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MADRAC

Malaysian Adverse Drug Reactions Newsletter
National Pharmaceutical Control Bureau, Ministry of Health Malaysia
This newsletter is also available on our website: http://www.bpfk.gov.my

SAFETY ISSUE OF CURRENT INTEREST

HYDROXYETHYL STARCH (HES)-CONTAINING PRODUCTS: NEW SAFETY UPDATES ON INCREASED MORTALITY AND RISK OF KIDNEY INJURY REQUIRING DIALYSIS

by Vidhya Hariraj

Background

All plasma expanders exert metabolic effects – either *favourable* effects such as correction of hypovolemia-induced lactic acidosis or renal failure, or *adverse* effects such as hypotonic solution-induced hyponatremia, hyperchloremic acidosis, and effects related to associated buffers (lactate, acetate). The plasma expanders most widely used worldwide are isotonic crystalloids and synthetic colloids.[1]

In mid-2013, the publication of three (3) studies that compared HES with crystalloids in critically ill patients **(CHEST**, **6S** and **VISEP)** triggered a safety review by regulatory authorities worldwide. These studies[2-4] showed that patients with severe sepsis treated with HES were **at greater risk of kidney injury requiring dialysis**. Two of the studies[3-4] also showed that there was a **greater risk of mortality** in patients treated with HES. Additionally, available data only showed **a limited benefit of HES in hypovolaemia** which did not justify its use considering the known risks.

CONTENT

To report an adverse drug reaction:

1. Visit http://www.bpfk.gov.my
2. Click on the red box: 'Reporting Medicinal Problems'.
3. Go to report as a healthcare professional online or via hardcopy.
4. Submit the form once completed.

Alternatively, please contact:

The Drug Safety Monitoring Centre,
National Pharmaceutical Control Bureau,
Ministry of Health
PO Box 319, Jalan Sultan,
46730 Petaling Jaya,
Selangor.

Tel : +603 78835550
Fax : +603 79567151

Actions by NPCB

In Malaysia, an interim communication was issued on 9 July 2013 to all healthcare professionals to restrict the use of HES products [Ref: *(93) dlm BPFK/17/4*]. The NPCB conducted an analysis of local reports, evaluation of clinical papers, and took into consideration the recommendations of other regulatory agencies including the United States Food and Drug Administration (US FDA) and European Medicines Agency (EMA). As a result, the Malaysian Adverse Drug Reaction Advisory Committee (MADRAC) in its 135th meeting on 25 October 2013 agreed on **restrictions** to the use of these infusion products in view of severe renal impairment and increased mortality.

The new safety updates for HES-containing products warrant that the HES solutions be used at the **lowest effective dose for the shortest period of time**. Treatment should be guided by continuous haemodynamic monitoring so that the infusion is stopped as soon as appropriate haemodynamic goals have been achieved. HES solutions should only be used for the treatment of hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient.

NPCB is in communication with the product registration holder to update the current prescribing information. A Follow-Up Safety Update Report will be issued and the NPCB will continue to monitor the situation. All healthcare professionals are requested to **report any suspected ADR** related to HES products to the Drug Safety Monitoring Centre.

Advice for Healthcare Professionals:

- ***Because of the risk of kidney injury and mortality, HES solutions must no longer be used in patients with sepsis, burn injuries or critically ill patients.***
- ***HES solutions are now contraindicated in patients with renal impairment or on renal replacement therapy.***
- ***The use of HES must be discontinued at the first sign of renal injury.***
- ***An increased need for renal replacement therapy has been reported up to 90 days after HES administration. Patients' kidney function should be monitored after HES administration.***
- ***HES solutions are contraindicated in severe coagulopathy. HES solutions should be discontinued at the first sign of coagulopathy. Blood coagulation parameters should be monitored carefully if administration is repeated.***

Product Information

Hydroxyethyl starch 6% injection is listed in the Ministry of Health (MOH) Drug Formulary, under prescriber category B (Medical Officers).[5] There are **nine (9)** registered products containing HES in Malaysia (*Table 1*).

