



Recall of medical devices — DePuy ASR™ Hip Resurfacing System and DePuy ASR™ XL Acetabular System

DePuy Orthopaedics conducted a global voluntary recall on 31 August 2010 of its DePuy ASR™ Hip Resurfacing System and DePuy ASR™ XL Acetabular System due to its association with higher rates of revision surgery. These are medical devices used in hip resurfacing and replacement surgeries.

Background

The DePuy ASR™ XL Acetabular System is used in hip replacement surgeries for people with hip joint damage from arthritis or injuries. It comprises of the acetabular cup, which is a metal liner that replaces the socket portion of the pelvis, known as the acetabulum. (See Figure 1 for illustration of a normal hip)

The DePuy ASR™ Hip Resurfacing System consists of two components, (i) a cap which is placed over the femoral head and (ii) the acetabular cup. Unlike in conventional hip replacement surgery where the femoral head is replaced, resurfacing of the hip preserves the femoral bone by placing a metal cap over the surface of the femoral head. The femoral head and neck are not removed. The acetabulum is replaced with the acetabular cup as in a total hip replacement surgery. Both ASR™ systems had been marketed locally since 2006.

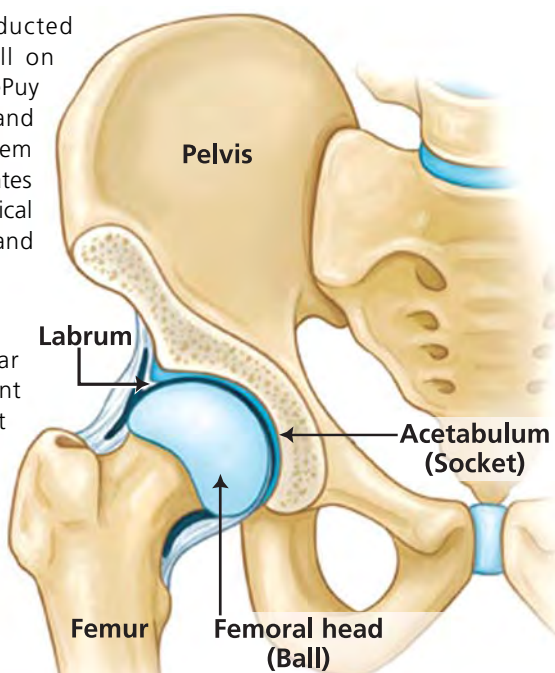


Figure 1. Illustration of a normal hip (Source: American Academy of Orthopaedic Surgeons)

DePuy Orthopaedics issued a notification or 'Field Safety Notice' in March 2010 to healthcare professionals following an analysis of post-marketing data, which suggested that a higher than expected number of patients who received the ASR™ systems required a second hip replacement surgery, i.e. revision surgery. A revision surgery is required in instances where there are mechanical faults in the artificial hip, warranting the removal of old implants and replacing them with new components.

Subsequently on 31 August 2010, DePuy Orthopaedics issued a voluntary global recall of its ASR™ XL Acetabular System and ASR™ Hip Resurfacing System due to higher rates of revision surgery observed in DePuy ASR™ products taking into account the data from the National Joint Registry (NJR) of England and Wales.

Data from the National Joint Registry (NJR) of England and Wales

In May 2010, the NJR of England and Wales informed the UK Medicines and Healthcare products Regulatory Agency (MHRA) that ASR™ acetabular cups had been identified from registry data as having higher than anticipated rates of revision surgery in hip resurfacing and total hip replacement procedures.

The NJR of England and Wales had carried out an analysis on outcomes following primary hip replacement based on data for 216,693 patients who had primary hip replacement procedures between 1 April 2003 and 31 December 2009. The analysis showed that the overall revision surgery rate following primary hip replacement was 1.0%, 2.1% and 2.9% at one, three and five years respectively.¹

Data from the NJR also revealed that the revision surgery rate at five years for patients who had received DePuy ASR™ Hip Resurfacing System and DePuy ASR™ XL Acetabular System, were higher than expected across the entire size range at 12% and 13% respectively (approximately 1 in 8 patients). The risk for revision surgery was noted to be highest with use of ASR™ head sizes below 50 mm in diameter and among female patients.

Adverse effects experienced by affected patients

Patients who reported problems with the DePuy ASR™ systems and required revision surgeries within the first five years post-surgery presented with a variety of symptoms including pain, swelling and difficulty in walking. A small number of patients implanted with these systems may also develop progressive soft tissue reactions to the metal debris generated as the metal components wear out over time.² While this condition may initially be painless, if left untreated, this reaction may cause pain and swelling around the joint and could damage some of the muscles, bones and nerves around the hip.³

continued on Page 2

CONTENTS

- Recall of medical devices — DePuy ASR™ Hip Resurfacing System and DePuy ASR™ XL Acetabular System page 1
- Suspension of sales of sibutramine page 2
- Bisphosphonates and atypical fracture risk page 3
- Update on varenicline (Champix®) and neuropsychiatric events page 4
- Summary of safety advisories issued by HSA, pharmaceutical and medical device companies page 5
- Restriction on the use of rosiglitazone page 6
- Daptomycin and eosinophilic pneumonia page 7
- Lamotrigine and aseptic meningitis page 8

