

## Reports of lymphadenitis following administration of BCG Vaccine SSI®

HSA would like to update healthcare professionals on the suspected reports of lymphadenitis following the administration of the Bacillus Calmette-Guérin (BCG) Vaccine Staten Serum Institute (SSI)®. This observation arose from the active surveillance and monitoring of vaccine adverse events (VAEs) at the sentinel site at KK Women's and Children's Hospital (KKH).

In 2009, HSA collaborated with KKH to initiate active surveillance for VAEs related to H1N1 vaccines in pregnant women and children. This was subsequently expanded to include all VAEs following childhood immunisation. This active surveillance system is different from the spontaneous adverse drug reaction reporting system in that potential VAEs are identified from patients' medical record and vaccination history when patients are first admitted into the hospital.

In Singapore, BCG vaccine is routinely given to newborns as part of the National Childhood Immunisation Schedule. Since June 2003, the BCG vaccine manufactured by SSI is the sole BCG vaccine registered in Singapore. BCG Vaccine SSI® contains an attenuated strain of *Mycobacterium bovis* (BCG), Danish strain 1331.

### Reports of lymphadenitis

#### A) Local reports (January 2009 to October 2011)

In 2009, there were 26 reports of BCG-associated lymphadenitis of which 23 cases (88%) presented as suppurative lymphadenitis\*. Of these, 22 cases required surgical intervention such as excision or incision and drainage; one case was lost to follow-up. In 2010, there were 25 reports of lymphadenitis. Sixteen cases (64%) presented as suppurative lymphadenitis which required surgical intervention. From January 2011 to October 2011, the reports of lymphadenitis increased to 53. Twenty-seven (51%) of these cases presented as suppurative lymphadenitis, of which 25 cases required surgical excision or drainage. The other two cases resolved without requiring surgical intervention. The remaining 26 cases were non-suppurative cases\*\*. The increase in number of non-suppurative cases captured could be partially due to the opening of a new specialist outpatient clinic at KKH in mid-2011 to specifically review paediatric referrals with mycobacterial infections including those with BCG-related complications through active case-finding.

Chart A provides a breakdown of the reports received from January 2009 to October 2011.

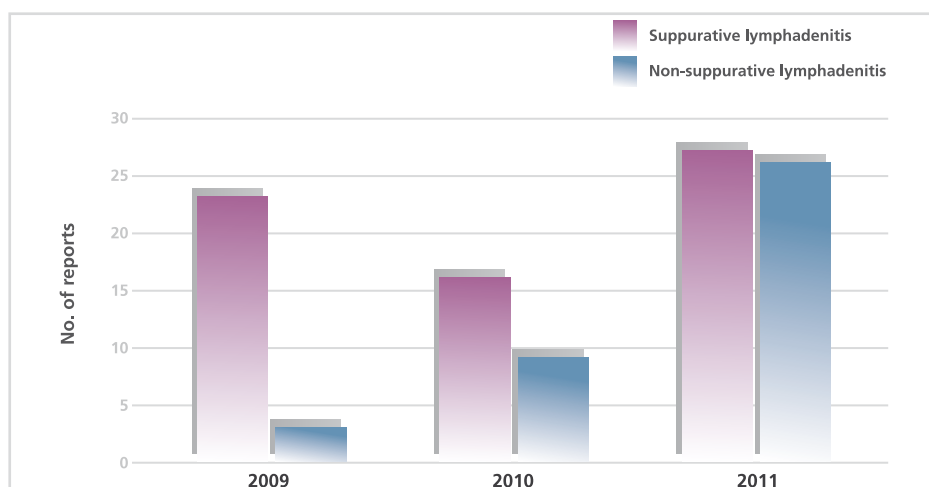


Chart A: Reports of lymphadenitis from January 2009 to October 2011.

\* BCG vaccine-associated suppurative lymphadenitis has been defined as the presence of fluctuation on palpation or pus on aspiration, the presence of a sinus, or large lymph nodes adherent to skin with caseous lesions on excision.<sup>1</sup>

\*\* The figures for 2011 have yet to be finalised as many non-suppurative cases are currently under further observation to determine if the lymph nodes may eventually suppurate or resolve without surgery.



#### B) Overseas reports

An increase in the number of suspected reports of BCG-associated suppurative lymphadenitis has also been identified in some countries such as Ireland and Latvia in recent years. However, the overall rate and pattern of VAEs remain consistent with the expected frequency of occurrence listed in the package insert of BCG Vaccine SSI®.

*continued on Page 2*

## CONTENTS

- Reports of lymphadenitis following administration of BCG Vaccine SSI®... Page 1&2
- Voluntary worldwide recall of drotrecogin alfa (Xigris®) ..... Page 2
- Birth defects in infants associated with *in utero* exposure to long-term, high-dose fluconazole ..... Page 3
- Recent Product Safety-related articles published on HSA website ..... Page 3
- Bleeding events associated with dabigatran etexilate (Pradaxa®) ..... Page 4
- Updates on adulterated health products reported to HSA ..... Page 5
- Suspension of the sales of Zerin® (paracetamol) tablets ..... Page 6
- Summary of safety advisories issued by HSA, pharmaceutical and medical device companies ..... Page 6
- Voluntary recall of Bayer Contour™ TS blood glucose test strips in Singapore ..... Page 7
- HSA's advisory on the use of the ID-Micro Typing System test cell reagent ID-DiaCell I-II-III ..... Page 7
- HSA's advisory on the use of pioglitazone ..... Page 8

continued from Page 1

## ■ Reports of lymphadenitis following administration of BCG Vaccine SSI® ■

HSA has been in contact with regulatory agencies overseas to better understand the trend of BCG-associated lymphadenitis over the past few years observed in their countries and the possible factors that could have contributed to the increase in numbers. The interim finding was that the observed rate of lymphadenitis was likely to be multi-factorial.

