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HSA Health Sciences Authority

Adverse Drug Reaction News

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Association between *UGT1A1* variant alleles and irinotecan-induced severe neutropenia

HSA would like to share with healthcare professionals information regarding the distribution of genetic variants of the enzyme uridine diphosphate glucuronosyl transferase 1A1 (*UGT1A1*) among the major ethnic groups in Singapore. *UGT1A1* plays an important role in the drug metabolism of irinotecan. The genetic variants are associated with a higher risk of irinotecan-induced severe neutropenia.

Irinotecan is locally registered for the treatment of patients with advanced colorectal cancer and is marketed under the following tradenames Campto® (Pfizer), DBL irinotecan injection concentrate® (Hospira) and Irinotel® (Fresenius Kabi). Common adverse events associated with irinotecan are diarrhoea, vomiting, nausea, and neutropenia. Irinotecan-induced neutropenia can be severe, occasionally leading to hospitalisation because of a significant risk of contracting life-threatening infections.

UGT1A1 variant alleles and their effect on irinotecan metabolism

Irinotecan is converted in the body to a metabolite called SN-38, which is 100 to 1000 times more potent than irinotecan itself.[1] SN-38 is inactivated primarily by UGT1A1 which glucuronidates SN-38 to an inactive metabolite, SN-38G (Figure 1). UGT1A1 is the same enzyme that mediates bilirubin conjugation. Glucuronidating activity is reduced when variants of the *UGT1A1* gene, *UGT1A1*28* or *UGT1A1*6* are present. *UGT1A1*28* contains 7, rather than 6, thymine-adenine (TA) repeats in the *UGT1A1* promoter region and reduces enzyme expression; *UGT1A1*6* represents a nucleotide change from guanine (G) to adenine (A) that causes an amino acid change from glycine to arginine and lowers the enzyme's activity.[2] As a result, patients with these variants have higher blood levels of SN-38 after receiving the same dose of irinotecan.

Polymorphisms in other *UGT* genes as well as *ABCB1*, *ABCG2*, *ABCC2* and *SLCO1B1* genes, which encode proteins involved in irinotecan transport, may also contribute to variation in irinotecan and SN-38 pharmacokinetics and severity of neutropenia, but the evidence is considerably less well developed than for *UGT1A1*6* and **28*.[3-8] No definitive clinical studies have been published yet on the impact of irinotecan dosage adjustment on response rate based on a patient's genotype. This is an active area of clinical research internationally.

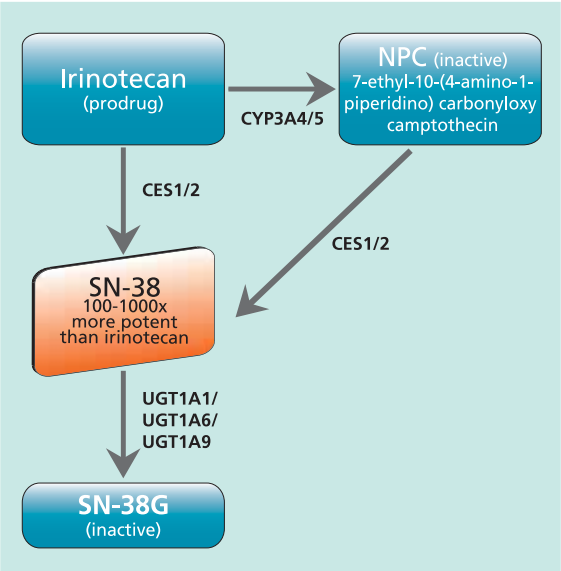

Figure 1 Shown here is part of the complex metabolic pathway of irinotecan.[2] CYP3A4/5 refers to cytochrome P450 3A4 and 3A5. CES1/2 refers to carboxylesterases 1 and 2. UGT1A1 is the main enzyme that catalyzes the conversion of SN-38 to SN-38G.

Regulatory activities in other countries

In 2005, the United States Food and Drug Administration (US FDA) amended the product label for Camptosar®, a brand of irinotecan used in the US, to warn of an increased risk of severe neutropenia among patients who are homozygous for *UGT1A1*28*.[9] This decision was reached after reviewing data from several clinical trials that supported the conclusion of a greater risk of Grade 3 or 4 neutropenia in patients homozygous for *UGT1A1*28*. Their analysis also showed a correlation between plasma concentrations of SN-38 and the probability of experiencing severe neutropenia.[10] Another meta-analysis of nine studies (821 subjects) from North

Photo contributed by National Cancer Centre

America and Europe, published in 2007, confirmed a significant association between *UGT1A1*28* genotype and severe neutropenia at doses greater than 150 mg/m^2, but no association was seen at lower doses (100-125mg/m^2).[11] In 2008, a clinical study from Taiwan demonstrated that patients who were either heterozygous or homozygous for *UGT1A1*28* had a higher rate of neutropenic fever and grade 3 or 4 neutropenia.[12]

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Figure 2 Genotype distribution of *UGT1A1*28*

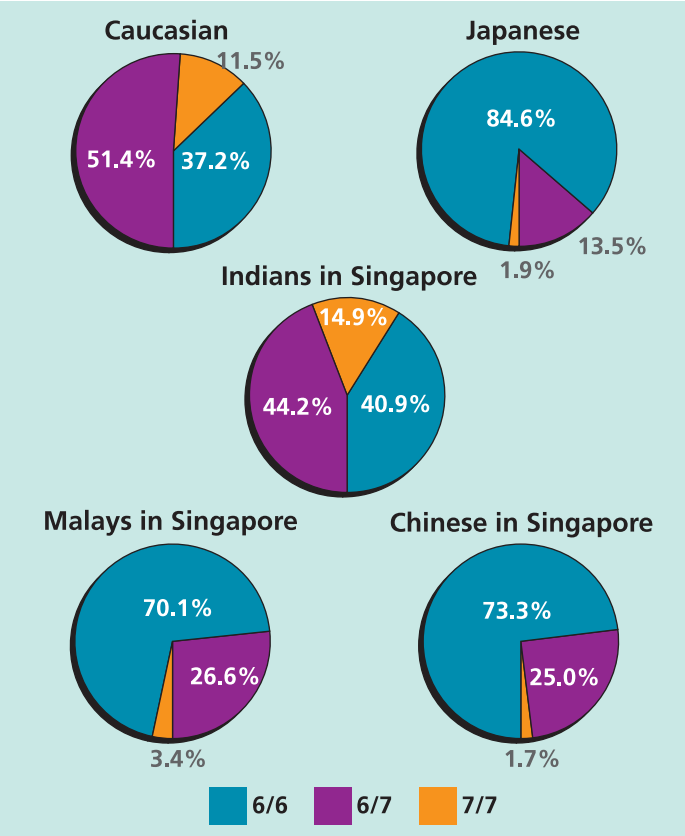
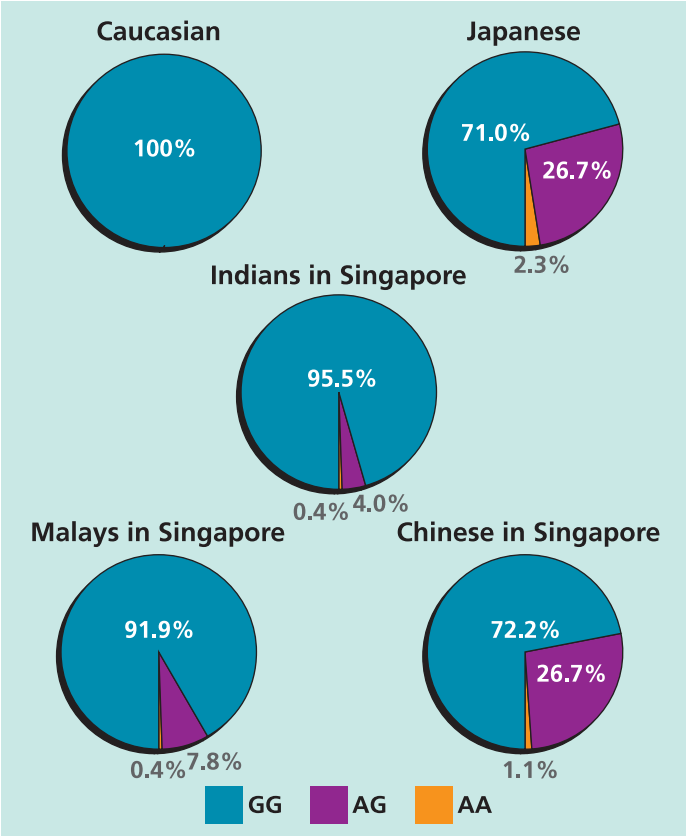


