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Adverse Drug Reaction News

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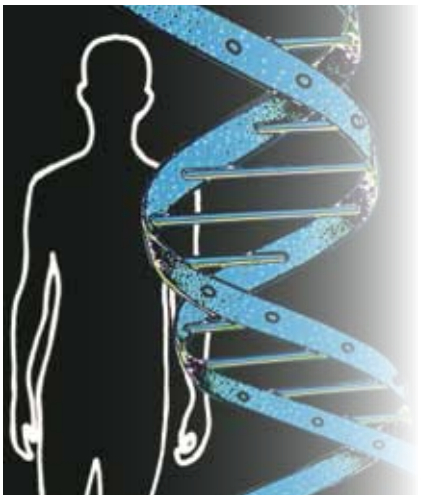
Recommendations for HLA-B*1502 genotype testing prior to initiation of carbamazepine in new patients



The Ministry of Health (MOH) has announced that genotyping for the HLA-B*1502 allele prior to the initiation of carbamazepine (CBZ) therapy in new patients of Asian ancestry is now considered the standard of care. These new recommendations by MOH and HSA have been made in consultation with experts in various fields such as neurology, psychiatry and dermatology, following the review of findings from local and international studies.

CBZ has been registered in Singapore since 1988 and is currently available as Tegretol® (Novartis (Singapore) Pte Ltd) and six generic products. It is indicated for the treatment of epilepsy and other conditions such as diabetic neuropathy, trigeminal neuralgia and bipolar disorders. While CBZ is an effective drug and the drug of choice for several conditions, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which are associated with significant mortality and long-term morbidity, have been reported with its use. Between 2003 and 2012, HSA received 131 local serious reports of CBZ-induced SJS/TEN (average of 15 reports per year). Since the beginning of this year, HSA has received five reports of SJS/TEN associated with the use of CBZ. A one-time HLA-B*1502 genotyping test helps distinguish high-risk patients who should avoid CBZ from low-risk patients who are able to continue to use this low-cost yet effective medicine.

SJS and TEN often begin with flu-like symptoms (fever, sore throat and fatigue), followed by development of a red or purplish rash and painful ulcers of mucous membranes. The skin lesions then progress to epidermal necrosis and detachment. SJS is diagnosed when epidermal detachment involves <10% of the body surface area, TEN when >30% of the body surface epidermal detachment is involved and SJS/TEN when 10-30% of the body surface epidermal detachment is involved. These conditions require hospitalisation and can be life-threatening and even fatal.

Summary of evidence to-date

The basis for these new local recommendations came from strong local and international data supporting an association between HLA-B*1502 and CBZ-induced SJS/TEN:

- A HSA-initiated multi-centre study at Changi General Hospital, Singapore General Hospital and National University Hospital found a strong association between the HLA-B*1502 allele and CBZ-induced SJS/TEN (Odds ratio [OR]=181, p<0.0001). The results are consistent with international data that HLA-B*1502 carriers have an elevated risk of developing SJS/TEN when taking CBZ.
- It is cost-effective to genotype all newly diagnosed epilepsy patients in Singapore and prescribe CBZ to those who are tested negative for HLA-B*1502 as compared to prescribing or avoiding usage of CBZ without knowledge of genotype. This was demonstrated in a study by the Duke-NUS Graduate Medical School, in collaboration with HSA.[1]
- Published studies have documented a strong association between the carriage of HLA-B*1502 allele and risk of CBZ-induced SJS/TEN among Han Chinese in Taiwan and Hong Kong.[2,3] Subsequent smaller scale studies have shown that other Asian ethnic groups such as Malays, Indians and Thais have similar associations.[4-6]
- A large prospective study in Taiwan (n=4,877) found HLA-B*1502 screening prior to the initiation of CBZ therapy to be successful in completely preventing CBZ-induced SJS/TEN.[7]

HSA's actions

HSA, together with MOH, has issued a Dear Healthcare Professional Letter on 30 April 2013 to communicate the new recommendations. Currently, HSA is working with the product licence holders of CBZ products to strengthen the package inserts to reflect the new recommendation that testing for the presence of HLA-B*1502 allele is highly recommended in new patients with Asian ancestry.