### Possible factors influencing BCG-associated lymphadenitis

Studies have revealed that the incidence of suppurative lymphadenitis is dependent on a number of factors including the strain of BCG vaccine and its constituents, host-related factors as well as administration techniques.<sup>2</sup>

Clustering of lymphadenitis in vaccination programmes are commonly associated with a change in vaccine strain, almost invariably to the Pasteur strain 1173P2 or Danish strain 1331. These strains are considered to be more reactogenic than others such as Tokyo strain 172 and Glaxo strain 1077 and more likely to produce large ulcers at the inoculation site and suppurative lymphadenitis.<sup>3-5</sup> It has also been reported that for BCG vaccines in general, the risk of lymphadenitis after vaccination increases with the number of colony forming

units (CFUs) in the vaccine.<sup>3</sup> Host-related factors such as serious immunodeficiency states like severe combined immunodeficiency (SCID) and AIDS are also associated with increased incidence of local as well as systemic disseminated BCG infection after vaccination.<sup>2</sup>

Intradermal administration technique<sup>3</sup> is also one of the determinants of the risk of lymphadenitis, and is most pronounced in infants aged under six months.<sup>6</sup> This is attributed to an increased risk of inadvertent subcutaneous injection for neonatal vaccination. It has been reported that the frequency of BCG-associated VAEs was lower when a papule was visible during the injection, reflecting that the injection was given intradermally.<sup>7</sup> Overdosing during intradermal BCG injection has also been found to increase the risk of VAEs including lymphadenitis, as some neonates receiving larger doses are more likely to overreact to the injection.<sup>7</sup>

### Discussion

Based on the number of local reports received at KKH, the estimated local incidence rates for BCG-associated suppurative lymphadenitis with BCG Vaccine SSI® are 0.58/1,000, 0.43/1,000 and 0.96/1,000<sup>#</sup> for 2009, 2010 and 2011 respectively. From these figures, the cases of suppurative lymphadenitis appear to have doubled this year, possibly attributed to the additional review of paediatric referrals with mycobacterial infections at the new specialist outpatient clinic at KKH.

<sup>#</sup> incidence based on figures to date and not extrapolated to end of 2011.

The incidence of suppurative lymphadenitis observed locally this year is comparable to background incidences reported in literature. The European summary of product characteristics of BCG Vaccine SSI® states that regional lymph nodes larger than 1cm is infrequent (between 1/100 and 1/1000) and that suppurative lymphadenitis is rare (<1/1000). However, the reported incidence of these VAEs varies widely (from 1.9/1000 to 31/1000) in various studies.<sup>7</sup>

In view of the observed trend in the local incidences of suppurative lymphadenitis related to BCG vaccination, the Vigilance Branch will continue to monitor the reports of lymphadenitis closely and review the data when the outcomes and doses administered for the year are finalised.

### HSA's advisory

Intradermal administrative technique plays an important role in minimising BCG-associated complications such as suppurative lymphadenitis. This consideration is important when administering reactogenic vaccines such as the BCG Vaccine SSI®. More details on the administration of the BCG Vaccine SSI® are available on the package insert of the product.

It is also advisable for healthcare professionals to inform parents of possible suppurative lymphadenitis following vaccination so that early treatment can be sought. The median duration of symptoms prior to patient's presentation at the clinic is two months. Healthcare professionals are strongly encouraged to report all suspected VAEs with BCG Vaccine SSI® to the Vigilance Branch of HSA.

### References

1. *Adv Tuberc Res* 1984; 21: 107-93
2. *Postgrad Med J* 2002; 78: 327-329
3. *Bull World Health Organ* 1990; 68(1):93-108
4. *Arch Dis Child* 2006; 91: 594-597
5. *Vaccine* 2005; 23: 2676-2679
6. *Clin Infect Dis* 2002; 34: 447-53
7. *Vaccine* 2009; 27: 6967-6973

The editorial team would like to thank Dr Thoon Koh Cheng, Head and Consultant (Infectious Diseases Services) from the Department of Paediatrics, KKH for his contribution to the above article.

## Voluntary worldwide recall of drotrecogin alfa (Xigris®)

Xigris® [drotrecogin alfa (activated)] was recently recalled from the global market by Eli Lilly and Company and the corresponding local recall of the product took place on 27 October 2011. The recall was due to new clinical trial findings of lack of efficacy of the product.

Xigris® is a recombinant form of human Activated Protein C, and has been licensed locally since August 2002 for use in the reduction of mortality in adult patients with severe sepsis (sepsis associated with acute organ dysfunction) who have a high risk of death.

The recent decision to withdraw Xigris® from the market was based on the results from the PROWESS-SHOCK study, where overall 28-day all-cause mortality was 26.4% in Xigris®-treated patients (n=846) compared to 24.2% in the placebo control group (n=834) with a relative risk of 1.09 (95% CI 0.92-1.28, p=0.31).