Figure 3 Genotype distribution of *UGT1A1*6*



In Japan, the Pharmaceutical and Medical Devices Agency (PMDA) also examined the evidence for an association between *UGT1A1* variants and neutropenia. The *UGT1A1*28* variant is much less common in Japanese compared to Caucasians (Figure 2). On the other hand, *UGT1A1*6* is not uncommon in Japanese, yet is absent in Caucasians (Figure 3). Clinical data obtained in Japanese who were given irinotecan doses ranging from 60 to 150mg/m^2 demonstrated that patients who were homozygous for *UGT1A1*6* or *UGT1A1*28* or double heterozygotes *(*6/*28)* had a lower ability to inactivate SN-38. Furthermore, the rate of Grade 3 or 4 neutropenia was 80% in homozygotes or double heterozygotes, 24% for *UGT1A1*6* or *UGT1A1*28* heterozygotes and 14% without either *UGT1A1*6* or *UGT1A1*28*.[13,14] In 2008, PMDA updated its product label for irinotecan to alert prescribers of the association between increased risk of serious adverse events and *UGT1A1*6* and **28* variants.[15]

Local Context

HSA has in consultation with the Pharmacogenetics Advisory Committee, reviewed the distribution of *UGT1A1* variants in the three major ethnic groups of Singapore — Chinese, Malay, and Indian using data from the National Cancer Centre[16,17] the National University Hospital,[18] and the Singapore Genome Variation Project.[19] Among Singapore Indians, the genotype distribution of the *UGT1A1*28* variant is comparable to Caucasians (Figure 2), while among Singapore Chinese, the genotype distribution of the *UGT1A1*6* variant is similar to Japanese (Figure 3). The prevalence of double heterozygotes *(*6/*28)* in Singapore is 6.9%, 1.2% and 2.9% in Chinese, Malays and Indians, respectively.[18]

In view of the available evidence of greater risk of irinotecan toxicity associated with *UGT1A1*6* and *UGT1A1*28* variants and its potential impact on our local population, the HSA Pharmacogenetics Advisory Committee has advised that the package inserts for irinotecan be updated.

Consequently, the package inserts of all irinotecan-containing products would be updated to include the following cautionary statements:

*"The active metabolite of irinotecan, SN-38, is metabolized predominantly by UDP-glucuronosyltransferase (UGT). It has been reported that patients who are homozygous (UGT1A1*6/*6 or UGT1A1*28/*28) or heterozygous (UGT1A1*6/*28) in allele UGT1A1*6, UGT1A1*28 of UGT may be at increased risk for serious adverse reactions (especially neutropenia) caused by reduced glucuronidation of SN-38. Added caution should be exercised when administering in such patients."*

A genotyping test for *UGT1A1*6* and *UGT1A1*28* variants is available at the National Cancer Centre, Tel: (6436-8320), and test results will be returned within 48 hours.

The era of genomics is producing an abundance of information about genetic variation within and across populations. As studies gradually dissect the information and establish linkages between genetic variations and response to drugs, they add to a body of knowledge that will help physicians tailor therapies for the individual characteristics of their patients.

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Increased myopathy with combination use of ER niacin/laropiprant (Tredaptive®) and simvastatin 40mg in Chinese patients

Results from interim analysis of HPS2-THRIVE study

HSA has recently been informed by MSD of the results of an interim analysis from an ongoing study, HPS2-THRIVE, which suggest a higher incidence of myopathy observed in Chinese patients on concomitant extended release (ER) niacin/laropiprant 2g/40mg (Tredaptive®, MSD) and simvastatin 40mg (with or without ezetimibe) treatment as compared to Scandinavian and British patients.

ER niacin/laropiprant is a lipid-lowering agent indicated for the treatment of dyslipidemia. It contains a combination of ER niacin, a lipid-modifying agent and laropiprant, a potent, selective antagonist of the prostaglandin D_2 (PGD_2) receptor subtype 1 (DP_1). Laropiprant is a novel agent that is added to the combination to suppress the PGD_2 mediated flushing that is associated with the use of niacin. Tredaptive® has been licensed for use in Singapore since March 2009.

Myopathy

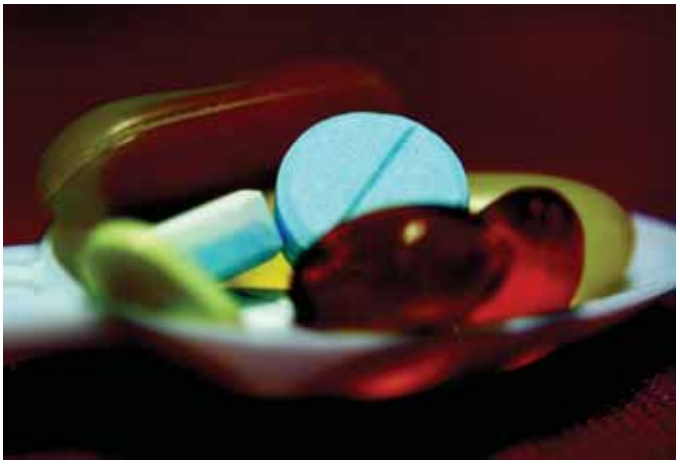
Myopathy and rhabdomyolysis are known adverse effects of HMG-CoA reductase inhibitors (statins), and the risk increases with higher doses and concomitant use of certain CYP3A4 inhibitors such as gemfibrozil and ciclosporin. Clinical trial data from 41,050 patients, whereby approximately 60% of them were treated with simvastatin for at least four years showed that the incidence of myopathy was approximately 0.02%, 0.08% and 0.53% at the doses of 20, 40 and 80mg/day respectively.[1]

HPS2-THRIVE study

HPS2-THRIVE is a double blind, randomised placebo controlled study to assess the long term clinical effects of increasing HDL-cholesterol with ER niacin/laropiprant in 25,000 patients with pre-existing atherosclerotic vascular disease who were receiving simvastatin 40mg daily (plus ezetimibe 10mg daily, where indicated). This study, sponsored by Oxford University, is currently conducted in China, UK and Scandinavia. The study is currently in progress and is expected to be completed in 2012.

(i) Interim safety analysis

An interim analysis conducted by the independent safety monitoring committee



revealed that the incidence of myopathy among approximately 4,700 UK/Scandinavian patients treated with Tredaptive® co-administered with either simvastatin 40mg or ezetimibe/simvastatin 10mg/40 mg is similar to the overall incidence of 0.08% reported in the prescribing information for simvastatin 40 mg.[1] However, in approximately 3,900 Chinese patients in the same treatment arm, the incidence of myopathy is higher than expected, with an approximate incidence of 0.9%. The risk of myopathy was not increased among 8,600 Chinese, UK, or Scandinavian patients in the control arm (placebo plus simvastatin 40mg or ezetimibe/simvastatin 10mg/40mg).

The events of myopathy among Chinese patients resolved with the discontinuation of therapy. No myopathy or rhabdomyolysis related deaths were observed in any patient cohort.

Baseline characteristics of randomised Chinese patients were similar to those of Scandinavian and UK patients except that they tended to be younger, diabetic, abstained from alcohol, had lower Body Mass Indexes (BMIs) and lower total cholesterol. 58% of the Chinese were statin naive as compared to 4% of the Scandinavia/UK patients at the time of screening. It was noted that the use of Traditional Chinese Medicines (TCMs) was more prevalent among Chinese patients with myopathy vis-à-vis all randomised Chinese patients (52.9% vs 37.5%). In addition, the following factors: age > 70 years, female gender and diagnosis of diabetes mellitus at baseline were also found to be more prevalent among Chinese patients with myopathy than among the entire Chinese study population. No trend was observed with other variables such as alcohol use, BMI, type or extent of statin use prior to enrolment and the use of ezetimibe as a component of the background lipid-modifying therapy.

(ii) Conclusion

The reason for the higher rate of myopathy in HPS2-THRIVE in the Chinese cohort who were on concomitant Tredaptive® and simvastatin 40mg with or without ezetimibe 10mg remains unknown currently. HSA is working with the company to update the local product insert of Tredaptive® to highlight this interim data on myopathy gathered from the HPS2-THRIVE study.

HSA's advisory

HSA has not received any local reports of rhabdomyolysis or myopathy associated with Tredaptive® or in combination with statins to date. Physicians prescribing the combined therapy of Tredaptive® with statins are advised to carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months or therapy and when dosage of either drug is increased.

Healthcare professionals are strongly encouraged to report adverse reactions of myopathy associated with Tredaptive® or Tredaptive® with statins combination treatment to the Vigilance Branch of HSA. HSA will continue to monitor the development of this safety issue and update healthcare professionals when new information arises.

References

1. *Singapore Package Insert for simvastatin (Zocor®, MSD)*

Finasteride and potential risk of male breast cancer

HSA would like to bring to the attention of healthcare professionals the potential risk of male breast cancer associated with finasteride.

Finasteride is a competitive and specific inhibitor of Type II 5α-reductase, an intracellular enzyme which metabolises testosterone into the more potent androgen dihydrotestosterone (DHT). The inhibition of Type II 5α-reductase results in a decrease in serum and tissue DHT concentrations.

Finasteride 5mg is indicated for the treatment and control of benign prostatic hyperplasia (BPH) by causing the regression of enlarged prostate thereby improving urinary flow and symptoms associated with BPH. At a lower strength of 1mg, it is indicated for androgenetic alopecia to increase hair growth and prevent hair loss. Finasteride has been licensed in Singapore since 1998 and is available under these brands: Proscar® and Propecia® (MSD); Finast® (Zyfas Medical Co) and Finasteride Mevon® (Novem Healthcare Pte Ltd)

UK Medicines and Healthcare products Regulatory Agency (MHRA)

In December 2009, the UK MHRA completed a review on the risk of breast cancer in men taking different strengths of finasteride for the various medical conditions, and concluded that an increased risk of male breast cancer associated with finasteride use cannot be excluded.[1,2] As a precaution, the package inserts of all finasteride-containing products in the UK were updated to include a warning on the risk of breast cancer.