Suspension of sales of sibutramine

Cardiovascular risks of sibutramine outweighs its modest efficacy

HSA has suspended the sales of sibutramine products with effect from 11 October 2010, following an in-depth benefit-risk assessment, which took into consideration the findings from the Sibutramine Cardiovascular Outcomes (SCOUT) study, use of the product in the local context and regulatory actions taken in other countries. The Vigilance Branch (VB), HSA, had consulted with its Pharmacovigilance Advisory Committee (PVAC) and a panel of clinical experts in endocrinology and cardiology before arriving at this regulatory decision. The licences of local sibutramine products have been suspended with effect from 22 November 2010.

Sibutramine has been licensed in Singapore since 2001 for use as an adjunctive therapy to diet and exercise for obese patients with a body mass index (BMI) >30kg/m², or for overweight patients with a BMI >27kg/m² with other obesity-related risk factors such as Type 2 diabetes mellitus (DM) or dyslipidaemia. It is marketed under four different brands in Singapore: Reductil® (Abbott), Ectiva® (Abbott), Reduxade® (Abbott) and Slenfig® (Apotheca Marketing Pte Ltd).

HSA's Review of the SCOUT Study

The SCOUT study was conducted as part of the requirement in Europe to monitor cardiovascular (CV) safety after the approval of sibutramine. This study was a randomised, double-blind, placebo-controlled, multi-centre study conducted in approximately 10,000 patients aged ≥55 who were obese or overweight and had a history of CV disease and/or Type 2 DM with at least one other CV risk factor treated over a six year period. The study results showed that there was a 16% increase in the risk of a primary outcome event of non-fatal myocardial infarction (MI), non-fatal stroke, resuscitated cardiac arrest and CV death in the sibutramine group as compared with the placebo group (HR: 1.16; 95% CI: 1.03 -1.31; p=0.02). There were also significantly more reports of myocardial ischaemia and ischaemic stroke in subjects taking sibutramine as compared to placebo.

The weight loss achieved in the SCOUT study was modest. At the end of 12 months, the mean weight loss achieved with sibutramine was up to 2.4kg more than placebo (4.3kg with sibutramine vs 1.9kg with placebo). After 12 months of treatment, no additional mean weight loss was achieved and it was not clear if the effect on weight loss could be maintained when sibutramine was stopped.

continued from Page 1

■ Recall of medical devices - DePuy ASR™ Hip Resurfacing System and DePuy ASR™ XL Acetabular System ■

Local situation

To date, 319 units of the ASR™ systems had been implanted locally, of which one case was reported to require revision surgery. However, further investigations had shown that the cause for revision surgery was not implant-related.

DePuy Orthopaedics has also implemented a series of recommended follow-up actions for patients implanted with the DePuy ASR™ Hip systems such as an annual follow-up for at least five years post-operatively and closer monitoring with necessary blood tests and MRI or ultrasound scans.

Healthcare professionals are encouraged to report adverse events suspected to be associated with the DePuy ASR™ systems or other medical devices to the Medical Device Branch of HSA.

[Note: Following the gazetting of the Health Products (Medical Devices) Regulations 2010 and Health Products (Medical Devices) (Exemption) Order 2010 under the Health Products Act (Chapter 122D) on 10 August 2010, articles related to medical device safety will be published in this bulletin]

References

- 1) National Joint Registry for England and Wales 7th Annual Report
- 2) Medicines and Healthcare products Regulatory Agency. Medical Device Alert Ref: MDA/2010/033
- 3) DePuy website. <http://www.depuy.com>

International Regulatory Actions Taken

(A) US Food and Drug Administration (FDA)

In October 2010, the US FDA recommended against the continued use of sibutramine following deliberations of its Advisory Committee meeting. In the subgroup analyses conducted on three predefined CV risk groups: (1) type 2 DM; (2) a history of CV disease; (3) a history of CV disease and type 2 DM, it was shown that the differences in magnitude of risk for CV events across the three subgroups were not statistically significant. Subsequently, sibutramine was voluntarily withdrawn from the US market.

(B) European Medicines Agency (EMA)

In January 2010, the Committee for Medicinal Products for Human Use (CHMP) conducted a safety review of sibutramine and concluded that the benefit-risk profile of sibutramine was no longer favourable. A suspension of sibutramine across the European Union (EU) was recommended and later adopted by the European Commission in August 2010. The marketing authorisation of the product will remain suspended throughout Europe until additional data becomes available on a patient population, whereby the benefit would outweigh its risks.

Local Situation

Following the release of the preliminary SCOUT results in January 2010, HSA updated healthcare professionals on the CV risks associated with the use of sibutramine and advised healthcare professionals not to prescribe the drug to patients with a history of CV disease. This advisory was reinforced in an article published in the April 2010 issue of the HSA Adverse Drug Reaction News Bulletin.