The PROWESS-SHOCK was a placebo-controlled study and was conducted to determine if Xigris® treatment provided significant mortality reduction improvement in patients with septic shock compared with placebo treatment. This study also assessed the effectiveness of Xigris® in reducing 28-day mortality in patients with septic shock. While the study showed no survival benefit, no new safety findings were observed. The reason for these unexpected results is not known. However, the company postulated that a contributing factor was the advances achieved in the standard of care for patients with sepsis and septic shock in the 10 years since completion of the original PROWESS trial. This was supported by the fact that the placebo mortality in PROWESS-SHOCK was considerably lower than predicted.

A Dear Healthcare Professional Letter was issued by Eli Lilly to healthcare professionals on 27 October 2011 to advise them to discontinue Xigris® in their patients and not to initiate treatment in new patients.

## Birth defects in infants associated with *in utero* exposure to long-term, high-dose fluconazole



This is an update on the overseas case reports of rare and distinct congenital anomalies in infants exposed *in utero* to chronic high-dose fluconazole during the first trimester of pregnancy.

Fluconazole (Diflucan®, Pfizer) is a triazole antifungal agent licensed locally for the treatment of cryptococcosis, systemic candidiasis, mucosal candidiasis, genital candidiasis, dermatomycosis and the prevention of fungal infections in patients with malignancies who are predisposed to such infections as a result of cytotoxic chemotherapy or radiotherapy. It is also available under several generics brands\*.

\* Generic brands of fluconazole licensed locally include Apo-fluconazole®, DBL fluconazole®, Diflazon®, Exomax injection®, Fluconazole Sandoz Infusion solution®, Fluconazole Redibag Solution for Infusion®, Medoflucon®, Mycorest®, Omastin® and Stalene®.

### US Food and Drug Administration (FDA)

In August 2011, the US FDA issued a drug safety communication informing that chronic, high doses of fluconazole (400 to 800mg/day) may be associated with a rare and distinct set of birth defects in infants born to mothers treated with the drug during the first trimester of pregnancy.<sup>1</sup> This risk does not appear to be associated with a single dose of fluconazole 150mg for treatment of vaginal candidiasis. The US pregnancy category for fluconazole indications (other than vaginal candidiasis) has been changed from category C to D. Pregnancy category D means there is positive evidence of human foetal risk based on human data. However, for high dose fluconazole, the potential benefits from the use of the drug in pregnant women with serious or life-threatening conditions may be acceptable despite its risks.

### Case reports of rare, distinct congenital anomalies

This safety alert by FDA was in response to several reports of rare, distinct congenital anomalies observed in infants whose mothers had received chronic daily treatment with 400mg to 800mg fluconazole during early pregnancy. The features seen in these infants include brachycephaly, abnormal facies, abnormal calvarial development, cleft palate, femoral bowing, thin ribs and long bones, arthrogryposis, and congenital heart disease. These defects are similar to those features observed in people with Antley-Bixler\*\* syndrome, a rare genetic disorder. Similar anomalies were also seen in animal studies following *in utero* fluconazole exposure.

Four of the reports involved the use of intravenous fluconazole for the treatment of coccidioidal meningitis while the fifth report involved a human immunodeficiency virus (HIV)-positive mother receiving oral fluconazole for vaginal candidiasis.

FDA added that available data in medical literature at this point in time do not suggest an association between low-dose oral fluconazole use in the first trimester of pregnancy and congenital anomalies. No consistent pattern of anomalies could be identified

from published epidemiological studies of *in utero* exposure to low doses of fluconazole where most patients received a single dose of 150mg. However, FDA also acknowledged that most of the studies were not large enough to accurately detect an increased risk for major birth defects or a rare or unique birth defect or syndrome.

\*\* *Antley-Bixler syndrome is a very severe, rare, autosomal recessive congenital disorder that is characterised by malformations and deformities affecting majority of the skeleton and other areas of the body*

### HSA's advisory

To date, HSA has not received any local reports of birth defects associated with *in utero* fluconazole exposure. Most of the local package inserts of fluconazole-containing products currently carry warnings on potential birth defects in infants associated with *in utero* exposure to chronic high doses of fluconazole. In view of the latest information, HSA will be working with companies to ensure that warnings on potential birth defects are further strengthened in the local package inserts of these products.

Healthcare professionals are advised to take into consideration the potential risks with long-term, high-dose use of fluconazole when prescribing the medication to women of child-bearing potential. Should chronic high-dose fluconazole be considered the treatment of choice in women of child-bearing potential, healthcare professionals are encouraged to rule out pregnancy and to emphasise the importance of using an effective birth control method. Healthcare professionals are encouraged to report any suspected adverse reactions associated with fluconazole to the Vigilance Branch of HSA.

### References

1. FDA Drug Safety Communication: Use of long-term, high-dose Diflucan (fluconazole) during pregnancy may be associated with birth defects in infants. <http://www.fda.gov/Drugs/DrugSafety/ucm266030.htm>

## Recent Product Safety-related articles published on HSA website

HSA's electronic publications of product safety-related articles are available at <http://www.hsa.gov.sg>.

All healthcare professionals are encouraged to visit HSA's website to access the latest product safety information.