HSA's advisory

In view of the new recommendation for CBZ, healthcare professionals are advised to take note of the following:

- CBZ should not be prescribed prior to the return of HLA-B*1502 test results. This is because of the possibility of development and progression of SJS/TEN in susceptible patients even after prompt discontinuation of the drug.
- The use of CBZ should be avoided and treatment alternatives are recommended in patients who are found to be positive for HLA-B*1502. Preliminary data have shown a suspected association between this allele and phenytoin-induced SJS/TEN, although the effect size is not as large.[4,8] As a precaution, patients who are identified to be positive for the HLA-B*1502 allele should also not be prescribed phenytoin.
- Genetic testing should not substitute for appropriate clinical vigilance and patient management. Although rare, patients negative for HLA-B*1502 could still develop SJS/TEN as the role of other factors such as drug dose, concomitant medications and co-morbidities have not been studied.

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Intravenous iron preparations and risk of allergic reactions

Intravenous (IV) iron preparations provide an alternative treatment for iron deficiency in patients who are unable to take iron supplements by mouth, or when oral iron supplements have not been effective. Although the risk of allergic or hypersensitivity reactions with IV iron is rare, these reactions could become serious or fatal if not managed promptly.

Background

There are two IV iron preparations registered in Singapore, which contain complexes of a polynuclear iron-hydroxide core bound to other molecules. Iron sucrose 20mg/mL (Venofer®) is indicated for the treatment of iron deficiency in patients who cannot tolerate or are non-compliant to oral iron therapy, in active inflammatory bowel disease where oral iron preparations are ineffective, or where there is a clinical need for a rapid iron supply. Iron carboxymaltose 50mg/mL (Ferinject®) is indicated for treatment of iron deficiency when oral iron preparations are ineffective or cannot be used. Both products are licensed by Vifor Pharma Asia Pacific Pte Ltd.

In June 2013, the European Medicines Agency (EMA) concluded that IV iron preparations continue to be beneficial, and released new recommendations to minimise the risk of allergic reactions with these preparations.[1] EMA's review of these products was initiated at the request of the French health authority (ANSM), which had reported serious allergic reactions, especially in pregnant women who had received IV iron preparations.

Review by the EMA[1]

Based on its review on IV iron preparations used to treat iron deficiency and anaemia, the EMA's Committee for Medicinal Products for Human Use (CHMP) recommended several measures to allow for the early detection and effective management of allergic reactions that might occur. This included advice that IV iron preparations should only be given in the presence of staff trained to evaluate and manage anaphylactic reactions in an environment with resuscitation facilities, as well as a reminder that caution is warranted with every dose of IV iron that is given, even if previous administrations had been well tolerated.

The CHMP also recommended that IV iron preparations should be avoided during pregnancy unless clearly necessary. In such cases, treatment should be confined to the second or third trimester, provided the benefits of treatment clearly outweighed the risks to the foetus, such as anoxia and foetal distress.

Local situation

Between 2002 and July 2013, HSA has received 20 local ADR reports associated with the use of IV iron sucrose or carboxymaltose preparations, of which 15 were related to allergic or hypersensitivity reactions, including one case of anaphylactic reaction. A further 14 reports were received for iron sucrose where the administration route was not specified. The majority of these reports also involved allergy-type reactions.

HSA is working with the company to strengthen the safety information in the local package inserts of IV iron preparations, including advice on monitoring and management of hypersensitivity reactions related to these products.

HSA's advisory

Healthcare professionals are reminded that all IV iron preparations can cause serious and potentially fatal hypersensitivity reactions. The risk of hypersensitivity is increased in patients with known allergies or immune or inflammatory conditions, as well as in patients with a history of severe asthma, eczema or other atopic allergy. Healthcare professionals are advised to adhere to the following precautions:[1]

- Physician vigilance is advised with every dose of IV iron that is administered. There are data indicating that allergic reactions may still occur even if previous doses were well tolerated.
- IV iron preparations should only be administered in the presence of staff trained to evaluate and manage anaphylactic reactions in an environment where full resuscitation facilities can be assured. The patient should be observed for adverse effects for at least 30 minutes following each administration. If hypersensitivity reactions or signs of intolerance occur, treatment must be stopped immediately and appropriate measures taken to handle such reactions.
- IV iron preparations should be avoided during pregnancy. If clearly necessary, treatment should be confined to the second and third trimester. In many cases, iron deficiency anaemia occurring in the first trimester can be treated with oral iron.

Healthcare professionals are also encouraged to report adverse reactions suspected to be associated with the use of IV iron preparations to the Vigilance Branch of HSA.

