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HSA UPDATES

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HSA UPDATES ON NEUROPSYCHIATRIC ADVERSE EVENTS SUSPECTED TO BE ASSOCIATED WITH OSELTAMIVIR (TAMIFLU®)

The Health Sciences Authority (HSA) is issuing this public document to share the background and local situation leading to its recent action to issue a Dear Healthcare Professional Letter (DHCPL)* on 31 Jul 2009, where the latter reminds healthcare professionals to be aware of possible neuropsychiatric adverse reactions arising from the use of Tamiflu in patients with influenza.

*[Note: * Dear Healthcare Professional letter (DHCPL) is one of HSA’s important communication tools to healthcare professionals (doctors, dentists, pharmacists) to advise and keep them updated on important safety issues relating to health products in a timely manner.]*

2 As a precautionary measure, healthcare professionals were advised in the DHCPL to inform their patients and caregivers of young patients, who are prescribed Tamiflu, of the remote possibility of the development of neuropsychiatric adverse events such as hallucinations and delirium, and that these patients be monitored closely.

3 The public is advised not to be unduly alarmed as these reports are rare and to consult their doctor should they experience any adverse reaction during treatment with Tamiflu.

Background

4 HSA has been closely monitoring the international developments of neuropsychiatric events suspected to be associated with Tamiflu since the alert was first raised in November 2005 by Japan's Ministry of Health and Labour Welfare. Events such as delirium with abnormal behaviour, suicidal ideation, panic attacks, hallucinations, convulsions, lowered level of consciousness and loss of consciousness with isolated cases resulting in fatal outcomes have also been

reported globally. These events were reported to occur primarily in children and adolescent patients.

5 Many of these serious neuropsychiatric cases were reported in Japan. Presently, establishing a direct cause-effect relationship between Tamiflu and such events is difficult due to incompleteness of the reports and the presence of confounding factors such as concomitant drugs and the presence of influenza illness. Also, such neuropsychiatric events were reported in patients with influenza who were not taking Tamiflu. Neuropsychiatric adverse events are known to occur during influenza, especially in but not confined to those with more severe forms of the illness

6 HSA's assessment of the global reports to-date is that the association between the neuropsychiatric events and Tamiflu remains unclear. Given the worldwide number of patients who have taken Tamiflu (estimated at about 58 million) since it was first marketed, it has also been assessed that the incidence of reports of serious neuropsychiatric disturbances with Tamiflu is very rare.

7 In 2006, HSA communicated the above safety issue via the HSA Adverse Drug Reaction Bulletin** (Dec 2006 issue) and worked with Roche, the drug company selling Tamiflu to send a DHCPL reflecting the above safety concern to all healthcare professionals.

*[Note: ** HSA Adverse Drug Reaction Bulletin is a newsletter sent to all healthcare professionals every four monthly to update them on new and emerging or major drug safety concerns and to promote the reporting of adverse drug reactions to HSA.]*

Local Situation To-date

8 HSA has received 6 reports of neuropsychiatric events including reports of disorientation, incoherent speech, hallucination and suicidal ideation suspected to be associated with Tamiflu from 2005 to 2009, 4 of which were reported recently. After our investigations into these reports, the causality of these adverse events with Tamiflu usage still remains unclear due to the presence of confounding factors such as the presence of influenza illness and concomitant medicines. It is to be noted that in 5 out of the 6 cases, the neuropsychiatric symptoms resolved after its first manifestation and in 3 of them, the patients continued to take Tamiflu without recurrence of the symptoms.

9 As a continuing follow-up on the situation, HSA has issued another DHCPL on 31 Jul 2009 to remind healthcare professionals to be aware of possible neuropsychiatric adverse reactions arising from the use of Tamiflu in patients with influenza. As a precautionary measure, healthcare professionals were advised to inform their patients and caregivers of young patients of the remote possibility of the development of neuropsychiatric adverse events and that these patients be monitored closely.

Public Advisory

10 *"As pharmacological agents, medicines bring with them beneficial effects and may cause side effects in certain patients. HSA has assessed that the benefits of using Tamiflu to treat early symptoms for patients at risk of serious influenza complications outweigh the potential risks that the medicine may cause. The wider prescribing of these medicines in a pandemic situation may reveal rare effects that have not previously been detected. HSA will continue to closely monitor the safety profile of Tamiflu and take the necessary actions to safeguard public health should the situation warrant."*, says Ms Chan Cheng Leng, Division Director of HSA's Pharmacovigilance and Compliance Division.

11 The public is advised not to be unduly alarmed and to consult their doctor should they experience any adverse reaction during treatment with Tamiflu. The common side effects of Tamiflu which may occur in patients taking the drug include headache, nausea, vomiting, stomachache and diarrhoea. The frequency of these side effects is reduced if Tamiflu is taken with food.