1. HSA warns against taking three health products found to contain potent western medicinal ingredients:
  - a. [冬革阿里] VALL-BOON TONGKAT ALI
  - b. [天麻杜仲七叶参] TIAN MA TU CHUNG SEVEN LEAVE GINSENG
  - c. [保胰康] PAO NI KANG (24 Aug 2011)
2. Drospirenone-containing combined oral contraceptives and risk of venous thromboembolism (26 Sep 2011)
3. Risk of neonatal extrapyramidal signs and/or withdrawal symptoms with antipsychotic drug use during third trimester of pregnancy (26 Sep 2011)
4. 5-alpha reductase inhibitors (5-ARIs) and an increased risk of high grade prostate cancer (3 Oct 2011)

## Bleeding events associated with dabigatran etexilate (Pradaxa®)

Recommendation to use with caution in the elderly and renally-impaired patients

HSA would like to alert healthcare professionals to serious cases of bleeding associated with the use of dabigatran and to remind them to closely monitor patients who are prescribed this medication, especially the elderly and those with renal impairment.

Dabigatran (Pradaxa®) has been licensed locally since August 2009 for the primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip or total knee replacement surgery. In June 2011, the indication for Pradaxa® was extended to include the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

Bleeding is a known side effect for dabigatran as it is an extension of its pharmacological effect. Based on clinical evidence, the risk of major or severe bleeding from dabigatran is rare, even though life-threatening or even fatal outcomes may occur. The local package insert of Pradaxa® currently carries warnings of this risk, including the recommendation to monitor for signs of bleeding or anaemia.<sup>1</sup> Additionally, the local package inserts recommend dose adjustments in the elderly and those with impaired renal function as well as close clinical surveillance in patients with low body weight (<50kg) and high body weight (>110kg). Dabigatran is contraindicated in patients with severe renal impairment.

### Recent advisory issued by the Japanese Ministry of Health, Labour and Welfare (MHLW)

In August 2011, the Japanese MHLW issued a safety advisory to warn of the potential for serious adverse events with dabigatran (Pradaxa®) which was approved in Japan in January 2011. This was following the death of five patients who were taking the drug. Between January and 11 August 2011, the patient exposure in Japan was about 64,000 people. At the time of publication of the advisory, there were 81 cases of serious side effects associated with dabigatran reported in Japan, including cases of gastrointestinal bleeding.

The five patients who had bleeding events contributory to their death were elderly, aged between 76 and 100 years old. They were prescribed with age-adjusted doses of dabigatran. The events leading to death include haemorrhage of the digestive tract, pulmonary alveolar haemorrhage, respiratory failure and haemorrhagic shock. The time to onset for these events ranged from eight days to 104 days. Two of these patients had taken aspirin concomitantly. Based on limited data available and a post-hoc estimation of creatinine clearance (CLcr), four of the patients were suspected to have severe renal impairment while on dabigatran therapy.

Physicians in Japan were advised to carefully monitor for signs of anaemia and bleeding and the need for immediate response should these side effects develop. They were also recommended to perform renal function tests before and during treatment, and to reduce the dose of dabigatran or stop treatment upon signs of renal impairment or bleeding.

### Scientific literature

Two clinical cases of major bleeding events in elderly patients were published in the Archives of Internal Medicine in August 2011.<sup>2</sup> These female patients were both above 80 years old, had moderate to severe renal impairment and had low body weight (≤45kg).



One of them had recurrent nosebleeds that stopped upon discontinuation of dabigatran, while the other developed massive rectal bleeding, had a cardiac arrest and died.

### Actions taken by the European Medicines Agency (EMA)<sup>3</sup>

As of 6 November 2011, a worldwide total of 256 spontaneous case reports of serious bleeding resulting in death in association with the use of dabigatran were recorded in the EudraVigilance database. Twenty-one out of these 256 cases were reported in the EU. EMA has noted that the rapidly increasing use of Pradaxa® worldwide as a result of the recent approval of a new indication (prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation) in several regions of the world and also the increased awareness about the drug could have led to higher than usual reporting of side effects related to the drug. Nonetheless, EMA's Committee for Medicinal Products for Human Use (CHMP) recommended further changes to the product

information in October 2011, including new recommendations for pre- and on-treatment renal assessment in patients prescribed with Pradaxa® to mitigate this safety issue. The CHMP will also review all case reports received to confirm that the frequency of occurrence of fatal bleedings has not increased and that the recommended product information is appropriate to manage the risk.

### Local situation

To date, HSA has received seven suspected adverse reaction reports associated with dabigatran. These included one case of bleeding, one case of deep vein thrombosis and blood clot in the heart and one case of stroke, all occurring in patients between 77 and 86 years old. The time to onset of these cases were a few months after the initiation of dabigatran. No concomitant medicines were reported and none of these cases had a fatal outcome.

### HSA's recommendations

Currently, the post-marketing experience of bleeding events associated with dabigatran has not altered its overall benefit-risk profile. Nevertheless, healthcare professionals are reminded of the contraindication on the use of dabigatran in patients with severe renal impairment (CLcr < 30 ml/min) and to consider the following recommendations when prescribing dabigatran:

#### a) Use in elderly patients with risk factors

In view that the reports were mainly in the elderly and occurred up to several months following the initiation of therapy, close surveillance for signs of bleeding or anaemia is recommended throughout the treatment period, especially for patients with risk factors, such as moderate renal impairment, concomitant antiplatelet therapy, and for patients above 75 years old.