Reference

1 *http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/IV_iron_31/WC500144875.pdf*

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■ **Recommendations for HLA-B*1502 genotype testing prior to initiation of carbamazepine in new patients** ■

References

1 *Neurology 2012; 79: 1259-67*
2 *Epilepsia 2007; 48: 1015-8*
3 *Pharmacogenet Genom 2006; 16: 297-306*
4 *Epilepsia 2008; 49: 2087-91*
5 *Indian J Dermatol Venereol Leprol 2009; 75: 579-82*
6 *Asian Pac J Allergy Immunol 2011; 29: 290-3*
7 *N Engl J Med 2011; 364: 1126-33*
8 *Pharmacogenomics 2010; 11: 349-56*

Where to test

The HLA-B*1502 test is available at the NUH Molecular Diagnosis Centre (MDC). Each test costs $187 (excluding GST) and the estimated turnaround time is two to four working days (see below). Subsidised patients from the MOH-funded restructured hospitals and institutions will qualify for a flat rate subsidy of 75% of the cost of the test. Clinicians may send their patients' samples directly to NUH MDC via the NUH Referral Laboratories (NRL), Tel: 6778 5171. For this test, 3 to 5ml of blood is to be collected in a 5-ml EDTA-anti-coagulated sample tube and kept at 4°C before despatch.

Operating hours of NUH MDC

Monday to Friday: 8.30am – 5.30pm
Saturday : 8.30am – 12.30pm
Sunday and public holidays: Closed
Tel: 6772 4384; 6772 4175

Cut-off time for arrival of test sample at NUH
(Note: Specimens received after cut-off time will be subjected to the next batch of testing)
Monday, 3pm; Thursday, 3pm

Corresponding latest despatch time of results

Tuesday, 6.30pm; Friday, 6.30pm

Restricted indications and new contraindication for trimetazidine-containing products

HSA would like to inform healthcare professionals about new restrictions on the use of trimetazidine-containing products arising from Servier's amendments to the local package inserts (PI) of Vastarel® and Vastarel MR®. These amendments, which are initiated by the company, are related to a recent scientific assessment carried out by the European Medicines Agency (EMA) involving the efficacy and safety of trimetazidine. HSA has reviewed these information and deemed the amendments necessary to maintain the positive benefit-risk balance of the products. HSA is also working with the product licence holders of all other locally-registered trimetazidine-containing products to update their PIs accordingly.

Background

Trimetazidine is a metabolic agent that potentiates glucose oxidation and maintains energy metabolism during ischaemia. Locally, trimetazidine has been licensed since 1998 for the treatment of episodes of angina pectoris and adjuvant symptomatic treatment of vertigo and tinnitus (Vastarel® and Vastarel MR®, Servier (S) Pte Ltd). It is also available as generic products, Metagard® (Zyfas Medical Co) and Metazin® (Medipharm Pte Ltd).

On 22 June 2012, the EMA's Committee for Medicinal Products for Human Use (CHMP) completed a review on the benefit-risk balance of trimetazidine-containing products.[1] This review was initiated by France, mainly due to concerns that the effectiveness of trimetazidine had not been convincingly demonstrated in any of the authorised indications. The studies supporting the authorised uses had several methodological weaknesses and only showed a small benefit. Additionally, there were reports of movement disorders such as Parkinsonian symptoms, restless leg syndrome, tremors and gait instability associated with the drug. These symptoms were seen in some patients with no previous history of Parkinsonian syndrome, and patients usually recovered fully within four months after discontinuation of treatment with trimetazidine.

The CHMP reviewed data from clinical studies, the published literature, spontaneous reports of adverse effects and data submitted by the companies that market products containing trimetazidine. Regarding the use of trimetazidine in angina pectoris, the Committee noted that the studies carried out to show its effects had some limitations and were often of short duration. Although the studies did not show that the benefits outweighed the risks for trimetazidine when used alone as first-line treatment, the studies supported the use of trimetazidine as add-on to existing treatments in patients who are not adequately controlled by or intolerant to other drugs for angina pectoris. The CHMP therefore recommended restricting the use of trimetazidine-containing products in the treatment of patients with angina pectoris to second-line, add-on therapy. For all other indications, the CHMP concluded that the benefits were not sufficiently demonstrated and therefore recommended their deletion from the marketing authorisation. In addition, the CHMP recommended new contraindications in patients with Parkinson disease, Parkinsonian symptoms, tremors, restless leg syndrome, and other related movement disorders.

The CHMP also contraindicated the use of trimetazidine in patients with severe renal impairment (creatinine clearance <30mL/min). In patients with moderate renal impairment, a reduced dose of 20mg of the immediate-release formulation twice daily or 35mg of the modified-release formulation in the morning was recommended.