As of 28 October 2010, VB has received three non-serious CV-related adverse reaction reports associated with the use of sibutramine describing sudden chest pain, palpitations, tachycardia, mild chest discomfort and elevated blood pressure. All three patients recovered following the discontinuation of sibutramine.

HSA's Assessment and Recommendations

The SCOUT study has added to overall knowledge that sibutramine is associated with an increased CV risk and HSA considered that this increased risk could also apply to patients for whom sibutramine can be prescribed because obese and overweight patients are likely to be at risk of CV disease. The results of SCOUT also did not confirm the assumption that small weight loss maintained over a few years may reduce CV risk of overweight patients or the conclusion that the achieved lower weight translates into a clinical benefit, i.e. prevention of serious CV events. On balance, HSA assessed that the increase in CV risk outweighs the modest efficacy seen and has recommended the suspension of sales of sibutramine with effect from 11 October 2010. This suspension will remain in place until there is available data to identify a group of patients for whom sibutramine's benefits clearly outweigh its risks.

A Dear Healthcare Professional Letter (DHCPL) was disseminated to all healthcare professionals on 11 October 2010 with the advisory to stop prescribing sibutramine, to review the therapy of existing patients who have been prescribed sibutramine and to consider suitable alternatives where appropriate. To date, more than 80 countries have either suspended or withdrawn the licence for sibutramine. Abbott has also ceased sales and marketing of its sibutramine products worldwide.

References

1. FDA News Release. Abbott Laboratories agrees to withdraw its obesity drug Meridia. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm228812.htm>
2. European Medicines Agency recommends suspension of marketing authorisation for sibutramine. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/01/news_detail_000985.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1&jsenabled=true

Bisphosphonates and atypical fracture risk

An update on label warnings and local ADR reports

HSA would like to draw healthcare professionals' attention to a recent implementation of label warnings regarding the risk of atypical femur fractures associated with the bisphosphonate class of drugs that are used in the treatment of osteoporosis. The bisphosphonate products that are affected by this label warning in Singapore include risedronate (Actonel® and Risedronate Mevon®), alendronate (Fosamax®, Apo-alendronate® and Tevanate®), ibandronate (Bonviva®) and zoledronic acid (Aclasta®). Bisphosphonates that are licensed for treatment of Paget's disease or high blood calcium levels due to malignancies are not affected by these additional labelling requirements.

Atypical femur fractures

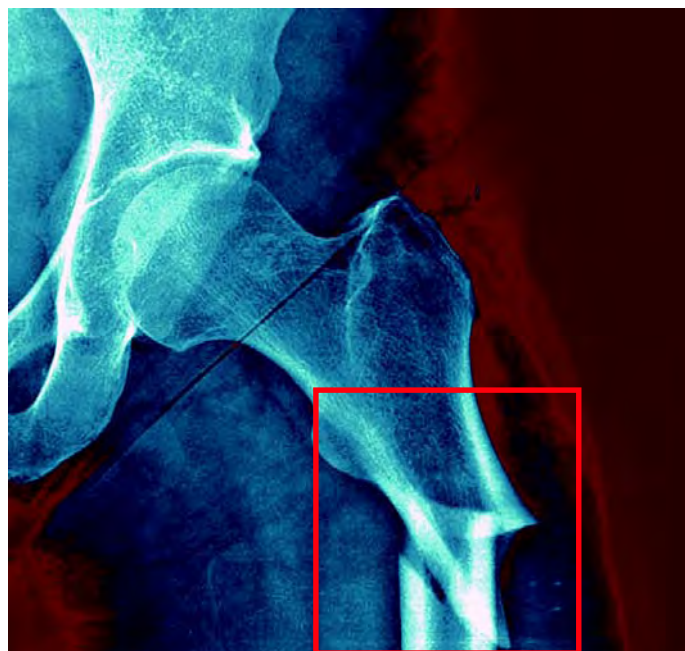
Atypical femur fractures can occur anywhere in the femoral shaft, from just below the lesser trochanter to above the supracondylar flare, and are transverse or short oblique in orientation without evidence of comminution. The fractures can be complete (involving both cortices) or incomplete (involving the lateral cortex only), and may be bilateral. Many patients report paradromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. The exact incidence of atypical femoral fractures is unknown but appears to be uncommon, accounting for less than 1% of hip and femoral fractures overall.

Review by US Food and Drug Administration (FDA)

Early this year, the US FDA embarked on reviewing the risk of atypical thigh bone fractures associated with the use of bisphosphonates in the treatment of osteoporosis.¹ In its recently completed review, the US FDA recommended that the package inserts of all bisphosphonates that are indicated for the treatment of osteoporosis be updated with precautions on the potential risk of these atypical femur fractures. This label change describes the uncertainty of the optimal duration of bisphosphonate use for the treatment of osteoporosis as this information has not been elucidated. Although the mechanism of this adverse event is not known, these atypical fractures may be related to long-term bisphosphonate use.