#### b) Renal assessment

Pre-treatment renal assessment should be done to exclude patients with severe renal impairment. While on treatment, renal function should be assessed in certain situations when it is suspected that the renal function could decline or deteriorate (eg, hypovolaemia, dehydration and co-administration of

continued on Page 5

## Updates on adulterated health products reported to HSA

Following the active promotion of adverse event (AE) reporting related to illegal health products via press releases and several roadshows conducted for family physicians, pharmacists and Traditional Chinese Medicine Practitioners (TCMP), 22 dubious health products suspected to cause AEs were reported to HSA's Vigilance Branch between January and November 2011. These products were subsequently confirmed through analytical testing to be adulterated with potent Western medicines. They were packaged as traditional herbal medicines and were reported by astute healthcare professionals and TCMPs, who suspected that their patients suffered from AEs caused by these products. In some cases, the rapid therapeutic effects of the herbal medicines raised the suspicion that they could be adulterated.

Responding to the call to report dubious health products to HSA, healthcare professionals have submitted more reports on such products this year, contributing to a significant increase in the detection of illegal products tested to contain adulterants. Among these products, about 70% were found to contain corticosteroids (eg, dexamethasone and prednisolone) as adulterants and were commonly promoted for the relief of pain and inflammation associated with chronic medical conditions such as arthritis. Due to the high proportion of steroids being used as adulterants in these products, Cushing's syndrome was one of the most common AEs presented by patients who unwittingly consumed such products. The majority of these products were obtained from overseas by the patients or through their family or friends.

Healthcare professionals play an important role in helping HSA detect potential adulterated products. A careful medical history taking, including the consumption of complementary medicines and the duration consumed would be useful in the detection of potential AEs related to these medicines as well as potential drug-herb interactions.

In October 2011, HSA issued a press release to alert the public against taking the following products:

### "ATHRI-Eze" – 人參活絡舒筋丸



"ATHRI-Eze" [人參活絡舒筋丸] was reported by a TCMP, who was suspicious of its rapid therapeutic effect when his patient experienced rapid relief of her chronic arthritic condition after taking it for only two weeks. The product was tested to contain three adulterants—dexamethasone, frusemide and paracetamol. It was promoted as a Traditional Chinese Medicine for the relief of backache, joint and muscular pain.

### "SEAR HEANG TIENCHI TU CHUNG WAN" – 麝香田七杜仲丸



A female patient in her 70's exhibited symptoms of Cushing's syndrome such as a bloated face, and these adverse effects were detected by her family physician. The patient had taken the product for over a year to treat the arthritic pain of her shoulders. The product was obtained by the patient through a friend and was subsequently tested to contain chlorpheniramine and dexamethasone. It was promoted to treat rheumatic pain and backaches.

### "WIKU JAHE KENCUR – AKUR MUJARAB" and "CAP WIJAYA KUSUMA – AN KI IT"



A 70 year-old patient was hospitalised for symptoms of dizziness and low blood pressure when he stopped taking these Jamu products. The adverse effects are likely caused by the sudden withdrawal of prednisolone, which was found as one of the adulterants in "Wiku Jahe Kencur (Akur Majarab)", which he took for about a year.

These two products were promoted as Malay Jamu medicines and were packed as sachets of brown powder. The labels claim to treat rheumatoid and arthritic conditions, swollen legs and stiff joints. The products were bought from overseas. "Cap Wijaya Kusuma (An Ki It)" was tested to contain phenylbutazone and paracetamol while "Wiku Jahe Kencur (Akur Mujarab)" was found to contain allopurinol, prednisolone and chlorpheniramine.

Healthcare professionals are encouraged to visit the HSA website at <http://www.hsa.gov.sg> for more details of the latest press releases and also our new website at <http://www.healthdangersonline.sg> for more information on the dangers of buying health products from dubious online sources.

continued from Page 4

### ■ Bleeding events associated with dabigatran etexilate (Pradaxa®) ■

certain medications). In patients older than 75 years old or with renal impairment, renal assessment at least once yearly is also recommended.

#### c) Anticoagulation tests

While routine monitoring of the anticoagulant effect of Pradaxa® is not required, testing of anticoagulant activity may be required in specific circumstances, such as surgery, overdose and bleeding. This can be done through thrombin time (TT), ecarin clotting time (ECT) and activated partial thromboplastin time (aPTT) tests. If ECT or TT is not available, the aPTT test provides an approximation of Pradaxa's anticoagulant activity. An aPTT of >80 seconds at trough was associated with an increased risk of bleeding when Pradaxa® was used in atrial fibrillation patients in a clinical study. The INR test should not be performed as it is unreliable in patients on Pradaxa®.

HSA is working with the company to strengthen the package insert for Pradaxa® with this information. HSA will also continue to closely monitor this safety concern and update our healthcare professionals on any new findings. All healthcare professionals are encouraged to report all serious side effects suspected to be associated with dabigatran to the Vigilance Branch of HSA.

#### References

1. Pradaxa® (dabigatran) package insert. Singapore approved 24 August 2009
2. Arch Intern Med. 2011;171(14):1285-1286
3. [http://www.ema.europa.eu/ema/index.jsp?curl=pages/news\\_and\\_events/news/2011/11/news\\_detail\\_001390.jsp&mid=WC0b01ac058004d5c1](http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/11/news_detail_001390.jsp&mid=WC0b01ac058004d5c1)

■ Check out our new website on the dangers of purchasing health products from dubious online sources at <http://www.healthdangersonline.sg> ■

## Suspension of the sales of Zerin® (paracetamol) tablets



HSA has recently suspended the licence of Zerin® tablets (containing paracetamol 500mg), manufactured by Jayson Pharmaceuticals Ltd and distributed in Singapore by Ziwell Medical (S) Pte Ltd, due to quality defects. A press release on this suspension was issued on 19 September 2011 to alert members of the public and to advise them to stop consuming the product.