Local situation & HSA's advisory

HSA has reviewed the assessment conducted by the CHMP and the amendments proposed by Servier. HSA's assessment and advisory is as follows:

- Trimetazidine-containing products should only be prescribed in adult patients as add-on therapy for the symptomatic treatment of stable angina pectoris inadequately controlled by first-line anti-anginal therapies or to patients intolerant to such therapy.
- Trimetazidine is no longer indicated for the symptomatic treatment of vertigo, tinnitus and visual field disturbances.
- Trimetazidine is contraindicated in patients with Parkinson disease, Parkinsonian symptoms, tremors, restless leg syndrome, and other related movement disorders.
- The occurrence of movement disorders such as Parkinsonian symptoms, restless leg syndrome, tremors, and gait instability should lead to definitive withdrawal of trimetazidine. A neurologist's opinion should be sought if Parkinsonian symptoms persist for more than four months after discontinuation of treatment.
- Trimetazidine is contraindicated in patients with severe renal impairment. For patients with moderate renal impairment and the elderly, the dose should be reduced.

The local PIs for Vastarel® and Vastarel MR® have been updated in June 2013 to reflect the restricted indications and new contraindication, as well as to strengthen the safety information. The PIs of Metagard® and Metazin® will subsequently be aligned to that of Vastarel®.

Although no local cases of movement disorders associated with the use of trimetazidine have been reported, healthcare professionals are advised to monitor their patients for possible movement disorders such as Parkinsonian symptoms and to discontinue trimetazidine permanently in these patients should such disorders develop.

Healthcare professionals are also encouraged to report adverse reactions associated with the use of trimetazidine to the Vigilance Branch of HSA.

Reference

1 *http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2012/06/WC500129070.pdf*

Check out the new look of the Medical Device Alert circular bringing you updates on cardiovascular implants

Adulterated health products detected from post-marketing surveillance programme

HSA has recently detected several adulterated health products through its regular post-marketing surveillance programme. This included Internet surveillance, product sampling from the market, and reports of adverse events from doctors and members of the public. These products were subsequently tested at the HSA Pharmaceutical Laboratory and found to be adulterated with potent western medicinal ingredients. The various products were promoted for different indications, including pain relief, rheumatism, slimming and skin whitening.

The packaging and presentation of the different adulterated products varied. Some slimming products were disguised as food supplements or beverages, such as "slimming orange juice" and instant drinks with "natural fruit extract". These products were often promoted with claims that the contents were 100% natural, of herbal origin and completely safe. Most of the time, it was difficult to tell that a product was adulterated solely from its appearance, save for the fact that they tended to be from dubious sources (e.g., sold over the internet or peddled by individuals). In other instances, the packaging might raise some suspicion, such as capsules packed in unlabelled zip-lock bags, or cosmetic creams with no ingredients listed on the packaging.

Investigations revealed that these adulterated products were obtained from different sources. Most of the slimming and cosmetic products were sold over the internet, including social media websites. The others were obtained overseas by the patients or through their family or friends, or sold by local retail shops or peddlers.

In June and July 2013, HSA issued three press releases to alert the public against taking the following products:

1 "MONTALIN" Jamu Pegal Linu Dan Asam Urat

An astute doctor had reported that two of her patients suffered from adverse effects after taking "MONTALIN", sold under the guise of traditional Jamu medicine for pain relief. One of the patients, in her 70s, who had taken the product for two weeks, was admitted to the hospital for sudden lower limb and facial swelling. The product was purchased from overseas by her relative. Another patient in her 60s experienced sudden weight gain and hyperglycaemia after three months of taking the product given by her friend.

Although adulteration with steroids was suspected by the reporting physician, testing by HSA detected only piroxicam and paracetamol in the product samples. It is possible that different batches of "MONTALIN" may contain different adulterants.

2 Orange capsules in zip-lock bags accompanied with a leaflet titled "百合保健素"

HSA received feedback from a member of the public who was concerned about the safety of some orange capsules sold by a local Chinese female. The product, to be taken orally or applied on the skin, purported to treat more than 40 medical conditions including arthritis, rheumatism, pneumonia, skin diseases, nephritis and sexually transmitted diseases.

The product was sold in small zip-lock bags of 30 capsules and accompanied with a leaflet titled "百合保健素" describing the indications and ingredients in Chinese, and a name card bearing the seller's contact details. A total of six adulterants were found in the capsules: betamethasone valerate, chlormethiazole, chlorpheniramine, famotidine, frusemide, and piroxicam.

