Cyclooxygenase-2 specific inhibitors

Use with caution in patients with risk of cardiovascular disease or renal dysfunction

On 30th September 2004, Merck Sharp and Dohme (MSD) made an independent decision to voluntarily withdraw Vioxx® worldwide.

The withdrawal was based on the findings of the APPROVe clinical trial, a multicentre, randomized, placebo-controlled, double blind 3-year study investigating the effects of 25 mg dose of rofecoxib on the recurrence of neoplastic large bowel polyps in 2,600 patients with a previous history of colorectal adenoma.

The trial was terminated prematurely at the 34th month due to an increased incidence of cardiovascular (CV) events in patients taking Vioxx®: 25 patients taking placebo versus 45 patients taking Vioxx® experienced a confirmed serious thrombotic event (including myocardial infarction and stroke). The absolute event rates were approximately 3 per 400 patient-years for placebo and 6 per 400 patient-years for Vioxx®, i.e. an absolute increase of approximately 3 thrombotic events per 400 patient-years of treatment. The difference in event rates was only apparent after 18 months of continuous intake of Vioxx®.

At the time of withdrawal, Vioxx® was approved for use in over 80 countries. It was registered in Singapore in 1999 at about the same time as in the United States and the United Kingdom. The risk of CV events was not detected in the pre-marketing clinical trials.

Is this a class effect?

There are 3 other cyclooxygenase-2 (COX-2) specific inhibitors currently registered in Singapore, namely celecoxib (Celebrex® and Onsenal®, Pfizer), valdecoxib (Bextra®, Pfizer) and etoricoxib (Arcoxia®, MSD). All except Onsenal® are indicated for the treatment of osteoarthritis, rheumatoid arthritis and acute pain. Onsenal® is approved for the regression and reduction of adenomatous polyps in patients with familial adenomatous polyposis. These 3 drugs are registered in many countries including the United Kingdom and Australia and were approved for marketing as they fulfilled the requirements for drug registration based on internationally accepted guidelines. They have different chemical structures, although they work similarly by selectively inhibiting the COX-2 pathways.

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Lamictal® and interaction with oral contraceptives

Post-marketing reports of breakthrough seizures, unexpected pregnancies and menstrual bleeding disorders have been received

Lamotrigine (Lamictal®, GlaxoSmithKline) is a phenyltriazine antiepileptic agent registered in Singapore in 1993.

A significant degree of drug interaction was reported in a recent clinical pharmacology study that investigated the effects of combined oral contraceptive (COC) pill, Microgynon 30® (contains ethinylestradiol: 30 mcg & levonorgestrel: 150 mcg) on the pharmacokinetics of lamotrigine and vice versa.

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Bisphosphonates and osteonecrosis of the jaw

A recent study has highlighted cases of osteonecrosis in patients treated with bisphosphonates, particularly for cancer patients. Bisphosphonates, known for their role in the treatment of osteoporosis, are also used in patients with bone metastases. The risk factors for osteonecrosis include chemotherapy, radiotherapy, and corticosteroids. This condition can lead to the death of bone tissue, leading to bone cavity, which can cause severe pain and affect oral health.

Over the last two years, cases of osteonecrosis of the jaw (ONJ) have been reported in patients treated with bisphosphonates, many of whom were cancer patients receiving chemotherapy and corticosteroids. In the majority of the cases, ONJ developed after tooth extraction although some developed the condition spontaneously. Many had signs of local infection including osteomyelitis.

One of the interesting case reports described osteonecrosis of the alveolar bone in three female patients undergoing chemotherapy for metastatic breast cancer. All three patients received pamidronate. Two of these patients developed bone necrosis after tooth extractions, but the third patient developed the condition spontaneously, resulting in an oroantral fistula. In all cases, histological examination of the lesions showed necrotic bone with no evidence of metastatic disease. There are other reports of patients receiving pamidronate or zoledronic acid and developed necrosis of the bone after dental extractions.

Data from the UK showed that cancer patients have an estimated four times higher risk of osteonecrosis at any site than the general population. Treatment with bisphosphonates is a standard of care in many types of bone complications of cancer. Therefore, it is not possible to determine if osteonecrosis of the jaw is related to bisphosphonates, concomitant drugs/other therapies, patient’s underlying disease, or other comorbid risk factors.