Local experience

A spike in local cases reporting atypical fractures associated with the use of alendronate was first brought to HSA's attention in early 2007. Acting on this safety signal, HSA solicited for similar reports from physicians and reviewed the local case reports together with published medical literature. Although the review did not establish that the fractures were directly associated with the use of alendronate, HSA published an article on this issue in March 2007 to alert healthcare professionals on this emerging safety issue. The article also highlighted the Ministry Of Health Clinical Practice Guidelines (MOH CPG) for Osteoporosis as it was noted that a large portion of patients who experienced atypical fractures did not have clinically diagnosed osteoporosis (defined by MOH CPG for Osteoporosis as a Bone Mass Density (BMD) T-score of -2.5 or lower) when they were prescribed alendronate. Considering that alendronate was the only bisphosphonate implicated in the local reports pertaining to atypical fractures at that time, the package inserts of all alendronate-containing products in Singapore were updated to include precautionary statements on this safety issue in 2008.



Radiograph of a subtrochanteric fracture

Current Situation

There are currently 14 registered bisphosphonate-containing products in Singapore that are indicated for the treatment of osteoporosis. To date, there are 82 local ADR reports of subtrochanteric fractures associated with bisphosphonates (78 with alendronate, two with risedronate and one with zoledronate). Majority of the patients who suffered fractures were female (~77%) and aged 60 years old and above (~83%). Where information on the duration of use was available, the onset of fractures ranged from two to eight years following the initiation of bisphosphonates therapy. The BMD T-score was reported for 15 of the patients; 12 of them had a BMD T-score higher than -2.5 prior to the initiation of bisphosphonates, i.e. from -2 to -1.3. These cases did not meet the criteria defined by MOH CPG for Osteoporosis as clinically diagnosed osteoporosis.

HSA is working with the licence holders of these products to strengthen the package inserts of all bisphosphonates licensed for osteoporosis treatment with warnings regarding the risk of atypical fractures.

Considering that atypical femoral fractures have been associated with long-term bisphosphonate use, healthcare professionals are encouraged to conduct periodic re-evaluation of the need for continued bisphosphonate therapy and to evaluate any patient who presents with new thigh or groin pain so as to rule out a femoral fracture. Healthcare professionals are encouraged to keep in mind the MOH CPG Guidelines for Osteoporosis when prescribing bisphosphonates for the treatment of osteoporosis. All serious adverse effects especially fractures suspected to be associated with bisphosphonates should be reported to the Vigilance Branch of HSA.

References

1. <http://www.fda.gov/Drugs/DrugSafety/ucm229009.htm>

Update on varenicline (Champix®) and neuropsychiatric events

HSA would like to update healthcare professionals on the local adverse drug reaction (ADR) reports and recent international developments related to varenicline (Champix®) that have taken place since our last report¹ on this issue in July 2008.

Varenicline (Champix®, Pfizer), a partial nicotinic acetylcholine receptor agonist, is licensed as an aid to smoking cessation treatment and was registered in Singapore in August 2007.

Regulatory updates from international agencies

(A) US Food and Drug Administration (FDA)

The US FDA had in July 2009, approved safety labeling revisions submitted by Pfizer Inc. which included a black-box warning regarding the risk for serious neuropsychiatric (NP) events.² This was following post-marketing reports of NP events such as psychosis, hallucinations, paranoia, delusions, hostility, agitation, suicidal ideation, suicide attempt and completed suicide in patients with and without pre-existing psychiatric disease.

While some NP symptoms may have occurred in association with nicotine withdrawal, it was also noted that there were cases reported in patients who had not yet discontinued smoking. The majority of cases occurred during treatment, but some were also reported after withdrawal of varenicline therapy.

FDA recommended that healthcare professionals advise patients to stop taking varenicline and contact a healthcare provider immediately if they experience agitation, depressed mood, and any changes in behavior that are not typical of nicotine withdrawal, or if they experience suicidal thoughts or behavior. Patients and their families/caregivers should also be alerted to the potential for changes in mood or behaviour during varenicline treatment and report any observed changes to their healthcare provider.

The FDA had also included label warnings on motor vehicle crashes, near-miss accidents and other unintentional injuries occurring in patients taking varenicline. Some of these cases reported somnolence, dizziness and loss of consciousness, or difficulty concentrating. On this basis, patients were advised to be cautious when driving and engaging in potentially hazardous activities until they know how varenicline will affect them.³

(B) Australia Therapeutic Goods Administration (TGA)

As of May 2010, the TGA had received 1,025 reports of suspected adverse reactions to varenicline of which 691 (67%) reported psychiatric symptoms such as depression, agitation, anxiety, altered mood and aggression. 206 cases of suicide-related events and 15 completed suicides in people taking varenicline were also reported to the TGA. The TGA has also urged healthcare professionals to discuss the possibility of these events with their patients and their families.⁴

