverse events were reported to occur primarily in children and adolescent patients. The events were also reported to occur very shortly after taking the first dose or first few doses of Tamiflu®.

It cannot be confirmed if these events are directly due to Tamiflu® as the reports had incomplete information and the patients were also taking other medications which might have possibly contributed to the observed neuropsychiatric events.

It is known that the flu can in itself cause such neuropsychiatric events especially in but not confined to those with more severe forms of the illness. As patients are taking Tamiflu® for the flu, it is difficult to differentiate if the observed neuropsychiatric events were the result of the flu, the medication or the effect of the medication and illness.

b) On Relenza®:
Similar neuropsychiatric events were also reported with zanamivir (Relenza®). As in the case of oseltamivir (Tamiflu®), it cannot be confirmed if these events are directly due to Relenza® as the reports had incomplete information and the patients were also taking other medications which might have possibly contributed to the observed neuropsychiatric events. Additionally,
it is known that the flu can in itself cause such neuropsychiatric events.

Caregivers of adolescents and young children are advised to monitor closely these patients or family members who are prescribed antivirals for signs of abnormal behaviour. They are also advised to contact their doctor immediately should such abnormal behaviour occur.

It is also important to note that patients with influenza, particularly children and adolescents, may be at an increased risk of seizures, confusion or abnormal behaviour early during their illness.

If such events occur after regular clinic opening hours, the public are advised to also visit the nearest emergency department or a 24-hour clinic for medical assessment.

In 2006, HSA communicated this safety concern to healthcare professionals through our regular drug safety newsletter, HSA Adverse Drug Reaction Bulletin. HSA had also worked with Roche, the manufacturer of Tamiflu, to issue a letter to healthcare professionals, alerting them of this safety concern.

Recently, HSA issued another advisory on 31 July 2009 to all healthcare professionals, updating and advising them of the recent reports of rare and unusual neuropsychiatric events.

HSA has also advised the drug companies selling Tamiflu® and Relenza®, Roche and GlaxoSmithKline respectively, to update the package inserts of these medicines with information to reflect the data on the neuropsychiatric events.

HSA will also continue to monitor closely the safety profile of antiviral medicines and the development associated with their use, both locally and internationally and will take necessary actions to ensure the safeguarding of public health, if warranted.
Antiviral Drugs - Concerns about Online Purchases

Q15. Antiviral drugs such as Tamiflu® are available for sale over the Internet. Should I order through the Internet and get the stock imported into Singapore?

HSA strongly discourages you from purchasing medicines, in particular Prescription-only-medicines (POM), from online pharmacies or other online sources (such as auction sites, blogshops, forum postings and spam emails), as it is usually not possible to verify the quality, safety and integrity of these products. Some of the risks associated with the purchase of medicines from the Internet are as follows:

i. Risk of Counterfeits
Websites may claim that their medications are approved by the authorities, local or overseas, but, without verification, there is a real risk that medicinal products supplied may be substandard or counterfeit versions. Counterfeit medicines may contain too much or too little of the active ingredients, and can contain adulterants and other unknown harmful substances. These make the medicines unsafe or ineffective or even more dangerous.

ii. Risk of Contamination with Unknown Substances
There is no assurance on the safety, quality and effectiveness of medicines ordered, as they are not evaluated by the authorities. Harmful chemicals or ingredients may be added and such medications can be addictive or harmful to your health.

iii. Risk of Poor Quality Products
Unapproved medicines may not have been manufactured under quality assurance procedures and programmes that regulatory systems require to protect the integrity (safety, quality and efficacy) of the product.

iv. Risk of Unsupervised Use
Some medicines, especially POM, are unsafe when taken without adequate medical supervision. You should not self-medicate with prescription-only medicines. A medical consultation ensures that the medication is appropriate for you and your condition; consultations help ensure that you are taking the drug properly, that it is working for you and that you are not having unexpected or life-threatening side effects.

v. Risk of Unsubstantiated/Exaggerated Claims
All details in approved medicines’ product labels and inserts are evaluated and cleared by regulatory authorities. Product labels and inserts of medicines ordered from overseas sites may carry wrong indications, and include instructions for use and information on possible side effects in a language which you do not understand.