Table 1: Hydroxyethyl starch (HES)-containing products registered in Malaysia

No.	Product name	Registration No.	Product Holder
1	Venofundin® 6% Solution For Infusion	MAL06100624X	B. Braun Medical Industries Sdn. Bhd.
2	Tetraspan® 10% Solution for Infusion	MAL08080867X	
3	Tetraspan® 6% Solution For Infusion	MAL08080866X	
4	Hemohes® 10% Intravenous Infusion In 500 ml Plastic Container	MAL19990613X	
5	Hemohes® 6% Intravenous Infusion In 500ml Plastic Container	MAL19990614X	
6	Voluven® 6% (Freeflex With Overwrap)	MAL20031761X	Fresenius Kabi Malaysia Sdn. Bhd.
7	Voluven® 6% Polyethylene Bottle (Bottlepack)	MAL20031760X	
8	Voluven® 6% (Freeflex Without Overwrap)	MAL20031759X	
9	Volulyte® 6% Solution For Infusion	MAL08111930X	

Since year 2000, the Drug Safety Monitoring Centre, NPCB, has received four (4) reports with eight (8) adverse events related to HES-containing products, as listed in *Table 2*:[6]

Table 2: Malaysian ADR reports on HES-containing products

No.	Product Name	Report No.	Age	Adverse Events	Outcome	MADRAC Causality
1	Venofundin®	07-08-1737A	28	Polyuria	Unknown	C3
2		08-07-2701A	12	INR increased, prothrombin time increased	Recovered	C3
3	Voluven®	10-09-5525A	46	Bronchospasm, rash, hypotension	Recovered	C3
4	Tetraspan®	12-11-08733A	18	Rash, face oedema	Recovered	C3

References:

1. Muller L, LeFrant JY. (2010). *Metabolic Effects of Plasma Expanders*. Transfusion Alter Transfusion Med. 11 (3):10-21.
2. Perner A et al. (2012). *Hydroxyethyl Starch 130/0.42 versus Ringer's acetate in severe sepsis*. N Engl J Med 367(2):124-134.
3. Brunkhorst FM et al. (2008). *Intensive insulin therapy and pentastarch resuscitation in severe sepsis*. N Engl J Med 358(2):125-39.
4. Myburgh JA et al. (2012). *Hydroxyethyl starch or saline for fluid resuscitation in intensive care*. N Engl J Med 367(20):1901-11.
5. Ministry of Health Malaysia Drug Formulary. http://www.pharmacy.gov.my/v2/ms/apps/fukkm [Accessed: 2 May 2013]
6. The Malaysian Adverse Drug Reaction Database, NPCB. [Accessed: 28 June 2013]

FEATURES

ACETYLCYSTEINE: NEW REGIMEN WITH REDUCED ADVERSE EFFECTS?

by Chan Yoke Jia and Rema Panickar

In a six-month period from September 2012 to March 2013, the NPCB received two reports on acetylcysteine causing anaphylactic shock. This fact, coupled with the publication of a study on adjusting the infusion time of acetylcysteine to reduce adverse effects, triggered an ongoing review regarding the safe use of this medication.

Background

N-acetylcysteine (NAC) is an acetylated derivative of the amino acid L-cysteine, which is converted in the body into metabolites capable of stimulating glutathione (GSH) synthesis, promoting detoxification, and acting directly as free radical scavengers.[1] Acetylcysteine is used in the treatment of paracetamol (acetaminophen) overdose to prevent hepatotoxicity.[2] It is also commonly used for off-label indications, including as a mucolytic agent, in non-acetaminophen-induced acute liver failure (NAI-ALF), severe alcoholic hepatitis, and prevention of contrast-induced nephropathy (CIN). Paracetamol overdose is one of the few toxicological emergencies with a specific antidote; however, the standard acetylcysteine administration regimen can be complicated, costly, and often causes adverse drug reactions (ADRs).

Recent changes in clinical practice

In September 2012, the Medicines and Healthcare Products Regulatory Agency (MHRA) in United Kingdom (UK) issued an alert to healthcare professionals on new guidance of IV acetylcysteine use in paracetamol overdose. The recommendations included an updated treatment nomogram, administration of the initial acetylcysteine dose over 60 minutes instead of 15 minutes to reduce risk of ADRs, and introduction of a weight-based dosing table to reduce dosage errors.[3]

New research findings

Several studies have been carried out to assess the effectiveness of oral versus intravenous acetylcysteine in treatment of paracetamol toxicity, with a recent meta-analysis concluding that both routes provide similar efficacy.[4]

A study was published by Bateman et al. in November 2013 on the reduction of acetylcysteine adverse effects by reducing the infusion period (*Table 3*) or giving antiemetic pretreatment.[5] This involved 222 patients from three UK hospitals who underwent randomisation into four parallel groups, as shown in *Table 4*.

