Oseltamivir (Tamiflu®, Roche) is an antiviral agent licensed by HSA in October 2000 for the treatment of uncomplicated acute illness due to influenza infection [Influenza A & B] in adults and children ≥ 1 year old who have been symptomatic for no more than two days and for the prophylaxis of influenza in adults and children ≥ 12 years old.

Recent post-marketing reports of CNS disorders

The Health Sciences Authority (HSA) has reviewed the data from the 103 post-marketing reports of neuropsychiatric adverse events suspected to be associated with oseltamivir received between August 2005 to July 2006. These include events such as delirium with prominent behavioral disturbances (n=14) and suicide attempts (n=1) including self-harm and suicidal ideation. The majority of the cases were reported from Japan (92%) and were predominantly for the treatment of influenza (97%). These were primarily among pediatric patients (67%) with an age range of 1.5 to 17 years old. There were three deaths; a 16 year-old boy and two adults who fell to their deaths. The patients who died were healthy before contracting influenza and receiving oseltamivir. Most of the adverse events occurred during the first day of oseltamivir use (1 to 2 doses).

Our assessment of the reports was that many of the cases lacked sufficient detail for causality assessment and largely originated from one country. Therefore, it is unclear at the present time whether these events were the outcomes of the direct adverse effect of the drug, genetic differences in metabolite handling of the drug in the Japanese patients, higher usage of oseltamivir in Japan or a coincident period of intensive monitoring of adverse events in Japan or a combination of any of these possible factors. Additionally, many events such as convulsions, delirium and depressed levels of consciousness are complications of viral encephalitis secondary to influenza making a direct causal link to Tamiflu® administration very difficult.

Nonetheless, considering the rapid temporal relationship of adverse event to the use of oseltamivir, and cases which reported positive de-challenge (n=65) where there was rapid and full recovery from neuropsychiatric adverse effects once oseltamivir was discontinued and/or lack of positive neuro-imaging findings in the reviewed reports (n=25), the local prescribing information of Tamiflu® will be updated to warn of the potential for the occurrence of neuropsychiatric adverse events. In addition, it also advised that patients with flu, particularly children may be at an increased risk of self-injury and confusion shortly after taking Tamiflu® and should be closely monitored for signs of unusual behavior.

Local situation

HSA has received three adverse drug reactions suspected with use of oseltamivir. They are one report of hepatitis, and two reports of suicide. The patient who committed suicide by falling to his death was prescribed oseltamivir at 75mg twice a day for flu and the adverse event was reported to have occurred on the 7th day. The causality however could not be established as it was reported that the patient was also taking other medications.
Eptifibatide and increased risk of bleeding in impaired renal function

Consider a lower infusion dose of 1mcg/kg/min for patients with CrCl between 30 – 50ml/min

The incidence of blood transfusions was also significantly increased in patients with CrCl ≤ 50ml/min on standard doses of eptifibatide similar to those in patients with normal renal function.

Background

Eptifibatide (Integrilin®, Schering-Plough) reversibly inhibits platelet aggregation by preventing the binding of fibrinogen, von Willebrand factor and other adhesive ligands to the glycoprotein IIb/IIIa receptors and is currently licensed by HSA for use in unstable angina or non-Q-wave myocardial infarction (UA/NQMI) and unstable angina in the UK.

Dosing recommendations in other countries

Eptifibatide (Integrilin®, Schering-Plough) reversibly inhibits platelet aggregation by preventing the binding of fibrinogen, von Willebrand factor and other adhesive ligands to the glycoprotein IIb/IIIa receptors and is currently licensed by HSA for use in unstable angina or non-Q-wave myocardial infarction (UA/NQMI) and unstable angina in the UK.

The local recommended dosing regimen for UA/NQMI is an intravenous bolus of 180mcg/kg followed by a continuous infusion of 2mcg/kg/min for up to 72 hours. For PCI, an intravenous bolus of 180mcg/kg is administered together with a continuous infusion of 2mcg/kg/min for a maximum of 18 – 24 hours. In all cases, a second bolus of 180mcg/kg is given 10 minutes after the first bolus. Eptifibatide has been approved for the prevention of abrupt closure of the treated coronary vessel and related acute ischaemic cardiac complications.