12 As patients with influenza, particularly children and adolescents, may be at an increased risk of seizures, confusion or abnormal behaviour early during their illness, the caregivers of adolescent and young children are advised to monitor closely these patients or family members who are prescribed Tamiflu for signs of abnormal behaviour, and to contact their doctor immediately should such abnormal behaviour arise.

13 A list of Frequently Asked Questions is attached in **Annex A** to address some common concerns.

HEALTH SCIENCES AUTHORITY 6 AUGUST 2009

- **About the Health Sciences Authority (HSA)**

The Health Sciences Authority (HSA) applies medical, pharmaceutical and scientific expertise through its three professional groups, Health Products Regulation, Blood Services, Applied Sciences, to protect and advance national health and safety. HSA is a multidisciplinary authority. It serves as the national regulator for health products, ensuring they are wisely regulated to meet standards of safety, quality and efficacy. It operates the national blood bank, Bloodbank@HSA, securing the nation's blood supply. It also applies specialised scientific, forensic, investigative and analytical capabilities in serving the administration of justice. For more details, visit <http://www.hsa.gov.sg/>.

- **About HSA's Health Products Regulation Group**

The Health Products Regulation Group (HPRG) of HSA ensures that drugs, innovative therapeutics, medical devices and health-related products are wisely regulated and meet appropriate safety, quality and efficacy standards.

- **About HSA Updates**

The “HSA Updates” seeks to provide current information, in a consistent and accurate manner, on topics of public interest. For all issues of HSA Updates, please visit www.hsa.gov.sg, click “News & Events”, and select “HSAUpdates”.

Media representatives are welcome to send any queries to the Corporate Communications Department @ HSA.

HSA UPDATES ON NEUROPSYCHIATRIC ADVERSE EVENTS SUSPECTED TO BE ASSOCIATED WITH OSELTAMIVIR (TAMIFLU®)

UNDERSTANDING OSELTAMIVIR (TAMIFLU®)

Like all other medicines, antiviral drugs 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®), to treat patients at risk of developing serious complications of influenza, the Health Sciences Authority (HSA) is providing a list of Frequently Asked Questions (FAQ) to address some common concerns associated with the use and effectiveness of oseltamivir (Tamiflu®).

FREQUENTLY ASKED QUESTIONS

Adverse Effects Of Oseltamivir (Tamiflu®)

Q1. What are the common adverse or unwanted effects of Tamiflu® and what should patients do to avoid these adverse effects?

The most common unwanted or adverse effects of Tamiflu® are nausea, vomiting, dizziness, stomachache, diarrhoea and headache.

Patients are advised to consume Tamiflu® with food to reduce the occurrence of these adverse effects. They should consult their doctors if they experience these adverse effects persistently or any other bothersome adverse effects.

Q2. What are the neuropsychiatric events suspected to be associated with Tamiflu® as reported in the news media?

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

[Delirium is a reversible mental condition 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.

It is important to note that these serious neuropsychiatric events are very rare, given the large number of patients who have taken the medicine without experiencing similar problems.

Q3. What is the advisory from HSA relating to these neuropsychiatric adverse events?

Caregivers of adolescents and young children are advised to monitor closely these patients or family members who are prescribed Tamiflu® 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.

Q4. What is HSA doing to address this safety concern?

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 professional, 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 will also continue to monitor closely the safety profile of antiviral medicines and the developments associated with their use, both locally and internationally and will take necessary actions to ensure the safeguarding of public health, if warranted.

Background Information on the Use of Oseltamivir (Tamiflu®)

Q5. How does Tamiflu® work?

The active ingredient of Tamiflu® is oseltamivir. It is an antiviral medicine that will interfere with the influenza virus' entry into uninfected cells. Tamiflu® disrupts the release of newly formed influenza virus from infected cells. Both actions prevent the H1N1 virus from spreading to uninfected cells.

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

Q6. Is Tamiflu® effective against the recent worrying H1N1 virus?

From data available to-date, oseltamivir (Tamiflu®) remains effective in treating infections caused by the H1N1 virus.

Oseltamivir (Tamiflu®) is one of the antivirals recommended by the Ministry of Health (MOH), Singapore for the treatment and/or prevention of infections caused by the H1N1 viruses. Doctors are advised to exercise clinical judgement when prescribing the antivirals for their patients, taking into account the risks versus the benefits of these drugs for the individual patient.

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® 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. The Tamiflu® capsules that my doctor prescribed to me has 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?

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.

Q9. 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.

Q10. How should Tamiflu® be stored?

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

Reconstituted Tamiflu® solutions should be stored in a refrigerator at temperatures from 2°C to 8°C. Do NOT freeze the oral Tamiflu® solution.

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