Table 3: Acetylcysteine regimens used in the study

UK Standard Schedule (Duration 20-25 hours)	Modified Study Protocol (Duration 12 hours)
• 150mg/kg in 200ml D5% over 15min • 50mg/kg in 500ml D5% over 4 hours • 100mg/kg in 1000ml D5% over 16 hours	• 100mg/kg in 200ml D5% over 2 hours • 200mg/kg in 1000ml D5% over 10 hours • 500ml of D5% over 20-25hours

Table 4: Criteria of the four patient groups used in study

Group	No. of subjects (n)	Pre-treatment		Acetylcysteine regimen	
		Ondansetron	Placebo	Modified (12 hours)	Standard (20-25 hours)
1	54	√		√	
2	55	√			√
3	54		√	√	
4	54		√		√

Adverse effects related to **vomiting** were reported in 39 of 108 (36%) patients assigned to the modified protocol (Groups 1 & 3) compared with 71 of 109 (65%) allocated to the standard regimen (adjusted odds ratio 0·26, 97·5% CI 0·13—0·52; p<0·0001).

Patients assigned to the modified regimen also reported less **anaphylactoid reactions** (five patients) compared to 31 in the standard protocol group (adjusted common odds ratio 0·23, 97·5% CI 0·12—0·43; p<0·0001).

Fewer patients (45; 41%) who received ondansetron **pretreatment** (Groups 1 & 2) suffered vomiting compared to those allocated placebo (65; 60%) [0·41, 0·20—0·80; p=0·003].

The findings of this study showed that a shorter (12 hour) acetylcysteine infusion period substantially reduced the frequency of both vomiting and serious anaphylactoid reactions when compared with the standard schedule (20-25 hours). The authors concluded that this shorter duration of acetylcysteine infusion offers simpler administration, possible reduction of adverse effects and administration errors, as well as a potential decrease in the length of hospital stay. However, further studies of novel and traditional biomarkers are needed to confirm the efficacy and safety of the modified regimen before widespread adoption into clinical practice.

Local scenario

In Malaysia, there are **17 registered products** containing acetylcysteine whereby **8** (47%) are in **parenteral** dosage form. Acetylcysteine is listed in the Ministry of Health (MOH) Drug Formulary under prescriber category A* (to be initiated by consultant/specialist for specific indications only).

The Drug Safety Monitoring Centre has received a total of 111 reports associated with acetylcysteine since 2000. In most of the cases reported, acetylcysteine was given as an antidote for paracetamol poisoning (83 reports; 75%).[6] Almost half the adverse events reported (54; 48.5%) involved skin reactions, such as rash (39 reports), itching (38) and urticaria (14). Other adverse events reported were vomiting (15), shortness of breath (14), nausea (7), and anaphylactic reactions (3).

Out of the three reported cases of anaphylactic shock after acetylcysteine infusion, two of the cases involved use of the drug for the prevention of contrast-induced nephropathy (CIN) and the remaining one was for paracetamol poisoning.[6] *Table 5* shows the summary of these reports.

Table 5: Malaysian ADR reports of anaphylactic shock after acetylcysteine infusion

	Case 1	Case 2	Case 3
Year of report	2006	2012	2013
Patient details	Age 27 years; Male	Age 30 years; Female	Age 74 years; Male
Indication	Paracetamol poisoning	Prevention of contrast-induced nephropathy	Prevention of contrast-induced nephropathy
Dose	9g over 15 min, then 3g over 4 hours	1.2g stat	10g over 60 min
Onset time	1 hour	1.5 hours	<1 hour
MADRAC Causality	C2	C3	C2
Outcome	Recovered after treatment with IV hydrocortisone	Recovered after treatment with IV hydrocortisone, IV chlorpheniramine, and nebuliser AVN	Recovered after treatment with IV hydrocortisone, IV chlorpheniramine and IM adrenaline

Conclusion

Further studies need to be conducted to determine the best route and regimen for acetylcysteine treatment, ensuring efficacy while reducing the potential for serious adverse effects. Healthcare professionals are reminded to **monitor** patients closely for any adverse reactions and **report** all adverse events suspected to be associated with acetylcysteine. The NPCB will continue to monitor this medication, including reports of off-label use, to ensure a positive risk-benefit ratio.