3 Slimming products containing sibutramine

HSA identified the following adulterated slimming products through its ongoing Internet surveillance:

- "VTOX Trim Up" (威特尔健美奇) Weight Loss Program
- "BONJOUR BONSOIR" the stage of weight management
- "CURVY Pearl Beauty" slimming orange juice
- "V12 Fruit Slimming"

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Adulterated health products detected from post-marketing surveillance programme

These products were labelled to contain natural ingredients and claimed to deliver fast results without adverse effects. Sibutramine, which has been withdrawn from the Singapore market due to an increased risk of serious cardiovascular events, was detected in these products. Investigations by HSA revealed that these products had been sourced from overseas and were sold through online platforms such as blogshops, forums and social media.

4 Cosmetic products containing mercury, hydroquinone, tretinoin and salicylic acid

Three types of "Tabita" cosmetic products were tested and found to contain hydroquinone and tretinoin, along with mercury and high levels of salicyclic acid. The three products identified were "Tabita Skincare Smooth Lotion", "Tabita Skincare Daily Cream" and "Tabita Skincare Nightly Cream".

HSA was alerted to these cosmetic products after receiving an adverse event report of a patient who had developed rashes on her face and neck after using "Tabita" products. In a separate report, another patient had concerns regarding the unexpected rapid whitening of the skin after use of the products. These adulterated cosmetic products were sourced from overseas and sold through the Internet.

The three "Tabita" cosmetic products were tested by HSA's Cosmetic Laboratory and found to contain the prescription medicines, hydroquinone and tretinoin, which are prohibited in skincare cosmetic products under the Health Products Act. Mercury and high levels of salicylic acid were also detected. The use of mercury as an ingredient in cosmetic products is also prohibited while cosmetic products are not permitted to contain salicylic acid levels exceeding 2%w/w.

Two other cosmetic products were tested and found to contain mercury, namely "Melati UV Whitening Vit E Cream" and "ESTHER Bleaching Cream (A) and (B)". These products were detected during regular post-marketing surveillance by HSA, and were sold in a number of retail outlets locally. Both products claimed to have effective skin whitening effects, although no ingredients were listed on the packaging.

HSA's advisory

Given the increasing trend of consumers turning to the Internet for purchase of health products, especially those for slimming and cosmetic purposes, healthcare professionals are encouraged to ask their patients about the use of such health products. Very often, patients may not realise that these products may contain medicinal ingredients that could affect their health and will not mention it to their doctors. The information may be important to physicians in making a differential diagnosis of the adverse events experienced by patients.

Healthcare professionals are also encouraged to alert the Vigilance Branch of HSA to any suspected adverse reactions in relation to the use of a health product. Frequently asked questions related to testing of suspected adulterated products are provided on page 6. HSA would like to take this opportunity to thank all healthcare professionals who have alerted us to suspicious health products and helped in our investigations.

What to report? You don't need to be certain, just suspicious!

HSA encourages the reporting of all suspected adverse reactions to drugs and other medicinal substances (including herbal, traditional or alternative remedies). In particular, please report the following:

1 All serious adverse events which:
   a) are life threatening or fatal,
   b) require in-patient hospitalisation or prolong existing hospitalisation
   c) cause persistent or significant disability or incapacity
   d) lead to congenital anomalies
   e) are medically significant

2 All adverse events to recently marketed drugs that have been introduced into Singapore in the recent 5 years, regardless of their nature and severity

Please do not be deterred from reporting because some details are not known. Online reporting is available at h*ttp://www.hsa.gov.sg/ae_online*. Forms can also be downloaded from the same website and submitted via the following methods:

- By mail to *Vigilance Branch* (refer to full address on page 8)
- By fax to *(65) 6478 9069*
- By email to *HSA_productsafety@hsa.gov.sg*

FAQs on the testing of suspected adulterated health products

What should I do if I suspect that a health product is adulterated?

Should a healthcare professional encounter a product which he suspects is adulterated, he could alert the Vigilance Branch (VB) through filling up of an adverse drug reaction (ADR) report. A VB officer would contact the healthcare professional to gather more information, such as details on the patient, product and ADR, to investigate the case and assess the causality. If the criteria for laboratory analysis are met, collection of the product for testing could be arranged.

What are the types of tests available?