(C) Health Canada (HC)

Health Canada informed healthcare professionals on 31 May 2010 that it had received serious NP reports such as depressed mood, agitation, aggression, hostility, changes in behaviour, suicide related events and worsening of pre-existing psychiatric disorder in patients treated with varenicline. These events were reported in patients with and without pre-existing psychiatric disorder. Some reported cases were confounded by symptoms of nicotine withdrawal. Alcohol intake was also observed to increase the risk of patients experiencing psychiatric adverse events during treatment with varenicline. HC advised patients taking varenicline to stop treatment and contact their healthcare provider immediately if such NP symptoms were observed.⁵



Reports from literature

1) Cohort study on varenicline and suicidal behaviour

In 2009, Gunnell *et al.* published their findings from a cohort study nested within the General Practice Research Database of UK in the British Medical Journal.⁶ The objective of the study was to determine whether varenicline was associated with an increased risk of suicide and suicidal behaviour compared to bupropion and nicotine replacement therapy (NRT).

A total of 80,660 men and women aged 18-95 years were prescribed a smoking cessation product between 1 September 2006 and 31 May 2008 and were followed up for primary outcomes such as fatal and non-fatal harm, as well as secondary outcomes such as suicidal thoughts and depression.

The results showed that there was no clear evidence that varenicline was associated with an increased risk of fatal or non-fatal self-harm. Compared with NRT, the hazard ratio for self harm among patients prescribed varenicline was 1.12 (95% CI: 0.67 - 1.88).

2) Case series of reports of thoughts and acts of aggression or violence toward others

Moore *et al.* published in the September 2010 issue of the Annals of Pharmacotherapy a case series of reports of thoughts and acts of aggression or violence towards others related to use of varenicline.⁷ The authors obtained 78 adverse event reports from the FDA MedWatch database, four reports from clinical trials and three others from published literature which contained medical terms describing possible acts or thoughts of aggression or violence.

The most frequent and common characteristics of the cases reviewed were: 1) an inexplicable and unprovoked event; 2) the victim of the aggression was anyone nearby; 3) there was no indication of a prior history of similar behaviour in the patient; 4) early onset of psychiatric adverse effects often before stopping smoking. In the 14 cases with dechallenge/rechallenge information, the psychiatric adverse effects resolved in 13 cases (93%) after discontinuation of varenicline.

On studying the characteristics of the reported events, the authors concluded that clear temporal relationship, lack of prior history to aggressive and violent behaviour, and unusual nature of these events strengthen the evidence that varenicline is associated with thoughts and acts of aggression or violence.

Local ADR reports

Since November 2008, the Vigilance Branch of HSA has received 13 ADR reports related to varenicline which have been assessed to be of probable or possible causality. Among these,

continued on Page 5

Summary of safety advisories issued by HSA, pharmaceutical and medical device companies

Summary of Dear Healthcare Professional Letters issued by HSA and/or pharmaceutical companies from November 2009 to November 2010. For details, please log on to MOHAlert via your professional board's website.

20 Jan 2010	— Changes to the prescribing recommendation for therapeutic drug monitoring of Rapamune® (sirolimus) [Wyeth]	7 Jun 2010	— Important update regarding anti-thymocyte globulin (Thymoglobuline®) [Genzyme]
18 Mar 2010	— The association of bevacizumab (Avastin®) with Hypersensitivity reactions and Infusion reactions [Roche]	2 Jul 2010	— Recall of a defective batch of Implanon® implant containing Etonogestrel 68mg [SOL Limited]
23 Mar 2010	— Update on the recent findings of porcine circovirus-1(PCV-1) DNA fragment in Rotavirus vaccine (Rotarix®)	31 Aug 2010	— Urgent Field Safety Notice: DePuy ASR™ Articular Surface Replacement and ASR™ XL Acetabular System [DePuy Orthopaedics]
1 Apr 2010	— Post-marketing reports of renal impairment associated with zoledronic acid 5mg solution for infusion (Aclasta®) [Novartis]	31 Aug 2010	— The recall of the DePuy ASR™ Articular Surface Replacement and ASR™ XL Acetabular System [DePuy Orthopaedics]
16 Apr 2010	— The association of isotretinoin (Roaccutane®) with severe skin reactions [Roche]	6 Sep 2010	— Important safety information regarding Actemra® (Tocilizumab) and Anaphylaxis [Roche]
11 May 2010	— Inappropriate use of and medication errors associated with Exelon® Patch (rivastigmine transdermal patch) [Novartis]	24 Sep 2010	— HSA's advisory on the use of rosiglitazone
18 May 2010	— Recommendations on the use of rotavirus vaccines- Rotarix® and RotaTeq® in Singapore	30 Sep 2010	— Product Recall: Peg-Intron® REDIPEN Injection [SOL Limited]
31 May 2010	— Updates on the Colleague Infusion Pumps in Singapore [Baxter]	11 Oct 2010	— Suspension of Sales of Sibutramine
3 Jun 2010	— Association of WinRho® SDF (Rho(D) Immune Globulin (Human)) with Intravascular Hemolysis (IVH) in the Treatment of Immune Thrombocytopenic Purpura (ITP) [Pharmaforte]	13 Oct 2010	— Suspension of sales of Reductil®, Ectiva® and Reduxade® in Singapore [Abbott]
7 Jun 2010	— Important update regarding imiglucerase (Cerezyme®) [Genzyme]	14 Oct 2010	— Rhinathiol 2% (carbocisteine) Children and Infant Syrup — Contraindication in children below 2 years old [Sanofi-Aventis]
		19 Oct 2010	— Recall of Velocity™ Injection Port and Applier (PT2XV), SAGB Quick Close Swedish Adjustable Gastric Band including Velocity™ Injection Port and Applier (BD2XV) and SAGB VC Swedish Adjustable Gastric Band including Velocity™ Injection Port and Applier (BD23XV) [Ethicon Endo-Surgery]
		16 Nov 2010	— Voluntary recall of "Oral Guard Antiseptic-Antiplaque Mouthwash"