References:

1. Kelly GS. (1998). *Clinical Applications of N-Acetylcysteine*. Alt Med Rev 3(2):114-127.
2. Gray A., Wright J., Goodey V., Bruce L. (2011). *Injectable Drugs Guide 1st Edition.* Pharmaceutical Press.
3. MHRA (2012). *Latest advice for medicines users. Paracetamol overdose: new guidance on treatment with intravenous acetylcysteine.* Drug Safety Update 6(2):A1.
4. Green JL, Heard KJ, Reynolds KM, Albert D (2013). *Oral and intravenous acetylcysteine for treatment of acetaminophen-toxicity: A systemic review and meta-analysis*. West J Emerg Med. 14(3): 218–226.
5. Bateman et al. (2014). *Reduction of adverse effects from intravenous acetylcysteine treatment for paracetamol poisoning: a randomised controlled trial.* The Lancet 383(9918):697-704 (Published online: 28 November 2013).
6. The Malaysian Adverse Drug Reaction Database, NPCB. [Accessed: 23 December 2013].

GUIDE FOR ADR REPORTERS

IMPROVING QUALITY OF REPORTS

Adverse drug reaction (ADR) reports are an important source of post-marketing drug safety data. As clinical trial data during drug development often do not identify all possible ADRs for a drug, post-marketing reports are essential to assess the benefit-risk ratio. However, in order for ADR reports to be useful, they have to be as complete as possible.

For ADRs involving certain drugs or conditions, specific information is needed to analyse the case, allow more accurate assignment of causality, increase signal detection, and facilitate action to be taken ensuring the safe use of medicines. Certain drugs also come under close monitoring by the NPCB when specific safety issues arise, requiring extra information to be obtained.

Currently, NPCB officers make every attempt to contact reporters to request for additional information whenever necessary. This task is undoubtedly time consuming, as more than 10,000 ADR reports are received annually in Malaysia, with 30-40% involving missing information. Besides that, attempts to obtain information often fail due to various factors, such as inability to trace the primary reporter or patient medical records.

The following table (*Table 6*) provides a guide on cases where specific additional information is required to improve quality of reports. Reporters are **strongly encouraged to include this information** in the reports submitted (written on the form, or by attaching additional pages if necessary).

Table 6: Additional information necessary for specific ADR cases

ADR cases involving:	Additional information	Rationale
All reports	Indication of suspected drug (as **specific** as possible) e.g.: 'pneumonia due to S. Pneumoniae'- not 'infection' or 'antibiotic'; 'lower back pain'- not 'painkiller' or 'NSAID'	To increase quality of reports submitted to WHO and assist causality assignment
Paediatric patients	Body weight	To distinguish ADR from drug toxicity/ inefficacy
Skin reactions	Specific description of reaction (type and location of rash) - attach the Cutaneous ADR classification form available on www.bpfk.gov.my	For more accurate causality assignment
Serious skin reactions (e.g. SJS, TEN, DRESS)	Designation of doctor who provided final diagnosis	Diagnosis should be confirmed by a dermatologist
Brand-switching	Name and MAL number of **both** brands involved	To identify brand/ batch problems
Drug use in pregnancy, post-delivery, breastfeeding or off-label use	Please mention this in the 'Relevant Medical History' section	To increase available data on such cases, where clinical trials are not carried out

ADR cases involving:	Additional information	Rationale
Suspected Drugs:		
Allopurinol	1. Specific indication 2. Category of prescriber 3. Renal function of patient 4. If prescribed for asymptomatic hyperuricaemia: - Name, address and tel. no. of primary prescriber	- Allopurinol is not indicated for the treatment of asymptomatic hyperuricaemia. - Approved MOH prescriber category: **A/KK** (consultant/ specialist/ family medicine specialist)
Antibiotics	Please state if patient was given an ADR/ allergy card and counselling	To avoid risk of patient being given the same drug repeatedly
Antidiabetics	Baseline and latest blood glucose readings	To differentiate ADRs from disease exacerbations
Antihypertensive agents	Baseline and latest blood pressure readings	
Corticosteroid	Indication (e.g. asthma, SLE)	
Antineoplastic agents	- List concomitant medication - Premedication(s) and administration time	Presence of concomitant medication will affect causality assignment
Noradrenaline	Other concomitant inotropes and medication	
Paracetamol	State the colouring agent and flavouring agent	To identify ADRs due to the excipient rather than active ingredient
Oral Antihistamines		
Statin causing skin reaction	Specify if reaction is related to photosensitivity	To identify specific type of skin reaction
Vancomycin	Rate of infusion and dose	To distinguish ADR from side effect of drug