Local case report

The bisphosphonates registered locally include alendronate, clodronate, etidronate, ibandronic acid, pamidronate, risendronate and zoledronic acid. Bisphosphonates are commonly used for the treatment of postmenopausal and corticosteroid induced osteoporosis, Paget’s disease, hypercalcaemia associated with malignancy and osteolytic and bone pain associated with metastatic bone disease.

To date, the Pharmacovigilance Unit has received one local report of a patient with jaw osteolysis and suspected osteomyelitis while he was on zoledronic acid (Zometa®) 4 mg injection. There is another report of exostosis and aseptic bone necrosis after a dental extraction during alendronate (Fosamax®) therapy.

Recommendation

The following recommendations have been made in the updated prescribing information of the pamidronate and zoledronic acid in the US:

- A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, corticosteroids, poor oral hygiene).

- Whilst on treatment, these patients should avoid invasive dental procedures, if possible. For patients who develop ONJ while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Clinical judgment of the physician should guide the management plan of each patient based on the individual benefit/risk assessment.

It has been highlighted that cases of avascular bone necrosis were reported with high doses potent nitrogen-containing bisphosphonates e.g. pamidronate and zoledronic acid. There is limited data to suggest that the other bisphosphonates may have similar, albeit less, effects on jaw bones as well. Healthcare professionals are encouraged to report all serious adverse reactions suspected to be associated with the use of bisphosphonates to the Pharmacovigilance Unit of the HSA.
Pergolide associated with cardiac valvulopathy
Two newly published studies add evidence to this potentially serious ADR

Cardiac valvulopathy has been reported to be rare (between >1/10,000 and <1/1000) in association with the use of pergolide (Celance®, Eli Lilly) based on post-marketing surveillance database. In Singapore, the ergot-derived dopamine agonist is indicated as an adjunctive treatment to levodopa, in the management of signs and symptoms of Parkinson’s disease and has been available since 1992. This potentially serious ADR prompted many regulatory agencies, including HSA, to list this adverse effect in the package insert of the drug last year.

Recently, this ADR was highlighted once again by Health Canada in response to two case-referent (non-prospective, non-randomised) studies1,2 where a significant number of patients treated with pergolide showed evidence of cardiac valvulopathy, suggesting that the condition may occur more frequently than what earlier postmarket reports suggested. However, as there are a number of limitations with the studies, the actual rate of cardiac valvular disease with pergolide cannot be determined at this time.

In its healthcare professional advisory, Health Canada advised physicians to assess/reassess for all patients the potential harms and benefits of ergot-derived dopamine agonists, including pergolide, against those of non ergot-derived dopamine agonists. Pergolide is not recommended in patients with a history of serious inflammation, fibrosis or cardiac valvulopathy, particularly in patients who experienced the events while taking other ergot derivatives.

It also advised that patients should undergo a cardiovascular evaluation (including an echocardiogram) to assess potential presence of an occult valvular disease before initiating treatment, and periodic clinical diagnostic monitoring (e.g. physical examination, X-ray, echocardiogram, CT scan) for development of valvular disease of fibrosis. The use of pergolide doses above 5 mg/day is not recommended, based on the post-market finding that the reporting rate for cardiac valvulopathy associated with pergolide may be greater with doses above the maximum recommended. However, cardiac valvulopathy has been reported in association with doses within therapeutic range.

Local reports
HSA has received 3 local reports of cardiac valvular abnormalities associated with the drug. The 3 patients were Chinese men, ages between 55 and 71 years. They had been taking the drug for a duration of 1.7 to 5.2 years before they were found to have cardiac valvular abnormalities such as mild mitral and tricuspid regurgitation and moderate aortic regurgitation after screening.

References

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Safety alert regarding medication errors - Reminyl® vs Amaryl®

Healthcare professionals are reminded to exercise caution during prescribing or dispensing

HSA was recently alerted by the local subsidiary of Johnson & Johnson about several incidents of prescribing and dispensing errors involving its product, Reminyl® (galantamine) and Amaryl® (glimepiride, Aventis) in the United States.

Reminyl® is approved for the treatment of dementia of the Alzheimer type and Amaryl® is indicated for the treatment of diabetes mellitus (non-insulin-dependent, type 2). Both drugs have been available in Singapore since 2001 and 1998, respectively.

According to the spontaneous reports submitted to US FDA and the US Pharmacopoeia, prescriptions have been incorrectly written, interpreted, labelled and/or filled due to the similarity in names between Reminyl® and Amaryl®. To-date, Johnson & Johnson has not received any reports of such errors outside the US.