continued from Page 4

■ Update on varenicline (Champix®) and neuropsychiatric events ■

there were two reports describing psychiatric effects such as mood swings, disconnected thoughts, abnormal dreams and depression. No reports of thoughts or acts of aggression or violence towards others were received. It is unknown if the patients were still smoking at the time the adverse reaction occurred.

Of note were three cases which described impaired judgement, impaired mental capability to drive or work and an inability to concentrate. One of these cases resulted in a non-fatal motor vehicle accident.

Other ADRs reported with varenicline included nausea, flu-like symptoms, somnolence, drowsiness, insomnia, loss of appetite, weakness, breathlessness, increased creatine phosphokinase and aggravation of skin allergy.

HSA's advisory

The local package insert of Champix® has been updated with warnings of NP reactions and suicidality. Healthcare professionals are reminded to inform their patients on the potential of occurrence of these NP symptoms, including violent and aggressive thoughts and to ask them to contact their doctor immediately should such symptoms occur. Additionally, in view of the cases of impaired judgement and impaired mental capability reported locally, patients prescribed varenicline should also be cautioned on driving, operating heavy machinery and engaging in potentially hazardous activities until they know how varenicline will affect them.

Healthcare professionals are encouraged to report adverse reactions suspected to be associated with varenicline to the Vigilance Branch. To aid in our assessment of the reports, healthcare professionals are urged to include relevant patient information such as concomitant psychotropic medicines, reactions to smoking cessation, history of mental illness, smoking, alcohol and substance use, suicidal ideation or suicide attempts or recent psychosocial stresses. These information will be useful in the causality assessment of these reports as the association of varenicline as NP symptoms may be confounded by factors such as the effects of nicotine withdrawal, the association of smoking and psychiatric conditions and the effects of smoking on the blood levels of some antipsychotics.

References

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5. Health Canada Dear Healthcare Professional Letter on Champix®. http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2010/champix_2_hpc-cps-eng.php
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Restrictions on the use of rosiglitazone

Restricted access programme and additional contraindications required to minimise cardiovascular risks

HSA is working with GlaxoSmithKline (GSK) to implement restrictions on the use of rosiglitazone in Singapore following the review of additional data about its associated cardiac ischaemic risks made available since our earlier review in 2007. Healthcare professionals will receive more information on the restricted access programme once the details have been finalised.

Rosiglitazone (Avandia®, GSK) is an oral agent for the treatment of type 2 diabetes mellitus. It belongs to the thiazolidinediones class of drugs and has been registered by HSA since 2000 for use as an adjunct to diet and exercise; as monotherapy or in combination with metformin or a sulfonylurea to reduce insulin resistance and lower elevated blood glucose in patients with type 2 diabetes mellitus. Rosiglitazone is also present in two other medicinal products registered in Singapore – Avandamet® (rosiglitazone and metformin) and Avandaryl® (rosiglitazone and glimepiride). To date, Avandaryl® is not marketed locally.



HSA's assessment of cardiovascular (CV) risk associated with rosiglitazone

On 24 September 2010, HSA issued a Dear Healthcare Professional Letter to inform about the new restriction on the use of rosiglitazone. This recommendation arose after an in-depth review, in consultation with the HSA Pharmacovigilance Advisory Committee (PVAC) and an expert panel of cardiologist and endocrinologists. The review took into consideration the findings of the various scientific analyses, including data from meta-analyses (Nissen and Wolski^{1,2}, GSK^{3,4}, US Food and Drug Administration^{5,6}), clinical trials, and observational studies. While the data available have their limitations and may not be completely definitive, a possible increased risk of myocardial ischaemic events associated with rosiglitazone cannot be excluded.