*SJS: Stevens-Johnson syndrome;
TEN: Toxic epidermal necrolysis;
DRESS: Drug reaction with eosinophilia and systemic symptoms

DISCLAIMER: *The list above is not exhaustive and additional information requested may vary depending on safety issues that arise.*

GUIDE FOR ADR REPORTERS

LABORATORY TESTING FOR SUSPECTED ADULTERATED PRODUCTS

The NPCB conducts laboratory testing to identify adulterants in product samples, including traditional products, food and cosmetics. As highlighted in the April 2013 issue of MADRAC Bulletin, adulterated medicinal and traditional products continue to be identified. Common adulterants found include **dexamethasone, prednisolone, sildenafil, tadalafil, chlorpheniramine** and **sibutramine.**

In order for laboratory testing to be conducted, a **sufficient amount** of sample and certain information are required. The following is a simple guide on sending product samples for laboratory testing when an adverse drug reaction occurs and adulteration is suspected.

1. Fill in the adverse drug reaction (ADR) reporting form for healthcare professionals (or Consumer Medications Complaints reporting form- for consumers who wish to report directly to the NPCB). Please include as many details as possible to ensure the report is useful.

   Important details:
   - Name and contact details of patient
   - Details of the ADR
   - Details of any concomitant medicines/ other products taken and underlying illnesses
   - Product name and label
   - Where it was obtained
   - Indication for which the patient was taking the product
   - Suspected adulterant (e.g. antihistamine, steroid) based on product indication and ADR
   - Name and contact details of reporter

2. Submit the ADR form together with the product sample. Please send as much sample quantity as possible. The quantities listed below are for the screening of **one suspected** adulterant only. Therefore, the quantity should be multiplied based on the number of suspected adulterants.

   Minimum quantities required for testing of one suspected adulterant are as follows:

Table 7: Minimum sample quantity required for laboratory testing for adulterants

Dosage Form	Minimum amount for one test	Total amount for confirmatory result
Tablet/ Capsule/ Pill	10g or 20 dosage forms	30g or 60 dosage forms
Liquid	40ml/ 40g	120ml/ 120g
Powder	10g	30g
Cream	10g	30g
Candy	10 candies	30 candies

3. Please **contact us** if you have any questions:
   The Pharmacovigilance Section,
   Drug Safety Monitoring Centre,
   National Pharmaceutical Control Bureau.

   Tel: 03-7801 8545 / 7801 8471
   Email: **fv@bpfk.gov.my**

Thank you for reporting!

REGULATORY MATTERS

PROTAXOS® (STRONTIUM RANELATE): INCREASED RISK OF SERIOUS HEART PROBLEMS

MADRAC recently discussed the increased risk of serious cardiac disorders associated with strontium ranelate, an osteoporosis drug, during its meeting held in December 2013. The committee decided to **restrict the use** of strontium ranelate to **severe/established** osteoporosis in women at high risk of fracture to reduce the risk of vertebral and hip fracture, and **severe/established** osteoporosis in men at increased risk of fracture. Recommendation was also made to **contraindicate** the use of strontium ranelate in patients with established, current, or past history of **ischaemic heart disease, peripheral heart disease, cerebrovascular disease** and/or **uncontrolled hypertension.**

The decision was based on pooled data from clinical studies in 7,572 post-menopausal osteoporotic (PMO) women. The PMO studies observed a higher percentage of myocardial infarction compared to the placebo group (1.7% versus 1.1%), with a relative risk of 1.6 (95% confidence interval, 1.07 to 2.38).[1]

Additionally, there was an imbalance in such events in two other studies, one in men with osteoporosis and another in patients with osteoarthritis. No increased risk of mortality was observed in all the studies.[1]

Local Scenario

In Malaysia, Protaxos® (Granules for Oral Suspension) has been available since year 2007 as the only registered product containing strontium ranelate. It is listed in the Ministry of Health Drug Formulary, under the prescriber category A* (to be initiated by consultants/ specialists for specific indications only).