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The incidence of blood transfusions was also significantly increased in patients with CrCl ≤ 50ml/min on standard doses of eptifibatide similar to those in patients with normal renal function.

Eptifibatide is also indicated as an adjunctive percutaneous transluminal coronary angioplasty for the prevention of abrupt closure of the treated coronary vessel and related acute ischaemic cardiac complications.

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Safety updates

An eptifibatide published in 2004 demonstrated that an infusion rate of 2mcg/kg/min is effective in patients with moderate (30 – 50ml/min) or severe renal impairment (CrCl < 30ml/min), the clearance rate of eptifibatide was about 50% lower and steady-state plasma levels was about 2 fold higher compared to those with normal renal function. The authors recommended a dose reduction from 2mcg/kg/min to 1mcg/kg/min in patients with CrCl ≤ 50ml/min.

Another recently published study evaluated the correlation of bleeding events among eptifibatide-treated patients undergoing PCI. The bleeding rates were 3% (27/977) in patients with CrCl ≤ 50ml/min and 9% (42/464) in patients with CrCl ≤ 50ml/min who received the standard eptifibatide infusion dose of 2mcg/kg/min, and 4% (23/593) in patients who received a reduced dose of 1mcg/kg/min (p=0.017).

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HSA would like to remind healthcare professionals of the potential risk of developing serotonin syndrome in patients taking 5-hydroxytryptamine receptor agonists (triptans) and Selective Serotonin Re-uptake Inhibitors (SSRIs) or Selective Norepinephrine Re-uptake Inhibitors (SNRIs). SSRIs are known to increase serotonin levels and possibly cause serotonin syndrome when used concurrently with serotonergic agents such as triptans.

In July 2006, the US Food and Drug Administration alerted healthcare professionals and the public of this potentially life-threatening interaction. The FDA reviewed 27 reports of serotonin syndrome reported from 1998 to 2002 in association with concomitant SSRIs or SNRIs and triptan use. Two cases were life-threatening and 13 required hospitalisation. It was found that some of the cases occurred in patients who had previously used both drugs concomitantly without experiencing serotonin syndrome.

The reported signs and symptoms of serotonin syndrome were highly variable and included respiratory failure, coma, myclonic-kinetic dyskinesia, diarrhea, nausea, vomiting, diarrhoea, sweating, tachycardia, hypertension, tachycardia, hyperreflexia, incoordinated movements, tremor, incoordinated movements, and/or gastrointestinal symptoms. In 15 cases, recent dose increases or addition of another serotonergic drug to an SSRI/triptan or SNRI/triptan combination were temporally related to symptom onset. The median time to onset of symptoms was one day, with a range of five minutes to six days.

HSA has not received any local ADR reports associated with this interaction and serotonin syndrome. However, healthcare professionals are reminded to consider the following when prescribing SSRIs/SNRIs or triptans:

1. To weigh potential risk versus benefit of prescribing concomitant SSRI/SNRI and triptan therapy and discuss the possibility of serotonin syndrome with the patient when prescribing both concomitantly.
2. To keep in mind that triptans are often used intermittently and that SSRIs, SNRIs or triptans may be prescribed by a different healthcare professional.
3. To be alert to the highly variable signs and symptoms of serotonin syndrome. Serotonin syndrome symptoms may include mental status changes (e.g. agitation, hallucination, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperhidrosis, incoordinated movements (e.g. hyperreflexia, incoordinated movements), and gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea).
4. To observe patients on concomitant therapy carefully, particularly during treatment initiation and dose increase.

Healthcare professionals are also encouraged to report suspected adverse reactions of this nature to the Pharmacovigilance Unit of HSA.