These 2 products have an overlapping strength (4 mg) and an overlapping dosage form (tablets). In addition, their generic names (galantamine vs glimepiride) might lead to their storage in close proximity.

Healthcare professionals are reminded to exercise special care when prescribing or dispensing these 2 products in order to prevent a mix-up.
Package insert amendments reflecting safety issues

HSA has approved the following package insert changes due to safety update from May to October 2004. Excerpts for selected major safety update are highlighted in the paragraphs below. For details please refer to http://www.hsa.gov.sg/cda/labelchanges.
Please note that there might be some time in the availability of the package insert which reflects the latest change(s).

<table>
<thead>
<tr>
<th>Month</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>May</td>
<td>Anzata® (Mayne Pharma); Augmentin® (GSK); Olyl Phenol® (Mayne Pharma); Parvolex® (Mayne Pharma); Sevoren® (Abbott Lab); Serevent® (GSK); Yfend® (Pfizer); Ultracet® (Johnson &amp; Johnson)</td>
</tr>
<tr>
<td>June</td>
<td>Cardioplegia Concentration® (DBL); Iressa® (AstraZeneca); Tralat® (Sanofi Synthelabo); Seretide® (GSK); Virumune® (Deltexpharm)</td>
</tr>
<tr>
<td>July</td>
<td>Asmanex® (Scherings-Plough); Erythromycin Lactobionate® (Mayne Pharma); Ponsitan® (Pfizer); Rhinocort® (AstraZeneca)</td>
</tr>
<tr>
<td>August</td>
<td>Anoxil® (GSK); Cordarone® (Sanofi Synthelabo); Dilantin® (Pfizer); Fraxiparine Forte® (Sanofi Synthelabo); Hycamtin® (GSK); Kerlone® (Sanofi Synthelabo); Losac® (AstraZeneca); Nolol® (Sunward); Propofol-Lipuro® (B Braun); Valcyte® (Roche)</td>
</tr>
<tr>
<td>September</td>
<td>Crestor® (AstraZeneca); Dogmatil® (Sanofi Synthelabo); Duxari® (Servier); Epilim® (Sanofi Synthelabo); Pentamide Isethionate® (Mayne Pharma); Phenytoin® (Mayne Pharma); Tenormin® (AstraZeneca); Zelmac® (Novartis)</td>
</tr>
<tr>
<td>October</td>
<td>Ascorbic Acid® (Mayne Pharma); Atacand® (AstraZeneca); Avloclor® (AstraZeneca); Cipram® (JDH Pharmaceutical); Controlx® (Deltexpharm); Cyclogest (Alpharma); Deltascone® (Sunward); Loette 21° (Wyeth); Noivadex® (AstraZeneca); Phenobarbital® (Mayne Pharma)</td>
</tr>
</tbody>
</table>

1. Amodarone (Cordarone®, Sanofi Synthelabo) Cordarone® is contraindicated in neonates or premature babies unless no alternative therapy is deemed appropriate. Cordarone® IV ampoules contain benzyl alcohol & there have been reports of fatal ‘gasting syndrome’ following the administration of IV solution containing this preservative. Intestinal pneumonia & severe respiratory complications have been reported with IV amodarone including fatal cases of pulmonary toxicity.

2. Betaxolol (Kerlone®, Sanofi Synthelabo) The use of Kerlone® is contraindicated with sulphoxide, bepridil, diltiazem, verapamil & while breast-feeding. This product contains lactose & is contraindicated in patients with the following conditions: congenital galactosaemia, glucose/galactose malabsorption or lactase deficiency syndrome.

3. Citalopram (Cipram®, JDH Pharmaceutical) Warning statements on clinical worsening & suicide risk in patients with major depressive disorder (both adults & children) have been included in the revised PI. Patients being treated with antidepressants should be observed closely for clinical worsening & suicidality, especially at the beginning of a course of drug therapy, or at the time of dose changes. The same precautions should be observed when treating patients with other psychiatric & nonpsychiatric disorders. Symptoms reported include anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia, hypomania & mania.

4. Nadroparin calcium (Fraxiparine Forte®, Sanofi Synthelabo) Fraxiparine® is contraindicated in patients with severe kidney failure (creatinine clearance <30 mL/min). It is also not recommended in mild to moderate kidney failure patients (creatinine clearance >30 & <60 mL/min).