### HSA's findings

HSA has suspended Zerin® tablets due to quality defects recently found with this product. From HSA's ongoing post-marketing surveillance, four reports of product defects regarding Zerin® tablets were investigated since August 2011. Investigations revealed that various batches of Zerin® tablets contained small foreign particles. Testing by HSA's laboratories has shown that the foreign particles were inert, non-toxic substances and assessed to pose minimal risk to consumers. Tests also showed that the paracetamol content in Zerin® tablets complies with registered specifications.

Although the health risk to the individual consumer was assessed to be low, the licence of Zerin® was suspended as a precautionary measure to prevent the exposure of members of the public to a product that is not compliant to quality standards. The sale and distribution of Zerin® tablets to all public healthcare institutions, private medical clinics and pharmacies have been discontinued since August 2011.

### HSA's actions and advisory

HSA has worked with the relevant drug companies and healthcare providers to ensure that there are sufficient supplies of other brands of paracetamol to meet national needs.

As an added precaution, HSA had suspended the local licences of all products manufactured by Jayson Pharmaceuticals Ltd. Besides Zerin® tablets, the other product marketed in Singapore is Histacin® (chlorpheniramine) 4mg tablets. The suspension of licence will disallow further sales of Histacin®.

There are more than ten alternative brands of paracetamol tablets available in Singapore. More information on the available brands of paracetamol tablets may be obtained from the HSA website at <http://www.hsa.gov.sg> using the "Online Information Search (Infosearch)" or "Medicinal & Health Products Search" function.

## 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 December 2010 to November 2011. For details, please log on to *MOHAAlert* via your professional board's website.

7 Dec 2010 – Caution against use of quinine in nocturnal leg cramps [Beacons]

7 Dec 2010 – Recall of Aqualift™ Dermal Filler

29 Dec 2010 – Voluntary recall of Care Wipes, Trihexid Chlorhexidine Mouth Rinse & Pearlie White Fluorinze Fluoride Mouth Rinse

31 Dec 2010 – Voluntary recall of Medisense® Optium™ blood glucose test strips and Optium™ point-of-care blood glucose test strips [Abbott Diabetes Care]

12 Jan 2011 – Voluntary recall of Apo-Warfarin 1mg Tablet (Batch No: JL4994 [Pharmaforte])

28 Jan 2011 – Important information regarding PegIntron® (peginterferon alfa-2b) single dose Redipen® and Intron A® (interferon alfa-2) Multidose Redipen [SOL Limited]

3 Feb 2011 – Presence of blocked needles in some ranibuzumab (Lucentis®) injection administration packs (Lot numbers: S0043, S0047, S0049A, S0049) [Novartis]

24 Mar 2011 – Serious adverse drug reactions related to the consumption of adulterated "Black Pills"

4 Apr 2011 – Important Information Regarding the proper insertion and removal technique for Implanon® (etonogestrel implant) [SOL Limited]

21 Apr 2011 – Recall of certain batches of NovoSeven® for Injection (eptacog alfa) 2.4mg vial to patient level [Novo Nordisk Pharma (S)]

4 May 2011 – New high quality injection needles in ranibuzumab (Lucentis®) injection administration packs [Novartis]

24 May 2011 – Restricted access programme for rosiglitazone-containing products

2 Jun 2011 – Communication on the association of MabThera® (Rituximab) with fatal infusion-related reactions in patients with rheumatoid arthritis [Roche]

9 Jun 2011 – Severe liver injury associated with the use of dronedarone (Multaq®) [Sanofi-aventis]

14 Jun 2011 – Recall of lot P262766 of Baxter's Potassium Chloride (KCl) Injection Highly Concentrated (200 mEq/L) due to failure to meet endotoxin specifications [Baxter]

14 Jul 2011 – Importance of inspecting vaccines for particulate matter or discoloration prior to use [MSD]

14 Jul 2011 – Precautionary recall of certain batches of Navelbine® injection (vinorelbine ditartrate) 10mg/mL [Orient Europharma Pte Ltd]

25 Jul 2011 – Communication on the higher incidence of new cases of ovarian failure observed in premenopausal women treated with Avastin® (Bevacizumab) [Roche]

8 Aug 2011 – HSA's advisory on the use of pioglitazone

8 Aug 2011 – Risk of oral birth defects in infants born to women treated with topiramate (Topamax®) [J&J]

23 Aug 2011 – ID-Micro Typing System test cell reagent ID-DiaCell I-II-III

25 Aug 2011 – Direct Healthcare Professional Communication on the association of Revlimid® (lenalidomide) with venous and arterial thromboembolic events [Celgene]