Two of the more common screening tests are screening for common poisons and toxic heavy metals. The common poisons test screens for common western drug classes such as analgesics, antipyretics, antibiotics, androgenic steroids, anti-asthmatics, antihistamines, anti-inflammatory agents, corticosteroids, CNS stimulants and anorectics, erectogenic agents, oestrogenic steroids, progestogenic steroids, and thyroid agents. Quantification tests for toxic heavy metals such as copper, lead, mercury, arsenic and cadmium are performed to determine if these have exceeded permissible limits.

Will HSA conduct testing for all suspected health products?

Testing of suspected health products can be conducted by HSA if it has been determined that laboratory analysis of the product is warranted as part of its investigations. Alternatively, the healthcare professional could send the product for testing, with the patient bearing the full cost of testing incurred.

HSA's decision on conducting testing for suspected health products is based on the strength of causality between the ADR and the suspected health product, in addition to the public health impact. Information related to the ADR and patient, as well as the product, will be important for our assessment (e.g., identifiable source of purchase, availability of package labelling or insert).

Examples of reports with a high index of suspicion that the product is adulterated and has contributed to the ADR include a product from a dubious source suspected to contain steroids resulting in Cushing's syndrome, or a patient experiencing rapid pain relief within the first few doses of taking the product. Upon completion of its investigations, HSA will take appropriate regulatory actions as deemed necessary to safeguard public health, such as the issuance of a press release to warn the public of the adulterated products, recalling the affected product, or tracing the source of the adulterated products.

In cases where HSA has assessed that the ADR may more likely be related to other causes (e.g., when confounding factors such as underlying disease or concomitant drugs could have caused the ADR, or when the product is from a reputable source and less likely to be adulterated), it is unlikely that HSA will test the product for adulterants. Instead, HSA will investigate the other causes suspected to be related to the ADR. Under this scenario, testing can be conducted if requested by the healthcare professional or patient, bearing in mind that the cost of testing will be borne by the patient.

What information does HSA require?

Healthcare professionals can aid in our investigations by providing us with the following information, where available:

- Patient details (e.g., age, sex, ethnic group)
- Description of the ADR
- Details of the product (e.g., name, ingredients, dosage, duration of consumption, indication for taking the product). Photos of the product and package insert can provide useful information as well.
- Source of the product
- Any underlying diseases or concomitant drugs
- Relevant lab tests and investigations

For more information on the reporting of suspected adulterated health products to the Vigilance Branch, please contact us at Tel: *6866 3538* or Email: *HSA_productsafety@hsa.gov.sg*.

HSA website revamp: YOUR Website, YOUR Views!

HSA will be revamping its website next year and would like to hear from healthcare professionals on how you think we can improve the website to enhance user experience and better meet your needs. This could be in terms of locating health product information, guidances on the registration of health products (drugs/biologics and medical devices) and information on local clinical trials, as well as receiving product safety alerts and news from us. Our current website also contains information on the legislations pertaining to the Medicines Act, Poisons Act and Health Products Act.

We hope you can spare a few minutes of your time to provide your feedback on the following topics:

Site-related

- What are some features from other similar sites that you wish to see included in this site?
- Why would you visit the HSA site? What kind of information do you look for?

Content- related

- Are you able to find information with ease? Do you think the information is presented in a user-friendly manner?
- What do you think about the content presentation? Is the content presented in a way that is easy to digest and understand? What could be done to improve the content presentation?

Consultation/Discussion Board/Alert System-related

- What mode of communication would you prefer to use (e.g., internet, email, SMS, smartphone applications, Facebook, Twitter)?
- What kind(s) of updates would you like to receive?
- What is your preferred mode of communication for receiving alert messages (e.g., internet, email, SMS, smartphone applications, Facebook, Twitter)?
- Do you think having an extranet (Consultation/Private discussion forum) will be helpful? If so, what kind(s) of information would you wish to share and receive via the extranet?

You may wish to email us at *HSA_productsafety@hsa.gov.sg* or call us at Tel: *6866 3538* to provide your feedback. Alternatively, you may also wish to complete our E-Survey at this weblink: *www.hsa.gov.sg/safetyinfo_and_recalls*.

We hope to hear from you by ***30 September 2013***. Your feedbackwill help us create a better HSA website for all!

Increase in antibody-mediated Pure Red Cell Aplasia (PRCA) cases with subcutaneous administration of Eprex® (epoetin alfa) in Singapore

Healthcare professionals to be vigilant to possible PRCA in users of erythropoiesis stimulating agents

HSA would like to update healthcare professionals on an unexpected increase in local cases of antibody-mediated Pure Red Cell Aplasia (PRCA) associated with subcutaneous administration of Eprex® (epoetin alfa, Johnson & Johnson Pte Ltd). These cases were reported between the period 2012 and 2013.