5. Nevirapine (Viramune®, Boehringer Ingelheim) Under the section of contraindication, it is advised that Viramune® should not be given to patients with severe hepatic dysfunction or pre-treatment ASAT or ALT >5x ULN until baseline ASAT/ALT are stabilised <5x ULN. Intensive monitoring has been extended to the first 18 months instead of the first 8-12 weeks. Women with CD4 counts >250 cells/mm³ had a 9 fold higher risk of rash-associated hepatic adverse events compared to women with CD4 counts <250 cells/mm³ (8.4% vs 0.9%). New ADR terms have been added to include severe & life-threatening hepatotoxicity & fatal fulminant hepatitis.

6. Progestrone (Cyclogest®, Alpharma) Cyclogest® is contraindicated in the following conditions: carcinoma of the breast or genital organs, liver dysfunction or disease, thrombophlebitis, thromboembolic disorders, cerebral apoplexy & porphyria.

7. Raubasine & almitrine (Duxari®, Servier) The drug is contraindicated in patients with peripheral neuropathy or history of peripheral neuropathy. Due to the presence of lactose, the product is contraindicated in patients with congenital galactosaemia, glucose & galactose malabsorption syndrome or deficit in lactase. The incidence of peripheral neuropathy is now quoted as 1/1000 instead of previously 5 cases per 100,000 patient-months.

8. Sodium Valporate (Epilim®, Sanofi Synthelabo) Epilim® is contraindicated in patients with known urea cycle disorders. New statements describing the following conditions have been included: hyperammonaemia, urea cycle disorders, ornithine transcarbamylase deficiency, weight gain, pregnancy & diabetic patients.

9. Sulpiride (Dogmatil®, Sanofi Synthelabo) Sulpiride is contraindicated in the following situations: prolactin-dependent tumours & use in combination with sulpiride or dopamine agonists (except in patients with Parkinson’s disease).

10. Tegaserod (Zelmac®, Novartis) Zelmac® is contraindicated in patients with severe renal impairment, severe or moderate hepatic impairment. Although no dosage adjustment is required in patients with mild hepatic impairment, caution is recommended in these patients as worsening of hepatic function might result in elevated exposure to tegaserod.

11. Voriconazole (Yfend®, Pfizer) Co-administration with ritonavir (400 mg Q12h) or efavirenz is contraindicated. Administration with ritonavir (400 mg Q12h) significantly decreased plasma voriconazole concentrations in healthy subjects. Efavirenz significantly decreased voriconazole plasma levels while voriconazole also significantly increased efavirenz plasma concentrations.
With this recent finding from the APPROVe study, a potential safety concern has been raised as to whether the increased thrombotic events seen with Vioxx® could be a class effect. Mechanistically, COX-2 specific inhibitors are known not to affect platelet function compared to non-selective NSAIDs which have potent and sustained antiplatelet effects that might provide cardioprotective benefits. In addition, because these drugs decrease systemic prostacyclin production without affecting platelet thromboxane production, there is a theoretical possibility that there may be an increase in the risk of a prothrombotic event.

Although the clinical trial data that have been submitted for the existing 3 COX-2 specific inhibitors were of durations less than 3 years as compared to the APPROVe trial, based on the available evidence to-date, there is insufficient information to make a conclusive CV statement of these existing COX-2 inhibitors. With this new information of increased CV risk to Vioxx®, the affected companies are embarking on or currently have clinical trials that will go on for longer duration, in order to ascertain the safety profile of these products. The US FDA will be holding an advisory committee meeting in February 2005 to review the safety issues of COX-2 inhibitors including defining the type of data that it will require before approving subsequent entrants in the class.

**What is HSA doing?**

HSA will closely monitor the international regulatory developments on COX-2 specific inhibitors which will take place over the next few months as well as closely monitoring the local ADRs to these drugs. Healthcare professionals will be updated on the regulatory position of HSA when more confirmatory evidence is found.

**Recommendations**

- Caution must be exercised when prescribing these drugs to patients at risk of CV conditions, such as patient with a history of hypertension or ischaemic heart disease. Patients should be advised to see their physician in the event of any worsening of heart disease symptoms.

- COX-2 inhibitors should be used with caution in patients with renal dysfunction or in the elderly as they have been reported both locally and worldwide to cause serious adverse effects, including acute renal failure. When used in these patients, the lower recommended dose should preferably be prescribed and patients should be closely monitored.

- Physicians are reminded that COX-2 specific inhibitors do not offer CV protection and are not substitutes for aspirin for prophylaxis of CV diseases because of their lack of effect on platelet function.