5 Sep 2011 – Voluntary recall of Bayer's Contour TS Blood Glucose Test Strips in Singapore [Bayer]

19 Sep 2011 – Suspension of the licence of Zerin® (Paracetamol) Tablets 500mg

12 Oct 2011 – Pulmonary arterial hypertension (PAH) reported with Sprycel® (dasatinib) [Bristol-Myers Squibb]

27 Oct 2011 – Withdrawal of Xigris® (drotrecogin alfa (activated)) from the market [Eli Lilly]

8 Nov 2011 – Important safety information on Stratterra® (atomoxetine) and increased blood pressure and heart rate [Eli Lilly]

## **Voluntary recall of Bayer Contour™ TS blood glucose test strips in Singapore**



Bayer Healthcare recently conducted a voluntary recall of the Bayer Contour™ TS blood glucose test strips in certain pack sizes in August 2011. Bayer Contour™ TS test strips are indicated for self-testing of blood glucose by diabetic patients and for healthcare professionals to monitor blood glucose concentrations in their patients. The affected pack sizes of the Bayer Contour™ TS test strips were recalled by Bayer Healthcare as their use may give inaccurate blood glucose results, which may be lower than the actual levels.

### **Background**

Bayer, following its routine internal analysis of their blood glucose products, reported recently to HSA that some patients using Bayer Contour™ TS blood glucose test strips from certain pack sizes may have received inaccurately low test results. The affected pack sizes of test strip vials were as follows :

- a) *2x25-count pack size*
- b) *25-count pack size*
- c) *10-count pack size*

Based on information provided by Bayer, the inaccurate readings were related to a packaging issue which, under certain conditions, could cause some test strips packaged in the smaller pack size vials to produce a reading of blood glucose level which is lower than the actual value. As a precautionary measure, the affected strips were recalled to prevent any potential risk of an erroneous reading that could result in the failure to treat incidences of elevated blood glucose levels. The 50-count pack size, which has been approved by HSA and not associated with similar problems, was introduced as an alternative to replace the above pack sizes.

### **HSA's actions and advisory**

A Dear Healthcare Professional Letter was issued by Bayer in August 2011, warning healthcare professionals of this safety issue. HSA also published a HSA Update on its website to alert the public of the potential safety concerns associated with the use of the affected batches of the test strips.

Patients have been advised to stop using the affected Bayer Contour™ TS test strips and to replace them with the unaffected Bayer Contour™ TS test strips from the 50-count pack sized vials. Bayer had offered replacements for the affected test strips. Healthcare professionals may wish to check if the Bayer Contour™ TS test strips used by their patients are from the affected pack sizes should they suspect that their blood glucose levels are not properly managed. They may also report any suspected defects or erroneous readings resulting from the use of the affected blood glucose test strips to the medical device company.

## **HSA's advisory on the use of the ID-Micro Typing System test cell reagent ID-DiaCell I-II-III**

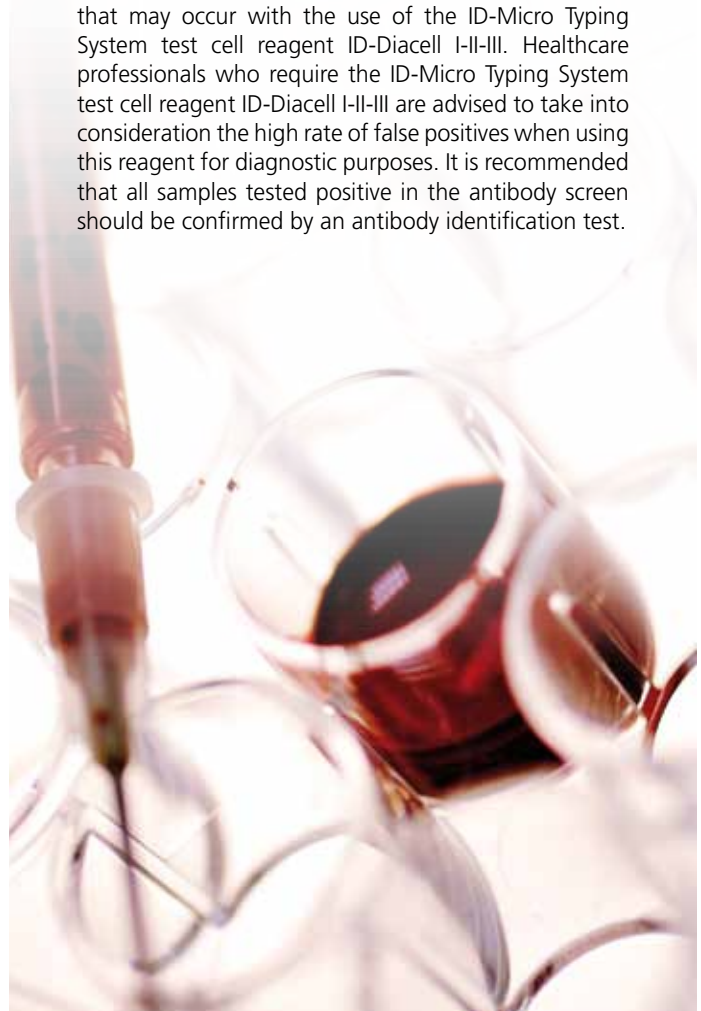
HSA would like to update healthcare professions on the reports it has received relating to the ID-Micro Typing System test cell reagent, ID-DiaCell I-II-III. The ID-Micro Typing System test cell reagent, ID-DiaCell I-II-III, is licensed in Singapore by Bio-Rad Laboratories (Singapore) Pte Ltd for the detection of antibodies that may be present against the antigens on red blood cells during compatibility testing for blood transfusion.