Examples of locally available products

**Triptans**
- Eletriptan (Relpax®), naratriptan (Naramig®), rizatriptan (Maxalt®), sumatriptan (Imigran®), zolmitriptan (Zomig®)

**SSRIs**
- Citalopram (Cipram®, Lexapro®), escitalopram (Lexapro®),氟西汀 (Fluoxetine, Fluoxene, Fluxetin, Fluoi, Fluxil, Magrilan, Proctin, Prodep, Zactil, Zetaflox, Zoloft®), fluvoxamine (Faverin®), paroxetine (Seroxat®, Prozac®), sertraline (Zoloft®)

**SNRIs**
- Duloxetine (Cymbalta®), venlafaxine (Effexor®)

Life-threatening cases of serotonin syndrome with SSR/SNRI-triptan combination

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References
Please note that there might be changes due to safety updates from previous issues.

Updates are listed at [Adverse Drug Reaction News](http://www.adrnews.com).

1. **Albendazole (Zentel®, GSK)**
   - Contraindicated in patients with CrCl<60ml/min.
   - New ADRs: elevations of hepatic enzymes (rare), erythema multiforme & SJS (very rare).
   - Phenytoin reduces the bioavailability of nifedipine. Fluoxetine, ritonavir & saquinavir may increase plasma conc. of nifedipine.

2. **Atenolol, nifedipine (Nif-ten®, AstraZeneca)**
   - Contraindicated in patients with severe left ventricular dysfunction & not to use chronically in patients with impaired cardiac output.
   - Not to use in history of severe hypotension, angina pectoris or previous infarction even in patients with no history of coronary artery disease.
   - Infrequently, severe & occasionally incapacitating bone, joint or muscle pain. Time to onset: 1 day to several months after starting therapy. Very rarely, hypotension has led to syncope or circulatory collapse in patients with underlying risk factors.

9. **Eletriptan (Relpax®, Pfizer)**
   - Insert changes due to safety updates from previous issues.

20. **Metformin (Glucophage®, Merck)**
   - Contraindicated in patients with CrCl<60ml/min.
   - Very rarely, pituitary adenomas. Interacts with hydrochlorothiazide-induced pulmonary edema with granulocytic infiltration & IgG deposition in alveolar membranes. New ADR terms include chest pain, erectile dysfunction, paraesthesia, & blurred vision.

12. **Flavoxate (Urispas®, IDS Pharmaceutical)**
   - Associated with increased risk of seizures e.g. severe hepatic cirrhosis, excessive use of alcohol or sedatives, diabetes or epilepsy.
   - Minimise consumption of alcohol because of adverse neuropsychiatric events (rare) or reduced alcohol tolerance.

13. **Gadobutrol (Gadovist®, Schering)**
   - Significantly higher incidence of cerebrovascular adverse events with risperidone vs placebo.
   - Patients with Parkinson's disease or dementia, mortality was increased vs placebo.
   - Concomitant use with clozapine & quetiapine: increased risk of neuroleptic malignant syndrome, dyskinesia, dystonia, akathisia. Concomitant use with selective serotonin reuptake inhibitor antidepressants: increased risk of serotonin syndrome.

15. **Hydrochlorothiazide, valsartan (Co-Diovan®, Novartis)**
   - Very rarely, severe & occasionally incapacitating bone, joint or muscle pain. Time to onset: 1 day to several months after starting therapy. Very rarely, hypotension has led to syncope or circulatory collapse in patients with underlying risk factors.

21. **Nifedipine (Adalat LA®, Bayer)**
   - Nifedipine may increase if taken with grapefruit juice.
   - Phenytoin reduces the bioavailability of nifedipine. Fluoxetine, ritonavir & saquinavir may increase plasma conc. of nifedipine.

24. **Risperidone (Risperal®, J&J)**
   - Findings in placebo-controlled trials:
     - a) significantly higher incidence of cerebrovascular adverse events with risperidone vs placebo;
     - b) in patients with Parkinson's disease or dementia with Lewy bodies, mortality was increased vs placebo.
     - c) concomitant use with clozapine & quetiapine: increased risk of neuroleptic malignant syndrome, dyskinesia, dystonia, akathisia. Concomitant use with selective serotonin reuptake inhibitor antidepressants: increased risk of serotonin syndrome.