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**continued from Page 1 • Lamictal® and interaction with oral contraceptives**

The study was conducted in healthy young female subjects. These subjects received Microgynon 30° and lamotrigine (titrated up to 300 mg) in accordance to standard prescribing information.

a) Decrease in lamotrigine serum levels

It was found that lamotrigine exposure was substantially reduced in the presence of the COC by an average of 52% and 39% in AUC and Cmax, respectively.

During the 'pill-free' week of COC, the pre-dose serum lamotrigine concentrations increased to approximately 2-fold higher than during Microgynon 30° co-administration.

b) Effect on COC

Lamotrigine has a modest reduction effect in levonorgestrel plasma concentrations (mean decrease of 19% AUC and 12% Cmax) and minimal effect on ethinylestradiol pharmacokinetics. Changes in serum follicle-stimulating hormone and luteinising hormone have been observed. The impact of these changes on ovarian ovulatory activity is unknown.

**Post-marketing reports**

There have been reports of breakthrough seizures, unexpected pregnancies and menstrual bleeding disorders occurring with the concomitant use of Lamictal® and hormonal preparations.

Other oral contraceptive and HRT treatments have not been studied but they may similarly affect the pharmacokinetic parameters of lamotrigine.

**Recommendation**

Physicians should exercise appropriate clinical management of women starting or stopping hormonal contraceptives during Lamictal® therapy and dose adjustment for lamotrigine may be necessary. Patients should be advised to promptly notify their physicians if they experience changes in their menstrual pattern.

The local package insert for Lamictal® has been amended to reflect the above findings. (Please note that there might be lag time in the availability of the package insert which reflect the latest change(s). Please refer to the company representative for details.)
Antidepressants and increased risk of suicidality in children and adolescents

Labels to be strengthened to warn of an increased risk of suicidality (suicidal thinking and behaviour) in children and adolescents

On 18th May 2004, the Health Sciences Authority (HSA) highlighted the emerging concerns raised internationally on the increased risk of suicidal ideation in patients under 18 years of age who are taking selective serotonin reuptake inhibitors (SSRIs) and related antidepressants for major depressive disorder (MDD).

Following the recommendations of its advisory committees, the US Food and Drug Administration (FDA) announced on 15th October 2004 that it would require manufacturers of all antidepressants to strengthen the label warnings to warn prescribers of an increased risk of suicidality (suicidal thinking and behaviour) in children and adolescents. In consultation with HSA’s Pharmacovigilance Advisory Committee and experts in the field of psychiatry, HSA has reviewed this development in the US and would like to provide the following update.

Findings of the US FDA’s review
The risk of suicidality for the antidepressants was identified in a combined analysis of short-term (up to 4 months) placebo-controlled trials of nine antidepressants, which included the SSRIs. In children and adolescents with MDD, the US FDA reviewed a total of 24 trials involving 4,400 patients. The analysis showed a greater risk of suicidality during the first few months of treatment in those receiving antidepressants. The average risk of such events was 4% for patients on antidepressants compared to 2% for those on placebo. No suicides occurred in these trials.

Conclusion on risk/benefit of antidepressants
There is an increased risk of suicidal ideation and behaviour in children and adolescents who are prescribed SSRIs and related antidepressants for MDD. This increased risk generally outweighs the possible benefits. Since the available data cannot exclude increased risk if this benefit when any single medication in these groups is consumed by patients under 18 years of age, HSA has adopted US FDA’s stand to apply this increased risk to all antidepressants.

In the case of adult patients with MDD, the risk/benefit ratio of the use of antidepressants, in general, remains favourable. Although there is some evidence that there may be an increased risk of suicide ideation in patients taking SSRIs, the overall proven efficacy of antidepressants in adult patients outweighs the possible risks.

Advisory
HSA advises that the use of any antidepressants in children and adolescents should be undertaken only within the context of comprehensive management of the patients, as outlined in the Clinical Practice Guidelines issued by MOH. Physicians should carefully monitor patients receiving antidepressants for possible worsening of depression or suicidability, especially at the beginning of therapy or when the dose is increased or decreased.

It is also important to note that children and adolescents who are currently treated with antidepressants should not have their medication discontinued abruptly as there may be withdrawal symptoms associated with abrupt discontinuation.

HSA will be following up with the relevant pharmaceutical companies to determine appropriate changes to the labelling or packaging of affected products.