### **Background**

The ID-Micro Typing System test cell reagent ID-Diacell I-II-III consists of human red blood cells from single donors intended for use in antibody screening with the Indirect Antiglobulin Test (IAT) and the NaCl test. Recently, Bio-Rad received reports of an unexpectedly high number of false positive reactions with the use of test cell reagent (cell III) of the ID-Micro Typing System test cell reagent ID-Diacell I-II-III. Bio-Rad has initiated investigations into the possible reasons that may have resulted in these false positive reactions. However, the preliminary tests on the corresponding reference material, using the Bio-Rad ID system, at Bio-Rad manufacturing site have not yet identified the root cause of this problem.

### **HSA's actions and advisory**

HSA had issued a Dear Healthcare Professional Letter in August 2011 to alert healthcare professionals to the potential risks of possible false positive reactions that may occur with the use of the ID-Micro Typing System test cell reagent ID-Diacell I-II-III. Healthcare professionals who require the ID-Micro Typing System test cell reagent ID-Diacell I-II-III are advised to take into consideration the high rate of false positives when using this reagent for diagnostic purposes. It is recommended that all samples tested positive in the antibody screen should be confirmed by an antibody identification test.



## HSA's advisory on the use of pioglitazone



HSA recently conducted a review of the benefit-risk profile of pioglitazone, taking into consideration the new findings of its association with a small increased risk of bladder cancer.<sup>1,2</sup> With advice from its Pharmacovigilance Advisory Committee (PVAC) and an expert panel of endocrinologists and oncologists, HSA concluded that the benefit-risk profile of pioglitazone remains favourable and had provided recommendations to guide doctors on the use of pioglitazone so as to minimise the risk of bladder cancer in patients prescribed with the medicine.

Pioglitazone (Actos®) is manufactured by Takeda and marketed in Singapore by Invida (Singapore) Pte Ltd since 2003. It is indicated for oral monotherapy in type 2 diabetes mellitus patients, particularly in overweight patients, inadequately controlled by diet and exercise and for whom metformin is inappropriate.<sup>3</sup> Pioglitazone is also indicated for oral combination treatment in type 2 diabetes mellitus patients with insufficient glycaemic control despite maximal tolerated dose of oral monotherapy with either metformin or sulphonylureas.<sup>3</sup>

### HSA's assessment of bladder cancer risk associated with pioglitazone

On 8 August 2011, HSA issued a Dear Healthcare Professional Letter to update healthcare professionals on the assessment of bladder cancer risk associated with the use of pioglitazone. The assessment took into consideration an in-depth review of findings from several clinical studies (**PRO**spective pioglit**A**zone **CL**inical **T**rial **I**n macro**V**ascular **E**vents (PR**O**active) study, **K**aiser **P**ermanente **N**orthern **C**alifornia (KPNC) epidemiological study and a French cohort study), as well as consultation with the HSA's PVAC and an expert panel of endocrinologists and oncologists.

Findings from the three studies suggest that the increased risk of bladder cancer associated with pioglitazone cannot be excluded. This is especially so when pioglitazone is used for more than 12 months and over a cumulative dose of more than 28,000mg.

### HSA's advisory

From this review, HSA has assessed that although the increased risk of bladder cancer associated with pioglitazone cannot be excluded, pioglitazone continues to be an important treatment alternative for a selected group of type 2 diabetes mellitus patients who are unable to tolerate or have inadequate response to metformin or sulphonylureas.

The package inserts of pioglitazone will be strengthened with the following restrictions and warnings:

- *The use of pioglitazone is contraindicated in patients with active or history of bladder cancer and in patients with uninvestigated macroscopic haematuria.*
- *Risk factors for bladder cancer should be assessed before initiating pioglitazone treatment. Some of the risk factors include: current or past history of smoking, family history of bladder cancer, exposure to chemicals in the workplace or to certain cancer treatments such as cyclophosphamide and radiation therapy to abdomen or pelvis.*
- *Bladder cancer occurs more commonly in elderly patients and in men compared to women. Caution should be exercised when pioglitazone is prescribed for this group of patients.*
- *Studies-to-date suggest that use of pioglitazone for more than a year may be associated with a small increased risk of bladder cancer.*
- *All patients prescribed pioglitazone should be counselled to seek medical attention if they experience blood in urine, urinary urgency, pain on urination, or back or abdominal pain, as these may be signs and symptoms of bladder cancer.*

Healthcare professionals are advised to review the treatment of patients on pioglitazone after three to six months (and regularly thereafter) to ensure that only patients for which the benefits of using pioglitazone outweigh the risks of bladder cancer continue treatment with pioglitazone. Existing patients on pioglitazone should also be reviewed to ensure that they are suitable candidates for pioglitazone therapy.

HSA is working with the product licence holder to amend the local package insert of pioglitazone to reflect the additional contraindications, warnings and precautions associated with its use. In addition, a patient information leaflet to guide patients on use of pioglitazone will also be developed.

Healthcare professionals are advised to adhere to the new recommendations when prescribing pioglitazone and to report all adverse reactions suspected to be related to pioglitazone to the Vigilance Branch of HSA.

### References

1. <http://www.fda.gov/Drugs/DrugSafety/ucm259150.htm>
2. [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Press\\_release/2011/07/WC500109176.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2011/07/WC500109176.pdf)
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