4. **Busulphan (Myleran®, GSK)**
   - Myleran® is not recommended due to risk of toxicity (metronidazole increases the trough levels of busulphan by ~80%). Itraconazole reduces clearance as both groups may be at increased risk of NMS & may exhibit increased sensitivity to Risperdal® (e.g. congenital QT syndrome).

3. **Bupropion (Wellbutrin®, GSK)**
   - In severe hepatic cirrhosis & clinical circumstances associated with increased risk of seizures e.g.

5. **Busulfan (Busulfex®, GSK)**
   - Very rare, severe & occasionally incapacitating bone, joint or muscle pain. Time to onset: 1 day to several months after starting therapy. Very rarely, hypotension has led to syncope or circulatory collapse in patients with underlying risk factors.

22. **Nimodipine (Nimotop®, Bayer)**
   - Extrapyramidal symptoms observed in neonate following use during last trimester.

7. **Diflucortolone, isoconazole (Travocort®, Schering)**
   - Hydrea® increases the risk of myeloid & lymphoid malignancy. Close monitoring is necessary in patients with clinically obvious immune deficiency, including (very commonly) sepsis, septicaemia; (commonly) decreased platelet count, tachycardia; & very rarely agitation.

10. **Epirubicin (Ellence®, Pfizer)**
   - Very rarely observed: generalized tonic clonic seizures, confusion, obtundation.

11. **Eptinezumab (ImmuCin® / Tysabri®, Biogen Idec)**
   - Very rarely, severe & occasionally incapacitating bone, joint or muscle pain. Time to onset: 1 day to several months after starting therapy. Very rarely, hypotension has led to syncope or circulatory collapse in patients with underlying risk factors.

16. **Etoposide (Epothilone®, Beiersdorf)**
   - Extrapyramidal symptoms observed in neonate following use during last trimester.

23. **Ranitidine (Zantac®, GSK)**
   - New ADR: Palmar plantar erythrodysaesthesia.

18. **Rofecoxib (Vioxx®, Merck)**
   - New ADRs: SJS, TEN, anaphylactic reactions during low-density lipoproteins haemodialysis patients dialysed with high flux membranes, anaphylactoid reactions.
Raloxifene (Evista®, Eli Lilly) is a selective estrogen receptor modulator (SERM) that binds to the estrogen receptor, leading to estrogen-agonist effects in some tissues and estrogen-antagonist effects in others. The drug was approved in Singapore in 1999 and is licensed for the treatment and prevention of osteoporosis in postmenopausal women.

In July 2006, The New England Journal of Medicine published the results of the Raloxifene Use for the Heart (RUTH) Study, designed to investigate possible cardioprotective effects of raloxifene in the elderly. The results suggest that raloxifene did not demonstrate to protect women against heart disease and could be associated with excess deaths from stroke.

The RUTH study
RUTH was an international, multicentre, randomised, double-blind, placebo-controlled trial. The two primary objectives were to determine the effect of raloxifene as compared with placebo on the incidence of coronary events (i.e. death from coronary causes, nonfatal [including silent] myocardial infarction, or hospitalisation for an acute coronary syndrome within 30 days of index admission) and invasive breast cancer.

A total of 10,101 postmenopausal women (mean age, 67.5 years) with coronary heart disease (CHD) or multiple risk factors for CHD were randomly assigned 60mg of raloxifene or placebo and followed for a median of 5.6 years and the median exposure to the study drug was 5.05 years.

Primary outcomes
There was no significant difference between raloxifene and placebo groups in the risk of primary coronary events (533 vs 553 events; hazard ratio, 0.95; 95% confidence interval, 0.86 to 1.07). Compared to placebo, raloxifene reduces the risk of invasive breast cancer (62 vs 70 events; hazard ratio, 0.86; 95% confidence interval, 0.71 to 1.07). Relative risk reduction, 0.14; absolute risk reduction, 1.2 per 1,000).