In addition, a review of a placebo-controlled one-year trial in patients with NYHA Class I and II congestive heart failure found a worsening or possible worsening of heart failure occurring in 6.4% of patients treated with rosiglitazone, compared with 3.5% of patients on placebo.⁷ Based on the recommendations of PVAC and the experts, HSA decided to implement additional restrictions to significantly limit the use of rosiglitazone to a group of patients who are unable to effectively control their blood glucose despite use of alternative anti-diabetic medications. This is to minimise the possible CV risks associated with the use of this drug.

Actions taken by other regulatory agencies

(A) US Food and Drug Administration (FDA)⁸

The US FDA had convened an Advisory Committee meeting in July 2010 to review the benefit-risk profile of rosiglitazone and has announced that it would significantly restrict the use of rosiglitazone and would introduce new detailed patient information procedures while it awaits additional information to help further clarify the benefit-to-risk profile of the product. Current users of rosiglitazone may continue with the medication if they are benefiting from it and acknowledge their understanding of the potential risks. New patients will be eligible for rosiglitazone only if they cannot achieve glycemic control with other medications. Doctors will have to attest to and document their patients' eligibility for treatment with rosiglitazone.

FDA is also requiring a re-adjudication of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes (RECORD) trial. This re-evaluation of data is to provide additional clarity about the findings as questions were raised about the potential bias in identification of CV events in this trial in the course of FDA's review

(B) European Medicines Agency (EMA)^{9,10}

The EMA has decided to suspend marketing authorization of the product until additional data becomes available to help further clarify the benefit-to-risk profile of rosiglitazone.

HSA's advisory

Based on current available scientific and clinical data, as well as recommendations from the PVAC and the expert panel of endocrinologists and cardiologists, HSA has assessed that a possible increased risk of myocardial ischaemic events associated with rosiglitazone cannot be excluded. However, it was assessed that the availability of rosiglitazone is still essential for a group of patients who cannot effectively control their blood sugar using

alternative anti-diabetic medications. To further minimise potential CV risks associated with the use of rosiglitazone, additional contraindications and restrictions would be imposed on the use of the drug. These restrictions include:

- 1) *Contraindication of rosiglitazone in patients with acute coronary syndrome, ischaemic heart disease, and all classes of heart failure.*
- 2) *Restriction of rosiglitazone to third-line usage in mono-, dual or triple oral hypoglycaemic therapy.*
- 3) *Recommendation that rosiglitazone is not for use in patients with peripheral arterial disease.*

For patients who are currently taking rosiglitazone, their physician may consider continuing treatment with this medication if the benefit-risk ratio is assessed to be favourable. All patients receiving rosiglitazone should be made aware of the potential CV risks.

HSA is working with GSK to develop and implement a programme to ensure that only selected patients who have been assessed by their doctors to be suitable for treatment receive rosiglitazone.

Healthcare professionals are strongly advised to adhere to the new recommendations when prescribing rosiglitazone and to monitor patients prescribed rosiglitazone closely for CV-related events. Any serious adverse reactions suspected to be related to rosiglitazone should be reported to HSA's Vigilance Branch.

References

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Daptomycin (Cubicin®) and eosinophilic pneumonia

HSA would like to bring to the attention of healthcare professionals the potential risk of patients developing eosinophilic pneumonia during treatment with daptomycin (Cubicin®, AstraZeneca).

Cubicin®, an antibacterial drug belonging to the class of cyclic lipopeptides, has been licensed in Singapore since July 2008 for the treatment of complicated skin and skin structure infections (cSSSI) and *Staphylococcus aureus* bacteraemia, including those with right-sided infective endocarditis.¹

Regulatory actions by the US Food and Drug Administration (FDA)

In July 2010, the US FDA reviewed published case reports of Cubicin®-associated eosinophilic pneumonia and conducted a review of post-marketing adverse event reports from the FDA's Adverse Event Reporting System (AERS).² FDA's review identified six cases of eosinophilic pneumonia reported to AERS between 2004 and 2010 that were most likely associated with Cubicin®. One additional case of eosinophilic pneumonia most likely associated with Cubicin® was identified in the medical literature. These occurred in patients ranging from 60 to 87 years old who were prescribed Cubicin® for off-label indications, including osteomyelitis (n=4), prosthetic hip infection (n=1), enterococcal endocarditis (n=1), and aortic valve endocarditis (n=1).

In all seven cases, eosinophilic pneumonia developed two to four weeks after initiating Cubicin® treatment, and improvement or resolution of symptoms was reported after Cubicin® was discontinued. Five of the seven cases received treatment with systemic corticosteroids. Two cases reported recurrence of eosinophilic pneumonia after Cubicin® was restarted.

FDA also identified a further 36 cases of eosinophilic pneumonia which were possibly associated with Cubicin® use.² Although these cases did not meet the full criteria used by FDA to define a likely association of eosinophilic pneumonia with Cubicin® use, they do provide additional support for a potential causal relationship.

Based on these reviews, FDA assessed that there appears to be a temporal association between Cubicin® administration and the development of eosinophilic pneumonia. FDA had also requested that Cubist, the manufacturer of Cubicin®, update the package insert to include a warning on this association. Cubist has fulfilled FDA's request and updated the US package insert accordingly.