UK MHRA's assessment

UK MHRA's review took into consideration data from clinical trials as well as post-marketing reports of male breast cancer associated with finasteride. In addition, the review also considered whether there was a plausible biological mechanism for male breast cancer to occur with the use of finasteride.

(i) Clinical trial data analysis

Data from studies of 5mg finasteride were reviewed and these include three placebo-controlled clinical trials of at least four years in duration, uncontrolled open-label extension studies and one short-term (less than one year) placebo-controlled clinical trial. From the data, 11 cases of male breast cancer were observed, of which three occurred in patients treated with placebo. Of the remaining eight cases, there was a case of male breast cancer recurrence in a patient treated with 5mg finasteride during the short-term clinical trial, two cases of male breast cancer in trials of at least one year in duration and five cases of male breast cancer in patients treated with 5mg finasteride during the placebo-controlled clinical trials of at least four years in duration.

In an analysis that included the 10 cases of male breast cancer observed in both controlled and uncontrolled trials of at least one year in duration, although the overall incidence of male breast cancer in patients who received 5mg finasteride was not significantly different compared to patients who received placebo (7.8 per 100,000 patient-years vs. 3.8 per 100,000 patient-years; p=0.328), the data showed that there was a trend towards male breast cancer occurring more frequently in patients who had received finasteride, than in those who did not.

No cases of breast cancer were reported in men treated with 1mg finasteride in controlled trials up to five years in duration as well as in open-extension studies up to six years in duration.

(ii) Post-marketing reports of male breast cancer

As of November 2009, 53 worldwide cases of male breast cancer in patients treated with finasteride have been received by the drug manufacturer, MSD. Of these, 50 occurred in patients aged between 54 to 88 years (mean age: 71 years) treated with Proscar® 5mg while the remaining three cases occurred in patients treated with Propecia® 1mg.

Of the 50 cases of male breast cancer reported with Proscar® 5mg, 14 (28%) reports could be properly evaluated due to inadequate information, in particular the time to onset of breast cancer. The time to onset of breast cancer was estimated to be approximately 44.4 months (median duration: 36 months), based on 36 (72%) reports. Out of these 36 reports, 27 (75%) cases occurred after at least one year of finasteride treatment and nine (25%) cases occurred after less than one year of finasteride treatment.

Of the three cases of male breast cancer reported with Propecia® 1mg, inadequate information and the relatively short times to onset in these cases makes the causal association between male breast cancer and finasteride unlikely. The time to onset of event was three months and six months respectively for two cases but was not known for the third case.

In addition, although finasteride was not approved for use in females, four case reports of female breast cancer were received with "off-label" use of finasteride in the United States. The time to onset in the female breast cancer cases ranged from 6 to 12 months, which were relatively short periods of exposure. It is also important to recognise that under-reporting of adverse drug reactions (ADR) is a recognised limitation as with all ADR-reporting schemes.

(iii) Possible biological mechanism

A possible mechanism to the increased risk of breast cancer with finasteride use could be related to its ability to increase endogenous testosterone and thus oestradiol levels. By inhibiting Type II 5α-reductase, the conversion of testosterone to DHT is prevented, thereby resulting in an increase in testosterone level. As oestrogens in men are derived from the conversion of testosterone to oestradiol and androstenedione to oestrone, an increase in testosterone with finasteride use may lead to a rise in oestradiol levels.

Local Situation

To date, HSA has not received any local reports of male breast cancer associated with finasteride. HSA is currently working with the companies to update the local package inserts of finasteride to include warnings to reflect the above safety issue. Healthcare professionals are advised to inform their patients taking finasteride to promptly report any changes in their breast tissue such as lumps, pain, gynaecomastia or nipple discharge to their doctors.

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

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Sitagliptin – a new class of antidiabetic agents and acute pancreatitis

The Health Sciences Authority (HSA) would like to bring to the attention of healthcare professionals, post-marketing reports of acute pancreatitis in patients treated with Sitagliptin (Januvia®, Janumet®, MSD).

Sitagliptin belongs to a new class of antidiabetic drugs known as dipeptidyl peptidase-4 (DPP-4) inhibitors. The inhibition of the enzyme DPP-4 slows down the inactivation of incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropin polypeptide (GIP) thereby prolonging the action of these hormones in glucose homeostasis. Locally, sitagliptin has been licensed as a single agent, under the brand name Januvia® since April 2007, and as a combination product with metformin under the brand name Janumet® since April 2008.

Post-marketing reports of pancreatitis[1, 2]

Between October 2006 and February 2009, the US Food and Drug Administration (FDA) has been receiving post-market reports of acute pancreatitis in patients treated with sitagliptin and sitagliptin/metformin. As of 9 February 2009, a total of 88 cases of acute pancreatitis were received by the US FDA, including two cases of haemorrhagic or necrotising pancreatitis. The most common adverse events reported were abdominal pain, nausea and vomiting.

Of these 88 cases of acute pancreatitis, hospitalisation was reported in 58 (66%) patients, four of which were critical cases admitted to the intensive care unit (ICU). Both patients with haemorrhagic or necrotising pancreatitis required extended stay in the hospital with medical management in the ICU.

Further analysis of the reported cases found that 19 (22%) cases of pancreatitis occurred within 30 days of starting sitagliptin or sitagliptin/metformin. A positive de-challenge was also seen in 47 (53%) cases where pancreatitis resolved once sitagliptin was discontinued. It was also noted that 45 (51%) of these cases were associated with at least one other risk factor for developing pancreatitis, such as obesity, high cholesterol and/or high triglycerides.

Actions taken by US FDA

The US FDA is working with the company to revise the prescribing information in the package inserts of sitagliptin and sitagliptin/metformin to alert healthcare professionals of this potentially serious adverse event. The prescribing information will be updated to include post-marketing reports of acute pancreatitis such as fatal and non-fatal haemorrhagic or necrotising pancreatitis. Healthcare professionals are also advised to monitor patients carefully for the development of pancreatitis after initiation and dosage increments of sitagliptin, and to discontinue sitagliptin or sitagliptin/metformin if pancreatitis is suspected while using these products.

Sitagliptin has not been studied in patients with a history of pancreatitis. Therefore, it is not known whether these patients are at an increased risk for developing pancreatitis and the medication should be used with caution and with appropriate monitoring in patients with a history of pancreatitis.

Local situation and HSA's advisory

To date, HSA has not received any local reports of acute pancreatitis associated with Januvia® or Janumet®. The local package inserts for Januvia® and Janumet® are being updated with the post-marketing reports of pancreatitis.

Physicians are encouraged to monitor their patients carefully for the development of pancreatitis after the initiation or dosage increments of sitagliptin and to advise their patients taking Januvia® or Janumet® to look out for signs and symptoms of acute pancreatitis including persistent severe abdominal pain which may be accompanied by nausea, vomiting and anorexia. Early recognition is important in reducing adverse health outcomes. When pancreatitis is suspected, Januvia® or Janumet® should be discontinued.

Healthcare professionals are also encouraged to report adverse reactions suspected to be associated with the use of Januvia® and Janumet® to the Vigilance Branch of HSA.

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2. *FDA Information for Healthcare Professionals: Acute pancreatitis and sitagliptin http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm183764.htm*

Illegal product – Huo Luo Jing Dan [活絡金丹] adulterated with undeclared medicinal ingredients

In Dec 2009, HSA issued a press statement to warn consumers not to take an adulterated product labelled "Huo Luo Jing Dan [活絡金丹]". This illegal product was detected through an adverse reaction report submitted by a doctor.

Details of the case report

A 54 year-old Chinese female was hospitalised after she developed difficulty swallowing and was later diagnosed with supraglottic oedema. It was caused by an aggravation of a neck abscess as her infection was not healing well. The doctor also observed that she had Cushingoid features such as "moon face". This prompted the doctor to report his suspicion on the association between the traditional medicine and the adverse effects experienced by the patient.

The patient was reported to have taken Huo Luo Jing Dan (活絡金丹) for 12 years to relieve arthritic pain. The product was packaged as a Traditional Chinese medicine (TCM) to improve circulation, to relieve pain, rheumatism and arthritis. Upon analysis of themproduct sample, three undeclared western medicinal ingredients were detected in the product, namely indomethacin, dexamethasone and prednisolone. The long-term consumption of steroids by the patient could have suppressed her immunity leading to the poor recovery from the infection. The Cushingoid features observed were also signs of long-term steroid consumption.

HSA's advisory

Healthcare professionals are encouraged to ask their patients about the use of complementary medicine while taking their medication history. The information may be useful to the doctor in making a diagnosis of the patient's condition and identifying potential adverse events associated with complementary medicines.