This picture is for illustrative purposes only and does not reflect all the Eprex® strengths reported in the PRCA cases.

Local PRCA cases reported from 2012 to 2013

The confirmed PRCA cases associated with Eprex® with date of onset between 2012 to June 2013 accounted for 90% of the total Eprex®-associated PRCA cases in the HSA Pharmacovigilance database since the reinstatement of the subcutaneous route for Eprex® in April 2009. While reporting rates cannot be used to estimate incidence rate, this is a disproportionately high number of PRCA cases reported compared to the baseline reporting trend.

During this period, nine PRCA cases were reported from two local healthcare institutions. One institution reported seven confirmed (antibody-positive) and one suspected (antibody status unknown) cases while another institution reported one confirmed case. All cases were reported with subcutaneous use of Eprex® in chronic kidney disease patients with duration of onset ranging from seven months to 19 months.

HSA is currently working with the company and healthcare institutions to monitor the situation closely and will take further regulatory actions when deemed necessary. A Dear Healthcare Professional Letter was issued on 13 June 2013 to inform Eprex® users about the increase in local PRCA cases.

Diagnosis and management of antibody-mediated PRCA

Antibody-mediated PRCA is a rare, serious disorder of erythropoiesis characterised by severe anaemia, low reticulocyte count, absence of erythroblasts, non-response to erythropoiesis stimulating agents (ESAs), and presence of neutralising antibodies against erythropoietin (EPO).[1-3] However, the mechanisms behind this immunological response remain only partially understood.[2,4] The patient generally presents with initial erythropoietic response to ESA treatment for six to 18 months and a stable haemoglobin level, followed by a sudden and rapid decline in haemoglobin level at a rate of approximately 1g/dL/week. The development of severe anaemia is refractory to dose increases of ESA, resulting in an increasing need for transfusions at approximately four units of packed red blood cells (RBCs) per month.[5] The shortest time interval between the start of ESA therapy and loss of efficacy reported in literature was two months and the longest time interval was 90 months.[1]

Haematological investigations in patients with PRCA revealed reticulocytopenia (<10,000 cells/mL) with generally normal white cell and platelet counts. Diagnosis of PRCA is confirmed through bone marrow examination and antibody assay showing normal bone marrow cellularity with an almost complete eradication of erythroblasts (<5% erythroblasts) and presence of neutralising anti-EPO antibodies.[5] Other known causes of PRCA include acquired PRCA in relation to tumours, autoimmune diseases, T-cell disorders and viral infections.[6] Anti-EPO antibodies produced in response to ESAs cross-react with exogenous ESAs and endogenous EPO.[1-3] Upon diagnosis of ESA-induced PRCA, cessation of ESA therapy is universally accepted as first-line therapy with supportive RBC transfusions when necessary to avoid severe and life-threatening anaemia.

History of PRCA associated with Eprex®

From 1998 to 2004, a rise in PRCA cases associated with the use of Eprex® was observed globally.[7] This unexpected increase in PRCA cases was attributed to several possible reasons, including substitution of human serum albumin with polysorbate 80 (a synthetic stabiliser), leaching from uncoated rubber stoppers, and breaks in the cold chain process which could lead to increased immunogenicity.[4,5] The association of PRCA with subcutaneous administration of Eprex® with polysorbate 80 and uncoated rubber stoppers was later corroborated by investigators from the Research on Adverse Drug Events and Reports (RADAR) project, who found that 95% of 191 haemodialysis patients with anti-EPO antibody-mediated PRCA were reported to have received Eprex® subcutaneously.[3]

In 2002, the European Union regulatory agencies contraindicated subcutaneous administration of Eprex® and mandated intravenous administration of Eprex® to haemodialysis patients. This resulted in a 90% decrease in the annual number of Eprex®-associated PRCA cases, as well as a decline in the exposure-adjusted incidence rates in these countries. With the introduction of Teflon-coated rubber stoppers in 2004, further reduction in reporting rates occurred. The subcutaneous route for Eprex® was eventually reinstated in most countries.

HSA's advisory

While HSA is investigating the unexpected increase in PRCA cases associated with subcutaneous Eprex® in chronic kidney disease patients in Singapore, healthcare professionals are advised to be vigilant to the possibility of PRCA occurring in ESA users.