Local situation and HSA's advisory

To date, HSA has received five local adverse drug reaction (ADR) reports associated with Cubicin®. Of these, one case reported eosinophilia, monocytosis and fever in a 79 year-old patient with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia. However, no respiratory symptoms were reported, suggesting that this ADR was likely generalised eosinophilia rather than eosinophilic pneumonia. In addition, the patient was on multiple medications, including vancomycin, which has been associated with eosinophilia.

HSA is working with the company to strengthen the local package insert for Cubicin® to include warnings that reflect the above safety issue. Physicians are advised to monitor their patients carefully for signs and symptoms of eosinophilic pneumonia after initiating Cubicin® treatment, including new onset or worsening fever, dyspnoea, hypoxic respiratory insufficiency, and diffuse pulmonary infiltrates on chest imaging studies. This condition improves when Cubicin® is discontinued and steroid therapy initiated.

Healthcare professionals are also strongly encouraged to report any adverse reactions suspected to be associated with Cubicin® to the Vigilance Branch of HSA.

References

1. Singapore Package Insert for daptomycin (Cubicin®, AstraZeneca).
2. FDA Drug Safety Communication: Eosinophilic pneumonia associated with the use of Cubicin (daptomycin). <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafety/InformationforPatientsandProviders/ucm220273.htm>



Notice to readers

The section on package insert amendments reflecting safety issues will no longer be published in this bulletin. Healthcare professionals are referred to the online publication of the package insert amendments on the HSA website at the following weblink: http://www.hsa.gov.sg/safety-related_label_amendments

Lamotrigine and aseptic meningitis

Overseas post-marketing cases of aseptic meningitis reported in adults and paediatrics treated with lamotrigine have recently been brought to the attention of the Vigilance Branch of HSA.

Lamotrigine (Lamictal® and Lamictal Dispersible®, GlaxoSmithKline) has been licensed for use since September 1993 for the treatment of epilepsy in patients over the age of two, and for the treatment of bipolar disorder in patients above 18 years old. The other generic brands available in Singapore include Apo-lamotrigine® (marketed by Pharmaforte Singapore Pte Ltd) and Lamitor® (marketed by Apotheca Marketing Pte Ltd).

Cases observed by the US Food and Drug Administration (FDA)

In August 2010, the US FDA issued a drug safety communication to warn that aseptic meningitis has been associated with the use of lamotrigine.¹ This observation arose from routine adverse event monitoring where a total of 40 cases of aseptic meningitis occurring in adults and paediatric patients taking Lamictal® were reported from the period December 1994 to November 2009. FDA has requested an update to the Warnings and Precautions section of the US package insert and the Patient Medication Guide to include information on this risk.

Details of the cases of aseptic meningitis

Among the 40 cases of aseptic meningitis reported to the US FDA, headache, fever, nausea, vomiting, nuchal rigidity, rash, photophobia and myalgia were noted. These symptoms occurred one to 42 days (mean: 16 days) after starting Lamictal®. Of the 40 cases, 35 patients (87.5%) required hospitalisation. There was one

report of death, although the cause of death was not thought to be the result of aseptic meningitis.

In majority of the cases, symptoms resolved after Lamictal® was discontinued. However, in 15 cases, a rapid return of symptoms occurring within 30 minutes to 24 hours (mean: 5 hours) following re-initiation of Lamictal® was reported. In these re-challenge cases, symptoms were frequently more severe after re-exposure.



Twenty-five (62.5%) of the aseptic meningitis cases contained data on cerebrospinal fluid (CSF) findings where CSF analysis showed a mild to moderate pleocytosis, normal glucose levels, and mild to moderate increase in protein. In addition, CSF white blood cell count differentials showed a predominance of neutrophils in most cases, although a predominance of lymphocytes was reported in approximately one third of the cases.

Some of these patients who developed aseptic meningitis had underlying diagnoses of systemic lupus erythematosus or other autoimmune diseases which are possible risk factors for aseptic meningitis. In addition, some patients also had new onset of other organ involvement (predominantly hepatic and renal involvement), which may suggest that some of the cases of Lamictal®-associated meningitis were part of a hypersensitivity or generalised drug reaction.

Local situation

Aseptic meningitis is a listed adverse reaction in the local package inserts for Lamictal® and Lamictal Dispersible®. To date, HSA has not received any local reports of aseptic meningitis associated with lamotrigine. Healthcare professionals are advised to be vigilant to the potential development of aseptic meningitis in subjects taking lamotrigine. Signs and symptoms of aseptic meningitis can include headache, fever, nausea, vomiting, nuchal rigidity, rash, photophobia, myalgia, chills, altered consciousness, and somnolence.

Healthcare professionals are encouraged to report any suspected cases of aseptic meningitis associated with lamotrigine to the Vigilance Branch of HSA.

References

1. FDA Drug Safety Communication: Aseptic meningitis associated with use of Lamictal (lamotrigine). <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm221847.htm>

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