Analysis of adverse event (AE) reports for year 2009

In the year 2009, the Vigilance Branch of HSA received a total of 21,641 local reports of suspected adverse events (AE) to health products. These reports were further screened and a total of 3,715 reports[1] were analysed and captured into the national database. Majority of reports analysed were associated with pharmaceuticals/biologics (90.6%) followed by vaccines (5.9%), complementary medicines (3.4%) and cosmetics (0.1%)

There has been a steady increase in the number of reports received and reviewed year on year. Chart A provides a breakdown of the number of reports analysed from 2000 to 2009 based on date of receipt and percentage of serious reports .

Gender and age

Based on the breakdown of the reports according to ethnic groups, Chinese patients constituted the highest proportion (65.1%), followed by Malays (12.2%) and Indians (11.9%). Majority of AEs were reported to occur in patients in the age group between 50 and 69 years. There were more reports of AEs occurring in females (58.7%) than males.

Source of AE reports

The reviewed reports were mainly from healthcare professionals working in the government clinics (47.9%), followed by public hospitals (39.2%), private clinics/hospitals (7.4%), pharmaceutical companies (5.4%) and community pharmacies (0.03%).

Review of AE reports

Of all the reports reviewed, 48.8% were classified as serious by the reporters.

The top 10 suspected active ingredients commonly reported to cause adverse events are listed in Table 1. Most of the AE reported, as classified by system-organ class were skin-related disorders (22.2%), followed by body as a whole (i.e. general disorders such as pain, fever, oedema) (15.5%), and respiratory disorders (10%). More information is shown in Table 2.

Drugs suspected of causing serious blood, hepatic and skin adverse reactions are listed in Table 3 on page 7.

AE reports associated with H1N1 Pandemic Influenza Vaccines

The H1N1 vaccination programme started on 3 November 2009 with the local distribution of Panvax® followed by Pandemrix®. As of 28 February 2010, approximately 425,000 doses have been distributed, out of which an estimate of 250,000 doses have been administered, with Panvax® being used in the majority of patients. As of 28 February 2010, HSA received 152 reports of suspected vaccine adverse events of which 89% were assessed as non-serious. The median age of the patients was 21 years (range: 5 months to 82 years). The majority of the events occurred within the first three days of vaccination. Table 4 shows a breakdown of the common vaccine adverse events.

Table 1: Top 10 drugs (by active ingredients) suspected of causing AEs

Top	Active Ingredients	No. of reports*
1	Atenolol	205
2	Simvastatin	199
3	Hydrochloro-thiazide	174
4	Amlodipine	117
5	Diclofenac	114
6	Naproxen	86
7	Docetaxel	75
8	Metoclopramide	75
9	Coamoxiclav	73
10	Cotrimoxazole	70

** More than one suspected drug may be implicated in an AE report.*

Table 2: Top 10 AEs by system-organ classes*

Top	System organ class	No. of reports (%**)
1	Skin & appendages	1398 (22.2)
2	Body as a whole	979 (15.5)
3	Respiratory	630 (10)
4	Nervous	581 (9.2)
5	Gastrointestinal	467 (7.4)
6	Metabolic & nutritional	372 (5.9)
7	Vascular (extracardiac)	280 (4.4)
8	Psychiatric	270 (4.3)
9	Musculoskeletal	267 (4.2)
10	Liver and biliary	196 (3.1)

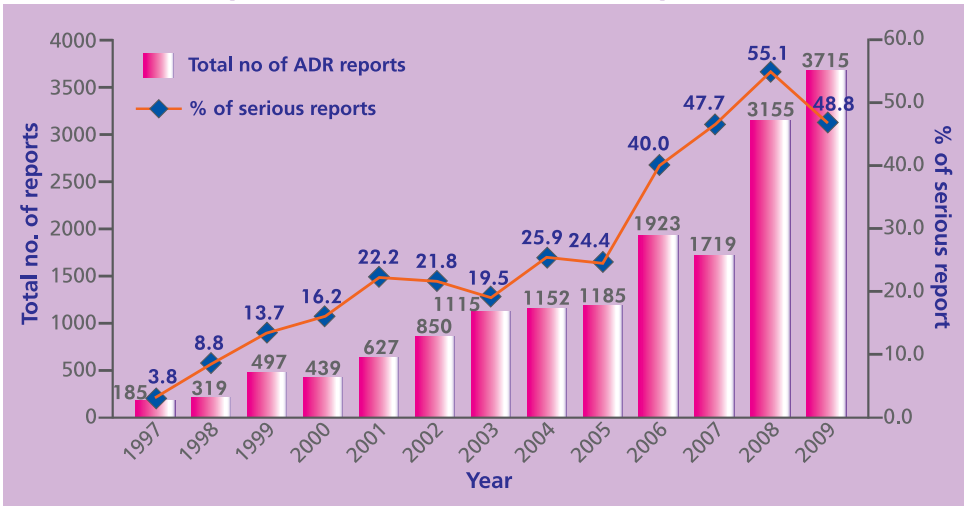
** The system-organ class refers to the adverse reaction terminology developed by the WHO. (NB: More than one AE term may be described in an AE report)*

*** % of total no. of AE terms quoted (n=3687)*

Table 4: Common adverse events associated with Panvax®

Suspected Adverse Event	% of Total Events
Hypersensitivity reactions (skin/respiratory tract)	30
Influenza-like illness	17
Application-site reactions and general disorders (e.g. fever, tiredness)	15
Nervous system disorders (e.g. giddiness, numbness, headache)	13
Musculoskeletal disorders (e.g. myalgia, body aches)	8
Gastrointestinal (e.g. nausea, diarrhoea)	6
Other system organ classes (e.g. urinary, ocular)	11

Chart A: No. of AE reports reviewed based on date of receipt and % seriousness



[1] *Not all reports received were reviewed as many reports lacked important details such as names of suspected drugs and AE descriptions. Non-serious reports such as rash and periorbital oedema were not included in the data analysis.*

continued from Page 6 ■ **Analysis of adverse event (AE) reports for year 2009** ■

Table 3: Drugs suspected of causing serious blood, hepatic and skin adverse reactions

Description	WHO preferred term	**Suspected drug** (number in bracket represents number of times the drug has been implicated+)
Blood disorders	Agranulocytosis/ neutropenia	Clozapine (5), Enalapril (1), Lamivudine (1), Naproxen (1), Omeprazole (1), Phenytoin (2), Sulfasalazine(1), Ticlopidine (1), Aciclovir (1), Aztreonam (1), Caspofungin (1), Ceftriaxone (2), Cisplatin (1), Clopidogrel (2), Dapsone (1), Docetaxel (1), Spironolactone (1), Ticlopidine (1), Tigecycline (2)
	Haemolytic anaemia	Ampicillin (1), Ceftriaxone (1), Dapsone (1), Sulbactam (1)
	Leucopenia	Azathioprine (1), Carbamazepine (1), Ceftriaxone (1), Chloramphenicol (1), Clopidogrel (1), Cotrimoxazole (2), Methimazole (1), Methotrexate (1), Mirtazapine (1), Phenytoin (1), Risperidone (1), Spironolactone (1), Valproate (1), Vancomycin (2), Zidovudine (1)
	Pancytopenia	Amoxacillin (1), Azathioprine (3), Herbal (2), Methotrexate (3), Piperacillin And Tazobactam (1), Sulfasalazine (1), Ticlopidine (1), Zidovudine (1)
	Thrombocytopenia	Anastrozole (1), Carbamazepine (4), Ceftriaxone (2), Chloramphenicol (1), Clozapine (1), Cotrimoxazole (1), Heparin (1), Phenytoin (1), Piperacillin And Tazobactam (2), Valproate (5), Vancomycin (2)
Hepatic disorders	Cholestatic hepatitis	Amoxicillin (1), Simvastatin (1)
	Hepatitis/hepatitis with jaundice	Allopurinol (1), Amlodipine (1), Aspirin (1), Azathioprine (2), Benzathine Benzylpenicillin (1), Carbamazepine (1), Carbimazole (1), Ceftriaxone (2), Chloramphenicol (1), Cloxacillin (1), Cotrimoxazole (1), Efavirenz (2), Fenofibrate (2), Herbal Extracts (4), Ibuprofen (1), Isoniazid (5), Lamotrigine (1), Lovastatin (1), Mycophenolate (1), Nevirapine (1), Paracetamol (1), Phenytoin (1), Pravastatin (1), Propylthiouracil (1), Pyrazinamide (1), Rifampicin (1), Sertraline (1), Simvastatin (8), Sulfasalazine (1), Tetracycline (1)
Skin disorders	Stevens-Johnson syndrome (SJS)/ toxic epidermal necrolysis (TEN)/ SJS-TEN	Aciclovir (1), Allopurinol (7), Alprazolam (1), Amoxicillin (5), Aspirin (1), Atropine (1), Benzylpenicillin or Penicillin (2), Carbamazepine (16), Cefalexin (2), Cefazolin (3), Ceftazidime (1), Ceftriaxone (1), Cefuroxime (1), Ciprofloxacin (1), Clarithromycin (1), Clindamycin (1), Cloxacillin (2), Coamoxiclav (5), Cotrimoxazole (6), Dapsone (1), Diphenoxylate (1), Doxycycline (1), Escitalopram (1), Etoricoxib (1), Fluconazole (1), Frusemide (1), Griseofulvin (1), Irbesartan (1), Lamotrigine (2), Levofloxacin (1), Mefenamic Acid (4), Metronidazole (1), Moxifloxacin (1), Naproxen (1), Nifedipine (1), Omeprazole (1), Paracetamol (2), Phenylbutazone (1), Phenytoin (1), Piperacillin And Tazobactam (1), Risperidone (2), Sulpiride (2), Vancomycin (1)

+ More than one suspected drug may be implicated in a single AE report.