Secondary outcomes
The overall incidence of stroke did not differ significantly between the treatment groups, but raloxifene was associated with an increased risk of fatal stroke (69 vs 39 events; hazard ratio, 1.49; 95% confidence interval, 1.05 to 2.04; absolute risk increase, 0.7 per 1,000 woman-years) and venous thromboembolism (VTE) (122 vs 71 events; hazard ratio, 1.44; 95% confidence interval, 1.06 to 1.95; absolute risk increase, 1.2 per 1,000 woman-years).

Raloxifene reduced the risk of clinical vertebral fractures (88 vs 97 events; hazard ratio, 0.89; 95% confidence interval, 0.70 to 1.11; absolute risk reduction, 1.3 per 1,000).

There was no significant difference between the treatment groups in the rates of death from any cause or overall death from cardiovascular events.

With these results, the authors concluded that raloxifene did not significantly affect the risk of CHD. The benefits of raloxifene in reducing the risks of invasive breast cancer and vertebral fracture should be weighed against the increased risk of venous thromboembolism and fatal stroke.

Local situation
HSA has not received any serious report of VTE or stroke suspected to be associated with raloxifene. The ADR reports submitted pertain to non-serious skin reactions, headache and insomnia.

HSA is working with the product licence holder to amend the local package insert of Evista® to reflect the conclusion of the RUTH study.
Presence of heavy metals in traditional Indian medicines – A case of lead poisoning by ayurvedic medicine, Endopile®

Local case report

A 31 year-old female patient was reported to have developed symptoms of lead poisoning after the consumption of Endopile® for one month. She presented with abdominal pain, nausea, vomiting, anaemia with basophilic stippling and Burton’s line (a bluish line on the free border of the gingiva). Upon hospitalisation, she was found to have a blood lead level of 2.7 µmol/L (normal upper limit: 0.4 µmol/L or 1.93 mg/L).

Endopile® is produced by two firms in India, Santhigiri Ayurveda and Siddha Vaidyasala. It is available as a yellow and pink capsule. The product is indicated for the treatment of piles and related symptoms and labelled to contain herbal ingredients.

In February 2006, the Health Sciences Authority (HSA) received a report that a patient had developed symptoms of lead poisoning after consuming Endopile® capsules. Laboratory analysis of Endopile® capsules conducted by HSA found the product to contain lead at more than 100 times the permissible limits (limit is 20 ppm) and mercury at 8 times the permissible limits (limit is 0.5 ppm). HSA has taken actions to recall the affected batch of product from the local market.

Presence of heavy metals in traditional medicines

As a practice of Ayurvedic medicine, herbal medicines are used to treat specific ailments. It is not uncommon to find traces of heavy metals in traditional medicines such as Ayurvedic medicine. According to the principles of Ayurvedic medicine, heavy metals are used in a detoxified state in these medicinal products because of their reputed therapeutic properties. However, should the detoxification process not be strictly followed during manufacturing, it is possible for the resulting product to contain high levels of heavy metals.

The presence of heavy metals such as lead, arsenic and mercury in traditional medicines has been reported worldwide with numerous literature published on this topic. For instance, the December 2004 issue of the Journal of the American Medical Association (JAMA) reported a study of commercially available Ayurvedic medicinal products sold in the Boston area, USA which found that 14 out of 70 (20%) of these products contained potentially harmful levels of lead, mercury and/or arsenic.

Conclusions

With the increasing popularity of the use of traditional medicines, healthcare professionals need to be vigilant of the possible adverse effects arising from the consumption of such products. A thorough medication history inclusive of the patient’s use of traditional medicines is important when evaluating a suspected adverse drug reaction. All healthcare professionals are encouraged to report suspected adverse reactions to traditional medicines to the Pharmacovigilance Unit of the HSA.

References
9. Acute phase: Headache, nausea, abdominal pain, diarrhoea, malaise, anaemia or reticulocytosis.