Since its registration, the Drug Safety Monitoring Centre, NPCB has received a total of 15 reports with 22 events for strontium ranelate. None were related to cardiovascular disorders. Majority of the reported adverse events involved the system organ class 'Skin and Appendages Disorders' (Stevens-Johnson Syndrome) and 'Gastrointestinal System Disorders' (gastrointestinal pain, lip ulceration, oral ulceration, stomach upset, black stool and loose stool).[2]

NPCB is currently working with the product holder to revise the local package insert for strontium ranelate with this updated risk information.

Related Information

Previously in April 2012, MADRAC had contraindicated strontium ranelate in patients with current or previous **venous thromboembolic events (VTE)**, including deep vein thrombosis and pulmonary embolism. The package insert of strontium ranelate was also updated with warnings on **life-threatening skin reactions** including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS).[3]

Reminder to Healthcare Professionals:

- ***Carefully evaluate patients for cardiovascular risk (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) and VTE risk before starting treatment with strontium ranelate.***
- ***Re-evaluate the need for continued treatment with strontium ranelate when treating elderly patients (over 80 years old).***
- ***All patients should be informed of the associated risk of serious adverse events (VTE, life-threatening skin reactions and MI) and to seek immediate medical attention if they experience any related signs and symptoms.***
- ***Do report all adverse events suspected to be associated with strontium ranelate in order to support a better benefit-risk assessment in the future.***

References:

1. Summary of cardiac safety results across all postmenopausal osteoporosis, osteoporotic men and osteoarthritis studies. [May 2013]
2. The Malaysian Adverse Drug Reaction Database, NPCB. [Accessed: 12 December 2013]
3. MADRAC Bulletin April 2012 edition.

XELODA® (CAPECITABINE): ASSOCIATION WITH SEVERE SKIN REACTIONS SUCH AS STEVENS-JOHNSON SYNDROME (SJS) AND TOXIC EPIDERMAL NECROLYSIS (TEN)

Xeloda® (capecitabine) is an anticancer agent registered in Malaysia since year 2000 for the following indications: advanced or metastatic breast cancer, stage III colon cancer, metastatic colorectal carcinoma, and oesophagogastric cancer *(*please refer to the approved package insert for the details)*.

Recently, NPCB was notified on new global **cases of severe skin reactions** such as Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), some with fatal outcome, during treatment with Xeloda®. However, these cases have been classified as rare. A Direct Healthcare Professional Communication (DHPC) has been issued by the company in consultation with NPCB.

As of June 2013, the Drug Safety Monitoring Centre, NPCB has received **26 adverse drug reaction (ADR) reports** related to Xeloda® **with 56 adverse events.** The main system organ class of disorders reported is 'Gastrointestinal System Disorders' (16 events such as nausea, vomiting, diarrhoea, mucositis), followed by 'Skin and Appendages Disorders' (13 events including itching, erythema, maculopapular rash). However, none were associated with SJS and TEN, or with a fatal outcome. The third highest class of adverse events is 'Body as a Whole' comprising of 12 events such as back pain, fever, fatigue, and PPE. Specifically there were 7 reports (12%) of Palmar-plantar erythrodysaesthesia (PPE), a condition known and documented in the current approved prescribing information of Xeloda®.

The WHO database contained 16 reports for SJS associated with Xeloda® from America (62%), Africa (25%) and Europe (13%). There were 13 reports of epidermal necrolysis, from Europe (77%), Australia (15%) and America (8%) respectively.

NPCB will continue to monitor the adverse events associated with Xeloda® and the local package insert will be updated with this new safety information.

Reminder to Healthcare Professionals:

- ***Xeloda® therapy should be permanently discontinued in patients who experience a severe skin reaction possibly attributed to the drug, and appropriate treatment should be promptly initiated.***
- ***Any suspected adverse reactions associated with the use of Xeloda® should be reported to NPCB.***

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JEVTANA® (CABAZITAXEL): POTENTIAL FOR MEDICATION ERROR DURING PREPARATION

Jevtana® is an anticancer agent registered in Malaysia since year 2011 to be used in combination with prednisone or prednisolone for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen *(*please refer to the approved package insert for the details).*

NPCB has recently been informed of reconstitution errors in the European Union with Jevtana® (cabazitaxel) that could lead to overdose, with an actual dose delivered that is 15-20% higher than the prescribed dose. The possible complications of overdose are exacerbation of adverse reactions such as bone marrow suppression and gastrointestinal disorders.