Most of the event reports were not serious and described already known adverse events that are associated with seasonal flu vaccines. This is consistent with the World Health Organisation's (WHO) finding that the safety profile of the pandemic vaccine is similar to what has been seen in seasonal flu vaccines, based on the over 150 million doses of vaccines that have been distributed.

Seventeen reports were assessed as serious by the reporting physicians. They include six reports of allergic reactions of varying severity: a case of anaphylaxis, exacerbation of pre-existing scleritis, Sweet's syndrome, puffy eyes and facial flushing and Churg-Strauss syndrome. Five of these patients have pre-existing medical conditions such as asthma or are known to be allergic to certain medications.

Seven other cases include a case of new onset diabetes, a case of dystonia, a case of persistent vomiting, two cases of facial palsy and two cases of H1N1 infection in patients who received vaccination more than two weeks prior to the onset of influenza illness. It is to be noted that no vaccine or drug is 100% effective and vaccination failure may still occur in certain instances.

Four of the other cases were reported in children and these include a case of high fever, a case of hypotonic-hyporesponsive episode and two cases of seizures. All the patients have since recovered or are recovering.

Other than the reports involving allergies such as anaphylaxis, puffy eyes, facial edema and vomiting which are known occurrences of vaccine adverse events, it cannot be concluded that H1N1 vaccines caused the other serious adverse events as they could be coincident events of natural progression of an underlying disease condition. The causality based on isolated cases of individual events cannot be established definitively as there are no confirmatory tests available for diagnosing an adverse event. Further observations are needed to confirm the causal link.

Reports on adulterated products

Through reports submitted by healthcare professionals, the Vigilance Branch was able to detect drug safety problems associated with adulterated products. These prompted three media alerts with consumer advisories that were issued on illegal traditional medicines found to contain undeclared western medicinal ingredients, namely Air Ikan Haruan (May 2009), Delima Raja Urat & Cao Gen Bai Lin Wan (June 2009), and Huo Luo Jing Dan (December 2009).

The adulterants found in these products were corticosteroids such as dexamethasone, prednisolone; antihistamines such as chlorpheniramine, pheniramine; anti-inflammatory agents such as indomethacin; and/or slimming agents such as sibutramine.

Conclusion

The effectiveness of the national adverse events monitoring programme relies primarily on the active participation of healthcare professionals to submit suspected adverse event reports. In addition, the quality of the report is also important to facilitate the Vigilance Branch to detect potential safety concern of health products in the market.

A recent report published by the WHO's Uppsala Monitoring Centre, the WHO collaborating centre for international drug monitoring programme has placed Singapore in the eighth position in terms of the number of valid adverse event reports contributed to the WHO global database, with an estimation of about 480 reports contributed per million inhabitants per year between 2004 and 2009. The Vigilance Branch would like to take this opportunity to thank healthcare professionals for your participation in the national adverse event monitoring of health products.

Osteonecrosis of the jaw (ONJ) associated with bisphosphonates

The Vigilance Branch of HSA would like to remind healthcare professionals of the risk of osteonecrosis of the jaw (ONJ) associated with the use of oral and intravenous bisphosphonates and also provide an update on the local cases of ONJ that HSA has received with bisphosphonates.

Bisphosphonates are inhibitors of osteoclastic bone resorption, indicated for the treatment of postmenopausal and corticosteroid induced osteoporosis; Paget's disease; hypercalcemia associated with malignancy and osteolysis and bone pain associated with metastatic bone disease. The bisphosphonates registered locally include alendronate, risedronate, clodronate, etidronate, ibandronic acid, pamidronate and zoledronic acid.

Bisphosphonate-related osteonecrosis of the jaw

ONJ, a severe and disabling bone disorder of the jaw, has been reported with the use of bisphosphonates in the medical literature since 2003.[1] To-date, many reports of ONJ from the literature implicate both the intravenous and oral bisphosphonates.[2-4] According to a recent study published in the Journal of Oral Maxillofacial Surgery in 2009, the risk of bisphosphonates-related ONJ is between 1 in 10,000 and 1 in 100,000. This incidence may increase to 1 in 300 after dental extraction.[3] In another article investigating the prevalence of oral bisphosphonate-related ONJ in Asian population, the estimated prevalence of oral bisphosphonate-related ONJ was found to be 0.05% to 0.07%.[4]

The mechanism underlying ONJ is unknown, but it has been postulated that bisphosphonates may inhibit new vessel formation, thereby resulting in impaired healing of the jawbone tissue. Well documented risk factors for ONJ includes a diagnosis of cancer, concomitant therapies (e.g. chemotherapy, radiotherapy, corticosteroids) and co-morbid conditions (e.g. anaemia, coagulopathies, infection, pre-existing oral disease). The typical signs and symptoms include severe jaw pain, soft-tissue swelling and infection, loosening of teeth, and exposed bone.

Local situation

To date, the Vigilance Branch of HSA has received one report of possible osteomyelitis with zoledronic acid use and 11 reports of osteonecrosis associated with several types of bisphosphonates – four after intravenous bisphosphonate use, and seven after oral alendronate use. Of the four reports of osteonecrosis concerning intravenous bisphosphonates, three of the reports

implicated zoledronic acid and one implicated pamidronate. More details of these 12 reports are listed in table 1 below.

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Table 1: Cases of Osteonecrosis associated with bisphosphonates use reported to HSA since 2004

No	Age, Gender	Bisphosphonate used	Indication for bisphosphonate	Description of ADR	Date of onset
1	71, Male	Zometa (zoledronate)	Multiple myeloma	Experiences jaw pain, X-ray and CT scan of mandible showed lytic lesion but no periosteal reaction. Query osteomyelitis	24/05/2004
2	71, Female	Zometa (zoledronate)	Multiple myeloma	Osteonecrosis of anterior maxilla after extraction that progressed to osteomyelitis	20/09/2004
3	66, Male	Zometa (zoledronate)	Multiple myeloma	Osteonecrosis of anterior maxilla and right mandible. Osteomyelitis	17/03/2004
4	64, Female	Pamidronate	Bone metastasis to rib/spine	Osteonecrosis/osteo myelitis of left maxiila.	01/08/2001
5	58, Female	Fosamax	Osteoporosis (Alendronate)	Osteonecrosis with secondary Osteomyelitis of left mandible.	12/01/2005
6	76, Male	Zometa (zoledronate)	Bone metastasis due to prostate cancer	Osteonecrosis of anterior maxilla, stable, 0.5mm exposed	08/07/2004
7	Unknown	Fosamax (Alendronate)	unknown	Osteonecrosis of the jaw	01/01/2007
8	Unknown	Fosamax (Alendronate)	unknown	Osteonecrosis of the jaw; gingival swelling	01/01/2007
9	85, Female	Fosamax Plus (Alendronate, Cholecalciferol (Vit D3))	Osteoporosis	Alendronate therapy was discontinued in Nov 06 when patient experienced bilateral femur shaft fracture. On 18 September 2007, patient was suspected to have developed osteonecrosis of jaw and was referred to a dentist for follow up. The reporter felt that the osteonecrosis of jaw was not related to therapy with alendronate since therapy with alendronate has been discontinued for a long time.	18/09/2007
10	82, Female	Fosamax (Alendronate), Fosamax Plus (Alendronate, Cholecalciferol (Vit D3))	Osteoporosis	Patient started therapy with alendronate sodium for treatment of osteoporosis in 2002 and in 2005, switched therapy to Alendronate + Colecalciferol (Vit D3). The patient complained to reporting physician that she had chronic ulcer in the gum for a year and biopsy indicated finding consistent with ulcer with infection which was subsequently diagnosed as bisphosphonate-related osteonecrosis of the jaw by an ENT specialist	01/01/2007
11	70, Unknown	Fosamax Plus (Alendronate, Cholecalciferol (Vit D3)	Osteoporosis	Osteonecrosis of jaw	01/01/2008
12	Unknown	Fosamax (Alendronate)	Osteoporosis	Osteonecrosis of jaw	01/10/2008

Erythropoietin stimulating agents (ESAs): A safety update

HSA would like to remind healthcare professionals of key safety issues associated with the use of erythropoietin stimulating agents (ESAs). There are four ESAs currently registered in Singapore – epoetin alfa (Eprex®, Johnson & Johnson), epoetin beta (Recormon®, Roche), darbepoetin (Aranesp®, Kyowa Hakko Kirin) and methoxy polyethylene glycol-epoetin beta (Mircera®, Roche). All these ESAs, except Mircera®, are indicated for the treatment of anaemia in patients associated with renal failure and for treatment of anaemia as a result of chemotherapy in cancer patients. Mircera® is licensed locally only for the treatment of anaemia associated with chronic kidney disease.