Although the increase in local ADR reports of PRCA are currently associated with Eprex®, PRCA related to other ESAs has also been reported previously.[7] Healthcare professionals are encouraged to report any suspected reactions with the use of ESAs to the Vigilance Branch of HSA.

HSA will update healthcare professionals on any new findings and regulatory actions taken arising from its investigations.

References

1 *J Am Soc Nephrol 2005; 16: S67-9*
2 *Nephrol Dial Transplant 2008; 23: 3053-5*
3 *Transfusion 2008; 48: 1754-62*
4 *Kidney Int 2012; 81: 727-32*
5 *Nephrol Dial Transplant 2005; 20: viii 18-21*
6 *Br J Haematol 2000; 111: 1010-22*
7 *N Engl J Med 2004; 351: 1403-8*

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Potential interaction between warfarin and health supplements containing vitamin K

Through the vigilance of an astute doctor, HSA was alerted to an adverse event (AE) involving warfarin and a health supplement containing vitamin K. Healthcare professionals are reminded to be aware of this potential interaction and to monitor the intake of vitamin K-containing health supplements for patients on warfarin therapy.

Local adverse event involving a change in the formulation of Centrum Silver®

In April 2013, HSA received an AE report from a doctor involving a 80-year old patient on long-term warfarin therapy and concurrent use of Centrum Silver® (Pfizer Pte Ltd). Centrum Silver® is a vitamin K-containing multivitamin which is targeted for consumers above 50 years old. The patient had been on the same warfarin dose for the past three years with International Normalised Ratio (INR) within the therapeutic range of 2–3. During a routine blood test, the INR was unexpectedly reduced to a sub-therapeutic level of 1, which might increase the risk of cardiovascular events such as stroke and thrombus formation. The doctor ruled out possible causes such as changes in diet and concomitant acute illnesses. There were also no recent changes in the patient's medication. After the doctor re-titrated the patient's warfarin dose, the INR eventually returned to therapeutic levels while the patient continued with the new formula of Centrum Silver®.

Further investigations revealed that the Centrum Silver® taken by the patient was a new formulation with an addition of 25mcg of vitamin K_1. Vitamin K_1 was not present in the earlier formulation. The new formulation had been available locally since March 2013 with a different packaging to indicate the change in formulation and carried the cautionary statement for multivitamins containing vitamin K: "Consult a healthcare professional prior to use if you are taking a blood thinner such as warfarin."

Following this AE report, HSA had worked with the company to issue a Dear Healthcare Professional Letter on 1 July 2013 to highlight the presence of vitamin K in the new formulation of Centrum Silver®.

Discussion

Small amounts of vitamin K_1 (e.g., 10–25mcg) contained in multivitamin supplements are generally considered safe in patients undergoing warfarin anticoagulation therapy.[1] However, patients with low vitamin K status could be more susceptible to potential interactions, resulting in oversensitivity of INR response to small changes in vitamin K_1 intake.

Three other case reports with this interaction were reported overseas in patients following initiation or cessation of a daily multivitamin containing 25mcg of vitamin K_1.[1] In one case, a 43-year-old woman on warfarin therapy developed a subcapsular hematoma of the right kidney after discontinuing her multivitamin containing vitamin K_1 25mcg without notifying her physician. In another case, a 77-year-old man on warfarin therapy started taking a multivitamin containing 25mcg of vitamin K_1 and developed a sub-therapeutic INR within 2.5 weeks. In a third case, an 80-year-old man's INR dropped to a sub-therapeutic level without any other apparent reason after starting a daily multivitamin containing 25mcg of vitamin K_1 two weeks earlier. Prior to that, he had stable INRs with his usual warfarin dosage.

HSA's advisory

While the amount of vitamin K allowed in health supplements is generally considered safe, healthcare professionals managing patients on warfarin are encouraged to monitor their patients' INRs and counsel them on their vitamin K intake from health supplements and food. In particular, patients should be made aware of the presence of vitamin K in health supplements, and to remain alert to any changes in packaging or formulation as in the case of Centrum Silver®. Healthcare professionals should also advise their patients to inform them before starting, stopping or switching health supplements.

Healthcare professionals are reminded to take into consideration the above when counselling patients on warfarin anticoagulation therapy, and to report any suspected AEs associated with the concurrent use of vitamin K-containing health supplements with warfarin to the Vigilance Branch of HSA.

Reference

1 *Ann Pharmacother 2003; 37: 1603-6*

Please send your enquiries, comments and suggestions to:

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All website references were last accessed on 1 August 2013.