Jevtana® reconstitution requires a **two-step dilution**. Each pack contains one vial of concentrate and one vial of solvent, both of which contain an overfill. The error occurred in the first step where the nominal volume of the solvent vial (4.5mL) was transferred to the concentrate vial instead of the entire fill volume (5.67mL).

To date, NPCB has not received any ADR reports for Jevtana®. A Direct Healthcare Professional Communication has been issued by the company regarding this issue in consultation with NPCB. The labels and package insert for the product have addressed the current recommendation. NPCB will continue to monitor this issue and reminds all healthcare professionals on the appropriate preparation instructions.

Preparation instructions for Jevtana® (cabazitaxel)

1- Initial dilution of the concentrate:
Always **transfer the ENTIRE content of the solvent vial** to the concentrate vial in order to reach a concentration of 10 mg/mL in the premix.

2- Preparation of the infusion solution:
From this 10mg/mL premix, the required volume should be taken and injected into the infusion container in accordance with the intended dose of Jevtana® to be administered to the patient.

RELATED PUBLICATIONS

Predictors of Serious Adverse Drug Reactions in Association with Complementary and Alternative Medicine in Malaysia

Drug Safety 2013, Vol. 36(9):800
The official journal of the International Society of Pharmacovigilance (ISoP)

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Introduction
In Malaysia, Complementary and Alternative Medicines (CAM) products are easily available and increasingly used. Our spontaneous reporting system has received many reports of serious adverse events associated with the use of CAM products. Yet, little is known about factors influencing the development of serious adverse drug reactions (ADRs) due to CAM products.

Aim
To identify risk factors associated with serious ADRs due to CAM products.

Methods
All adverse reactions associated with CAM products (including CAM health supplements) submitted to the National Pharmaceutical Control Bureau (NPCB) between 2000 and 2012 were reviewed and analysed. ADRs were considered serious if the reactions led to death, hospitalisation or prolongation of hospitalisation, that were life threatening, or that caused significant disability. A multiple binary logistic regression was used to identify factors associated with serious ADRs in the reports.

Results
From a total of 43,444 reports received by NPCB, 732 (1.7%) involved CAM products. Of 732 patients, 220 (30.1%) developed serious ADRs, of which 27 died. Twelve deaths were attributed to unregistered products. Patients mainly use CAM products for health maintenance (31.8%), for the treatment or prevention of minor ailments (17.9%), for chronic illnesses (32.4%), weight loss (5.2%) and also for serious illnesses such as cancer (1.1%). Multiple binary logistic regression analysis revealed three variables (patient having concomitant diseases, ethnic group and indications of CAM use) to be predictive of the ADRs seriousness. The odds of someone experiencing serious ADR were about two-fold compared to someone without concomitant diseases [odds ratio (OR) 1.91, confidence interval (CI) 1.12-3.25]. Being Chinese was associated with increased odds of experiencing serious ADRs compared to being Malay [OR 2.35, CI 1.61-3.44]. The odds of someone experiencing serious ADRs also increased if CAM products were used for chronic illnesses compared to if the products were used for health maintenance [OR 1.66, CI 1.12-2.47]. The variables age, sex, and concomitant drugs were not significant predictors of serious ADRs.

Conclusions
The proportion of serious ADRs associated with CAM products was high, with several deaths. Chinese patients, those who used CAM products for chronic illness, and patients with concomitant diseases were at an increased risk for developing serious ADRs. The findings could be useful for planning strategies to prevent serious ADRs due to CAM products.

Give Your Patients a RiMUP Today!

Consumer Medication Information Leaflets (or *Risalah Maklumat Ubat untuk Pengguna- RiMUP*) contain basic information on a specific medication in a format suited for the general public. Currently, our website contains RiMUPs in two languages for over 600 products. You may search for a RiMUP by brand name or active ingredient. Topics covered include:

- what the medication is used for
- how it works
- what precautions to take
- what to do if a dose is missed
- possible side effects

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The 3 Clicks