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■ **Osteonecrosis of the jaw (ONJ) associated with bisphosphonates** ■

HSA's advisory

An article was previously published in the December 2004 issue of the HSA ADR bulletin highlighting osteonecrosis of the jaw with bisphosphonate use.[5] In view of the local reports of bisphosphonate-related ONJ and the fact that its complications may result in significant chronic pain, dysfunction and disfigurement, healthcare professionals are reminded to be aware of the potential risk of ONJ when prescribing bisphosphonates to their patients. Warnings on the risk of ONJ have been highlighted in the local package inserts for all bisphosphonates registered locally.

Healthcare professionals should consider the need for dental examination with appropriate preventive dentistry for patients with concomitant risk factors for ONJ (eg, cancer, chemotherapy, corticosteroids, and poor oral hygiene) before bisphosphonate treatment. Additionally, physicians are advised to inform patients to avoid invasive dental procedures if possible, while on treatment with bisphosphonates. Dental surgery may exacerbate the condition in patients who develop ONJ while on bisphosphonate treatment.

Healthcare professionals are encouraged to report adverse reactions suspected to be associated with the use of bisphosphonates to the Vigilance Branch of HSA

References

1. *J Oral Maxillofac Surg 2003; 61:1104-7*
2. *J Oral Maxillofac Surg 2003; 61:1115-7.*
3. *J Oral Maxillofac Surg 2009 May; 67 (5 suppl): 35-43*
4. *Osteoporosis International 2009 Jul 25.*
5. *HSA ADR News Bulletin. December 2004, Vol 6; No 3*

Safety issues associated with the use of ESAs

Shorter time to tumour progression

Several studies conducted in cancer patients showed higher mortality or shorter time to tumour progression in patients randomized to receive an ESA as compared to placebo. The types of cancers investigated include breast, head and neck, non-small cell lung cancers. In some of these trials, patients were treated with ESA to achieve haemoglobin levels > 12g/dL. This level is higher than the recommended haemoglobin target level for ESA therapy, which is ≤ 12g/dL. Other trials included anaemic patients who were not on chemotherapy or radiotherapy.[2]

Cardiovascular-related adverse events

In 2006, the New England Journal of Medicine (NEJM) published an editorial and two clinical studies (CHOIR and CREATE) in patients with chronic renal failure not on dialysis. The Correction of Haemogloblin and Outcomes in Renal Insufficiency (CHOIR) and Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) trials addressed safety concerns with the use of ESAs in the treatment of anaemia of chronic renal failure (CRF). In these studies, patients who were randomised to receive an ESA to achieve higher haemoglobin levels (13.5g/dL in CHOIR and 13.0 to 15.0g/dL in CREATE) experienced more serious adverse cardiovascular outcomes such as congestive heart failure hospitalisation, non-fatal myocardial infarction, non-fatal stroke as compared to those who received an ESA to achieve lower haemoglobin levels (11.3g/dL in CHOIR and 10.5 to 11.5g/dL in CREATE).

Thrombovascular adverse events

In 2009, the results of a prospective, open-labelled, randomized, parallel-group study at 80 centres were published.[3] The study documented a higher incidence of deep vein thrombosis and similar rates of other clinically relevant thrombovascular events with epoetin alfa versus standard of care for blood conservation in subjects who did not receive prophylactic anticoagulation before spinal surgery. The authors recommended that antithrombotic prophylaxis be considered when erythropoietin is used in the surgical setting.

As ESAs collectively have the same mechanism of action, the above safety concerns are applicable to all ESAs.

Actions taken by other regulatory agencies

In the United States and European countries, the product information of ESAs have been updated to reflect the above safety information.[4] In addition, the US Food and Drug Administration (FDA) also requires all healthcare professionals to discuss the risks associated with the use of ESAs with their patients prior to prescribing ESAs.

Conclusion

To date, there are no local reports of ADR associated with tumour progression or cardiovascular/thrombotic events in cancer patients using ESAs.

The local package inserts of the ESAs carry the above mentioned safety information associated with the use of ESAs. Healthcare professionals are advised that the target haemoglobin concentration for all indications of ESAs should not exceed 12g/dL.

References

1. *http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm126481.htm*
2. *Spine 2009, Nov 1;34(23):2479-85*
3. *http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200297.htm*
4. *http://www.ema.europa.eu/pdfs/human/press/pr/33396308en.pdf*

An update on the National Immunisation Registry (NIR) and H1N1 vaccination records

Introduction

The National Immunisation Registry (NIR) of Singapore is a database system designed to collect and maintain accurate, complete and current vaccination records of children from birth to 18 years of age in Singapore. The objective is to promote effective and cost-efficient disease prevention and control in line with the aims of the National Childhood Immunisation Programme (NCIP).

Physicians can log into the system using accounts linked to their MCR numbers to perform notifications as well as check vaccination details of their patients. Parents can use their SingPass to log into NIR and access their children's vaccination details. This system has been established since 2003 and is the source of data for studies on Childhood Immunisations.

Currently, the system is maintained by the Research & Strategic Planning Division of Health Promotion Board (HPB).

Notification of H1N1 vaccination to NIR

Towards the end of 2009, the NIR system was enhanced to allow for H1N1 vaccination notifications in preparation for the H1N1 vaccination exercise.

Notification can be done through various means: e-reporting through the Health Professional Portal (HPP) and hard-copy forms specially prepared for this purpose.

The patient exposure data is important for the benefit-risk assessment of H1N1 vaccines and this registry of all patients vaccinated would enable the Ministry of Health (MOH) and HSA to keep track of the number of doses administered and calculate the incidence rate of any adverse event that might occur. The data collected would also allow HSA to identify any batch-related quality issue of the vaccines.

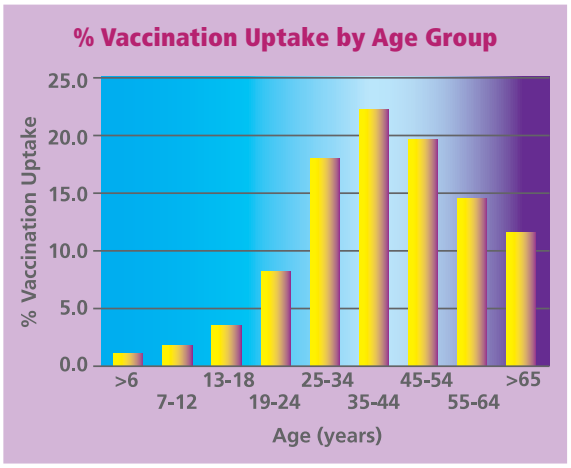

Chart A: Vaccination uptake by age group

As of February 2010, NIR processed records from 1,140 different sources (hospitals, polyclinics, private clinics, etc) and more than 210,000 notifications, out of the 420,000 doses distributed. The vaccination data collected showed that majority of the patients who received the H1N1 vaccination were adults, with the highest uptake in the age group of between 35-44 years. Please refer to Chart A for the detailed categorisation of vaccination uptake by age group.

HSA would like to thank all healthcare professionals for filing the notifications with NIR and strongly encourage those who have not done so to submit H1N1 vaccinee particulars, including the batch number of the vaccine to NIR. The data captured would ensure an accurate profiling of the safety of H1N1 vaccines.

The editorial team would like to thank Mr Andrew Chong, Senior Manager from the Research & Strategic Planning Division of the Health Promotion Board for his contribution to the above article.

Cessation of the marketing of Mediaxal® in Singapore

In May 2009, the French Medicines Agency (AFSSAPS) identified very rare cases of cardiac valvular disorders associated with the use of benfluorex (Mediaxal®, Servier) during its routine post-marketing surveillance. This prompted the re-evaluation of the benefit-risk ratio of the product by the AFSSAPS, which led to the agency's decision to suspend the marketing authorisation of Mediaxal® in France on 24 November 2009 and cease exportations of the product from 30 November 2009. Servier Laboratories has also stopped the marketing of Mediaxal® in Singapore as a consequence of the AFSSAPS' decision.

Background

Benfluorex is an antihyperlipidaemic agent that is used for decreasing the intestinal absorption of triglycerides, decrease lipid synthesis and also facilitate the cellular penetration and utilisation of glucose. It is a derivative of fenfluramine with an appetite suppressant action, which is the reason for its preferential use in overweight type 2 diabetic patients.

Mediaxal® has been marketed in France for at least 30 years as an adjuvant to dietary control in the treatment of overweight type 2 diabetic patients.

Cases of cardiac valve disease

Between its launch in 1976 and September 2009, a total of 45 cases of cardiac valve disease in patients exposed to benfluorex had been reported to the French national pharmacovigilance system. At the end of September 2009, the AFSSAPS was informed of the preliminary results of the REGULATE Study, carried out by Servier laboratories, which had been initiated before the emergence of the safety signal. The objective was to compare the efficacy and safety of two antidiabetic agents, benfluorex and pioglitazone, as adjuncts to sulphonylurea therapy over a 52-week period. A total of 847 type 2 diabetic patients were included. The preliminary results, based on the comparison of echocardiographic examinations at baseline and after 1 year of treatment, showed the emergence of functional valvular abnormalities that were trivial but occurred more frequently with benfluorex than with pioglitazone (26.5% vs. 10.9%; $p<0.0001$). Morphological valve abnormalities were also observed twice as often with benfluorex than with the comparator (2.6% vs. 1.3%; $p<0.264$).

Regulatory actions taken

The French Marketing Authorisation Committee examined all data related to the benefit and risk of benfluorex in its current use conditions as "adjuvant to appropriate diet in overweight diabetics" and concluded that the modest efficacy data in the management of type 2 diabetes does not outweigh the risk of cardiac valve disease. The French Committee hence suspended the marketing authorisation for proprietary medicinal products containing benfluorex with effect from 30 November 2009.

Local situation

Mediaxal® has been registered in Singapore since June 1990 for the treatment of abnormalities of lipid metabolism, which is a different indication from that in France. To date, HSA has not received any adverse reaction reports associated with the use of Mediaxal®.

In view that the cessation of exportation of Mediaxal® from France will affect the supply of Mediaxal® to Singapore, Servier has voluntarily ceased the marketing of this product locally with effect from 30 November 2009. Physicians who have prescribed Mediaxal® to their patients were advised to re-evaluate the treatment of their patients and to switch to appropriate alternative therapies.

Package insert amendments reflecting safety issues

HSA has approved the following package insert changes due to safety updates from May 2009 to September 2009. Please note that due to space constraints, the list published is not exhaustive and you are encouraged to refer to the following website for the complete listing with details **http://www.hsa.gov.sg/safetyinfo_and_recalls.** Please also note that there might be some lag time in the availability of the package insert which reflects the latest change(s)

1. Acetylsalicylic acid, clopidogrel (Coplavix®, Sanofi-Aventis) Special warnings: Patients with genetically reduced CYP2C19 function have lower systemic exposure to active metabolite of clopidogrel & diminished antiplatelet responses, generally exhibit higher cardiovascular event rates following myocardial infarction than patients with normal CYP2C19 function. Drugs that inhibit CYP2C19 may reduce levels of active metabolite of clopidogrel & reduce its clinical efficacy. Possible interaction between clopidogrel & all proton pump inhibitors. Interactions: CYP2C19-inhibitors eg, omeprazole,fluoxetine, fluconazole, ticlopidine, ciprofloxacin.

2. Adefovir (Hepsera®, GSK) Special warnings: Calculate patient's creatinine clearance (CrCL) before initiating therapy. Should not be administered concurrently with tenofovir DF or tenofovir DF- containing products including Truvada® (emtricitabine/tenofovir DF combination tablet) & Atripla® (efavirenz/emtricitabine/tenofovir DF combination tablet). New ADRs: Myopathy, osteomalacia (both associated with renal proximal tubulopathy), hypophosphatemia, pancreatitis, Fanconi syndrome, proximal renal tubulopathy.

3. Alendronate & Alendronate, colecalciferol (Fosamax® & Fosamax Plus®, MSD) Precautions: Caution in patients with active upper GI problems, e.g. dysphagia, oesophageal diseases (including known Barrett's oesophagus), gastritis, duodenitis, or ulcers. Known risk factors ONJ eg, smoking. Interaction: NSAIDs. New ADR: Dysgeusia.

4. Aripiprazole (Abilify®, Bristol-Myers) Precautions: Temporally related leukopenia/neutropenia & agranulocytosis reported. Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) & history of drug-induced leukopenia/neutropenia. Monitor complete blood count of patients with history of clinically significant low WBC or drug-induced leukopenia/neutropenia frequently during 1st few months of therapy & discontinue Abilify® at 1st sign of clinically significant decline in WBC in the absence of other causative factors.

Monitor patients with clinically significant neutropenia for fever or other symptoms/signs of infection & treat promptly. Discontinue Abilify® in patients with severe neutropenia (absolute neutrophil count <1000/mm^3) & follow WBC until recovery.

5. Bicalutamide (Casodex®, AstraZeneca) New ADR: Cholestasis. Rare CV effects eg, angina, heart failure, conduction defects including PR & QT interval prolongations, arrhythmias & non-specific ECG changes observed. Thrombocytopenia reported uncommonly.

6. Ciclosporin (Sandimmun®, Novartis) Special warning: Activation of latent Polyomavirus infections that may lead to Polyomavirus associated nephropathy (PVAN), esp. to BK virus nephropathy (BKVN), or to JC virus associated progressive multifocal leukoencephalopathy (PML) observed in patients receiving ciclosporin. Often related to high total immunosuppressive burden. Consider in differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms. Serious &/or fatal outcome reported.

7. Clozapine (Clozaril®, Novartis) Special precautions: Increased risk of cerebrovascular adverse events seen in dementia population though an increased risk also cannot be excluded for other patient populations. Use with caution in patients with risk factors for stroke & elderly patients with dementia. Studies suggest elderly patients with dementia-related psychosis treated with antipsychotic drugs are at increased risk of death. Risk factors for higher risk of death include sedation, presence of cardiac or pulmonary conditions. Interactions: CYP-450 1A2 inducers eg, tobacco smoke. Plasma clozapine concentration may be increased on sudden smoking cessation. CYP-450 1A2 inhibitors eg, ciprofloxacin. New ADRs: New onset diabetes, obsessive compulsive symptoms, pneumonia & lower respiratory tract infection (potentially fatal).

8. Ethinylestradiol, etonogestrel vaginal ring (Nuvaring®, Schering-Plough) Contraindication: Known pre-disposition for venous or arterial thrombosis, with or without hereditary involvement such as Activated Protein C (APC) resistance, antithrombin-III deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinemia & antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant). Special warnings: Combined oral contraceptive (COC) increases risk of venous thromboembolism (VTE) but increased risk is less than risk of VTE in pregnancy estimated as 6 cases per 10,000 pregnancies. VTE is fatal in 1-2% of cases. Most important risk factor for cervical cancer is persistent human papilloma virus (HPV) infection. Long term use may increase risk but may also be due to confounding effects eg, cervical screening & use of barrier contraceptives. Deterioration of Crohn's disease & colitis ulcerosa reported in association with use of hormonal contraceptives. Interactions: Concomitant use of antimycotic ovules may increase chance of ring disconnection. May decrease plasma & tissue concentrations of lamotrigine. New ADRs: Vaginal infection, hypersensitivity, increased appetite, hypoaesthesia, hot flush, constipation, alopecia, eczema, urticaria, muscle spasms, pain in extremity, dysuria, micturition urgency, pollakiuria, penis disorders, amenorrhoea, breast discomfort, breast enlargement, breast mass, breast tenderness, cervical polyp, coital bleeding, dyspareunia, ectropion of cervix, fibrocystic breast disease, female genital pruritus, menorrhagia, metrorrhagia, pelvic discomfort, Premenstrual syndrome, uterine spasm, vaginal burning sensation, vaginal odour, vaginal pain, vulvovaginal dryness, increased blood pressure, irritability, malaise, oedema, sensation of foreign body.

9. Fluticasone (Avamys® nasal spray, GSK) New ADRs reported post-market: Anaphylaxis, angioedema, rash, urticaria.

10. Fluvoxamine (Faverin®, Solvay) Warnings: Obsessive compulsive disorders (OCD) associated with increased risk of suicide-related events. Conditions may be co-morbid with major depressive disorder. Same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with OCD. Close supervision of patients & those at high risk esp. in early treatment & following dose changes. Clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed increased risk of suicidal behaviour with antidepressants compared to placebo in patients <25 yrs. Use of fluvoxamine associated with development of akathisia, most likely to occur within 1st few weeks of treatment. Increasing the dose may be detrimental in such patients. Nausea, sometimes accompanied by vomiting, is the most frequently observed symptom associated with fluvoxamine treatment. Usually diminishes within 1st 2 weeks of treatment. Withdrawal reactions may occur on stopping therapy. Symptoms reported: dizziness, paraesthesia, headache, nausea & anxiety. New ADRs: Hyperhydrosis, angioneurotic oedema, akathisia/psychomotor restlessness, dysgeusia, micturition disorder, neonatal drug withdrawal syndrome. Cases of suicidal ideation & suicidal behaviours reported during therapy or early after treatment discontinuation.

11. Fusidic acid (Fucidin®, Leo Pharma) Contraindication: Concomitant treatment with statins. Interaction: Co-administration of systemic Fucidin® & HMG-CoA reductase inhibitors causes significantly increased plasma concentrations of both agents which may result in elevation of creatine kinase level & risk of rhabdomyolysis, muscle weakness & pain. New ADR: Rhabdomyolysis.

12. Glucagon (Glucagen®, Novo Nordisk) Contraindication: Hypersensitivity to lactose. Special warnings: Persons given glucagon in connection with diagnostic procedures may experience discomfort e.g. nausea hypoglycaemia & BP changes, esp. if they have been fasting.

13. Haemophilus influenzae type b vaccine (Hiberix®, GSK) Warnings & precautions: Potential risk of apnoea & need for respiratory monitoring for 48-72h should be considered when administering primary immunisation series to very premature infants (born = 28 weeks of gestation) & esp. for those with a previous history of respiratory immaturity. Vaccination should not be withheld or delayed in this group of infants. New ADRs reported post-market: Anaphylactic & anaphylactoid reactions, angioedema, hypotonic-hyporesponsive episode, febrile or afebrile convulsion, syncope or vasovagal responses to injection, somnolence, apnoea in very premature infants (= 28 weeks of gestation), urticaria, extensive swelling of vaccinated limb, injection site induration.

14. Irbesartan (Aprovel®, Sanofi-Aventis) Special warning: Not to be initiated during pregnancy. Unless continued therapy with angiotensin II receptor antagonists considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments with established safety profile for use in pregnancy. When pregnancy is diagnosed, stop treatment immediately, start alternative therapy if required. Pregnancy: Not recommended during 1st trimester. Contraindicated in 2nd & 3rd trimesters.

15. Montelukast (Singulair®, MSD) New ADRs: Upper respiratory infection, hostility, somnambulism, hepatitis (including cholestatic, hepatocellular & mixed-pattern liver injury).

16. Palivizumab (Synagis®, Abbott) New ADRs: Thrombocytopenia, convulsion.

17. Promethazine (DBL Promethazine® inj, Hospira) Contraindications: Intra-arterial administration contraindicated due to likelihood of severe arteriospasm & possibility of resultant gangrene. Subcutaneous administration is contraindicated, as solution is an irritant & may produce necrotic lesions. Precautions: Promethazine is highly caustic to intima of blood vessels & surrounding tissues. IV administration can cause severe tissue injury including gangrene, which may require surgical intervention including fasciotomy, skin graft, &/or amputation. Severe tissue injury may result from perivascular extravasation, unintentional intra-arterial injection, & intraneuronal or perineuronal infiltration. Prescriber should be aware of early sign of tissue injury including burning or pain at injection site, phlebitis, swelling & blistering. Stop injections immediately if symptoms occur. Extreme care is required, if administered via a venous access site in the hand or wrist. All routes of administration can cause damage to tissues. Administer promethazine intravenously if benefits outweigh risks in an individual patient eg, in emergency situations where IM injections are contraindicated. Extreme care must be taken to avoid extravasation or intra-arterial injection. Stop injections immediately if patient complains of pain during injection. Rapid IV infusion may cause transient fall in BP & may increase risk of severe tissue injuries.

18. Sodium valproate (Epilim®, Sanofi-Aventis) Special warning: Counsel female patients of childbearing potential regarding risks associated with pregnancy due to potential teratogenic risk to foetus. Interaction: Panipenem. Undesirable effects: Hyponatraemia & enuresis (very rare). Pregnancy: Increased incidence of minor or major malformations including neural tube defects, craniofacial defects, malformation of the limbs, cardiovascular malformations, hypospadias & multiple anomalies involving various body systems reported in offspring born to mothers with epilepsy treated with valproate.

19. Sorafenib (Nexavar®, Bayer) Special warning: Co-administration of neomycin may cause decrease in sorafenib bioavailability. New ADRs: Hyperthyroidism, interstitial lung disease-like events, SJS.

20. Ticlopidine (Ticlid®, Sanofi-Aventis) New ADRs: Fulminant hepatitis, eosinophilia.

21. Varenicline (Champix®, Pfizer) Warnings & precautions: Serious neuropsychiatric symptoms reported post-market: Changes in mood (including depression & mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, agitation, anxiety, & panic, suicidal ideation, suicide attempt, & completed suicide. Reported cases may have been complicated by symptoms of nicotine withdrawal in patients who stopped smoking. Depression, rarely including suicidal ideation, reported in smokers undergoing a smoking cessation attempt without medication. Symptoms have occurred in patients taking Champix® who continued to smoke, most during treatment, some following discontinuation. Events have occurred in patients with & without pre-existing psychiatric disease; some patients have experienced worsening of their psychiatric illnesses. Safety & efficacy not established in patients with serious psychiatric illness e.g. schizophrenia, bipolar disorder, & major depressive disorder. Hypersensitivity reactions including angioedema, extremities, & neck (throat & larynx) reported post-market. Infrequent reports of life-threatening angioedema requiring emergent medical attention due to respiratory compromise. Other post-market reports: Rare but serious skin reactions, including SJS & erythema multiforme; traffic accidents, near-miss accidents in traffic, or other accidental injuries.

22. Varicella virus vaccine (Varivax®, MSD) New ADRs: Anaphylactic shock, angioneurotic oedema, facial oedema, peripheral oedema. **Varicella-zoster virus vaccine (Zostavax®, MSD)** New ADRs: Arthralgia, myalgia, injection-site rash, injection-site urticaria, transient injection-site lymphadenopathy.

23. Warfarin (Marevan®, GSK) Interactions: Anticoagulant activity may be increased by HMG-CoA reductase inhibitors eg, simvastatin, lovastatin, rosuvastatin, & fluvastatin. Cholestyramine & orlistat may decrease absorption of vitamin K & thus increase coumarin anticoagulant activity. More frequent monitoring of coagulation status may be required in change in intake of some foods, food supplements, vitamin supplements, fruit juices, teas, & herbal medicines (eg, green leafy vegetables, broccoli, cranberry juice, glucosamine) as these may affect anticoagulant response.

Sibutramine and cardiovascular risk – An interim regulatory update

The Vigilance Branch, HSA would like to provide healthcare professionals with an interim regulatory update concerning the recommendation by the European Medicines Agency (EMA) to suspend the marketing authorisation of sibutramine across the European Union on the basis of a large clinical trial, the Sibutramine Cardiovascular OUTcomes (SCOUT) study.

Sibutramine is licensed in Singapore for use as an adjunctive therapy within a weight management programme for obesity (BMI 30kg/m^2 or higher), or overweight patients (BMI 27kg/m^2 or higher) if there are associated obesity-related risk factors such as type 2 diabetes or disorders in lipid metabolism. It is marketed locally as Reductil® (Abbott), Ectiva® (Abbott), Reduxade® (Abbott) and Slenfig® (Apotheca Marketing).

The SCOUT study and regulatory actions taken overseas

The SCOUT study was a randomised, double-blind, placebo controlled study in approximately 10,000 obese and overweight patients with cardiovascular disease and/or type 2 diabetes treated over a six year period. The results of the study showed that patients treated with sibutramine experienced a 16% increased relative risk of cardiovascular events such as myocardial infarction and stroke compared with placebo-treated patients (hazard ratio 1.161 [95% CI 1.029-1.311]; p=0.016).

European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) has completed a review of sibutramine based on new safety information from a large clinical trial, the SCOUT study and concluded that the cardiovascular risks of sibutramine outweighs its benefits. It was found that the mean weight loss achieved with sibutramine in all clinical trials was modest, with sibutramine decreasing body weight by approximately 2-4 kg more than placebo. During the review, CHMP also noted that the use of sibutramine in the SCOUT study for most of the patients was not in accordance with its prescribing information, as sibutramine is contraindicated in patients with known cardiovascular diseases. Nevertheless, the Committee considered that an increased risk can also apply to patients for whom sibutramine could be prescribed because obese and overweight patients are likely to be at risk of cardiovascular disease. Following this recommendation, the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) announced on 21 January 2010 that it would suspend the marketing authorisation of sibutramine.

The US Food and Drug Administration (FDA) also reviewed the data and concluded that there was a small increased absolute risk (11.4% of patients using sibutramine versus 10% of patients using placebo) of heart attacks and strokes in patients with a history of cardiovascular disease who are using sibutramine. The FDA did not suspend marketing authorisation of sibutramine in the US but had requested for the manufacturer to add a new contraindication to the drug label stating that sibutramine is not to be used in patients with a history of cardiovascular disease, including those with a history of coronary artery disease, congestive heart failure, tachycardia, peripheral arterial artery disease, arrhythmia or cerebrovascular disease (stroke or transient ischaemic attack) and inadequately controlled hypertension (>145/90 mmHg). The US FDA is also awaiting the full study report of the SCOUT study before making further regulatory decisions.

Besides the US FDA, other regulatory agencies such as Australia's Therapeutic Goods Administration (TGA) and New Zealand's Medsafe have also not withdrawn sibutramine from their markets.

Local status

In Singapore, all four licensed sibutramine-containing products currently carry sufficient risk warnings on cardiovascular safety. ***Sibutramine is <u>contraindicated</u> in patients with a history of coronary artery disease, congestive heart failure, tachycardia, peripheral arterial artery disease, arrhythmia or cerebrovascular disease (stroke or TIA) and inadequately controlled hypertension (>145/90 mmHg).***

To date, HSA has received three cardiovascular system-related adverse reaction reports that were associated with the use of sibutramine. In these three reports, patients either had a slight elevation in blood pressure or palpitation following the consumption of sibutramine. All three patients have recovered following the discontinuation of the use of sibutramine products.

Healthcare professionals are strongly advised to adhere to the licensed indications of sibutramine and not prescribe the drug to patients with the above mentioned contraindications. Based on our review, sibutramine products in Singapore currently carry sufficient warnings with regard to cardiovascular safety. HSA awaits the full study report to determine if further regulatory actions are needed to minimise the risk associated with the product. Appropriate recommendations will be made upon completion of this review

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