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Adverse Drug Reaction News

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Consumer health product recalls

Voluntary recalls of mouth rinses and cleansing wipes

Over the recent months, the following four products were voluntarily recalled by their distributors following detection of *Burkholderia cepacia (B. cepacia)* in certain batches of the products:

- "Oral Guard Antiseptic-Antiplaque Mouthwash" by Medimex Singapore
- "Trihexid Chlorhexidine 0.2% Mouth Rinse" by Trident Pharm Pte Ltd
- "Pearlie White Fluorinze Fluoride Mouth Rinse" by Corlison Pte Ltd
- "Care Wipes" by Tai Sun Paper Products Pte Ltd (Singapore)

The consumer level recall was initiated as a precautionary measure to safeguard public health as the contaminated products may pose a health risk to susceptible individuals with health problems. This article provides an overview and update of the events to date.

Background Information

B. cepacia was first detected in *"Oral Guard Antiseptic-Antiplaque Mouthwash"* in early November 2010 after samples of the product were sent for microbial tests as part of HSA's product quality sampling checks. The microbial test reports revealed the presence of *B. cepacia* in certain batches of the product.

Following the detection of microbial contamination in the above mouthwash, HSA stepped up its quality surveillance testing of health products that are marketed in Singapore. A risk-based approach towards product sampling was taken, which took into consideration the products most likely to be contaminated by *B. cepacia*. HSA tested a range of likely affected health products including mouthwashes, cleansing wipes and alcohol swabs used in hospitals and the more commonly used mass-market brands. The results of these tests revealed two other mouthwashes (Trihexid, Pearlie White) and one brand of cleansing wipes (Care Wipes) to be similarly contaminated.

"Oral Guard Antiseptic-antiplaque Mouthwash", *"Trihexid Chlorhexidine 0.2% Mouth Rinse"* and *"Pearlie White Fluorinze Fluoride Mouth Rinse"* are mouthwashes which contain either chlorhexidine gluconate or cetylpyridinium chloride as the active ingredient and are labelled for use in a number of dental conditions such as dental plaque, mouth ulcers and maintenance of general oral hygiene. *"Care Wipes"* is a brand of disposable skin cleansing wipes.

Burkholderia cepacia (B. cepacia)

Burkholderia cepacia (B.cepacia)[1] is a gram-negative bacterium that is commonly found in water such as tap water, soil, and other environmental sources. It poses little medical risk to healthy people. However, individuals who are immunocompromised, and those with certain health problems like chronic lung diseases (particularly cystic fibrosis) may be more susceptible to severe infections with this bacterium.

Reports of *B. cepacia*-contaminated products overseas[1-3]

B. cepacia is known to contaminate health products. There have been reported cases of *B. cepacia* detected in a variety of products in other countries such as the United States (US), Australia and Canada. The types of products affected include mouthwashes, mouth gels, nasal sprays and hand sanitisers.

A recent case in November 2009 involved the recall of three lots of Vicks Sinex Nasal Spray by Procter & Gamble[2] in the US, Germany and the United Kingdom. The company detected *B. cepacia* in the product during routine quality control at its plant located in Germany. The company's analysis showed that the problem was limited to a single batch of raw material mixture involving three lots of product sold in the US, Germany and the UK. No reports of illness were received by the company.

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Quinine sulphate and serious haematological reactions

The Vigilance Branch of HSA would like to highlight that quinine sulphate is known to be associated with serious and life-threatening haematological reactions. Healthcare professionals are advised not to use it off-label for the management of nocturnal leg cramps due to its unfavourable benefit-risk profile for this condition.

Currently, there is a brand of quinine sulphate registered locally, namely Quinine Sulphate Tablets 300mg (Beacons Pharmaceuticals Pte Ltd) and is only indicated for the treatment of *Plasmodium falciparum* malaria resistant to other antimalarial drugs.

Reports from reference agencies

(A) US Food and Drug Administration (FDA)

In the US, quinine sulphate is only approved for the treatment of uncomplicated *P. falciparum* malaria. The FDA had concluded in their recent evaluation that the data is inadequate to establish the efficacy of quinine in the treatment of nocturnal leg cramps. Taking into consideration that leg cramps do not lead to serious consequences, the benefits of using quinine to treat leg cramps is outweighed by the risks of potentially fatal haematological reactions. The FDA is thus taking measures to ensure that quinine is used only for the approved treatment of uncomplicated malaria.[1]

(B) Australian Therapeutic Goods Administration (TGA) and New Zealand Medsafe

Quinine sulphate is indicated for the treatment of chloroquine-resistant malaria caused by *P. falciparum* in Australia and New Zealand. It is also approved for the treatment of myotonia in New Zealand. TGA, as well as the New Zealand Medicines and Medical Devices Safety Authority (Medsafe), had previously conducted reviews of adverse drug reaction reports associated with the use of quinine. Both agencies had similarly concluded that the benefit/risk profile of quinine no longer supported its use for the prevention and treatment of nocturnal leg cramps. As a result, TGA and Medsafe had required the licence holders of quinine products to remove nocturnal leg cramps from the indications of quinine-containing products.

Local situation

To date, HSA has received one adverse reaction report of thrombocytopenia and haematoma following use of quinine sulphate for the management of leg cramps. The 73 year-old Chinese female had been on quinine sulphate 300mg daily for approximately two years before the onset of the adverse reactions. She was also on two other concomitant drugs, rofecoxib and meloxicam, which might have contributed to the adverse reactions.

In view that nocturnal leg cramps is not an approved indication of quinine sulphate locally, HSA had requested the company to further strengthen the warnings on the package insert for quinine sulphate tablets:

> *"Quinine may cause unpredictable serious and life-threatening hematologic reactions including thrombocytopenia and hemolytic-uremic syndrome/thrombotic thrombocytopenic purpura (HUS/TTP) in addition to hypersensitivity reactions, QT prolongation, serious cardiac arrhythmias including torsades de pointes, and other serious adverse events requiring medical intervention and hospitalization. Chronic renal impairment associated with the development of TTP, and fatalities have also been reported. The risk associated with the use of quinine in the absence of evidence of its effectiveness for treatment or prevention of nocturnal leg cramps, outweighs any potential benefit in treating and/or preventing this benign, self-limiting condition."*

To alert healthcare professionals on the potential serious adverse reactions that have been reported for quinine sulphate tablets, a Dear Healthcare Professional Letter was also issued by Beacons Pharmaceuticals Pte Ltd in November 2010 to highlight these safety updates.[2] A copy of this letter is available from the MOHAlert archives which can be accessed via the respective healthcare professional board or council websites. Healthcare professionals are strongly advised to adhere to the licensed indications of quinine sulphate, and to report any suspected adverse reactions associated with its use to the Vigilance Branch of HSA.

References

1) *FDA Medwatch: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm218424.htm*
2) *HSA website. Dear Healthcare Professional Letters (DHCPL). http://www.hsa.gov.sg/DHCPL*

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■ Consumer Health Product Recalls – Voluntary recalls of mouth rinses and cleansing wipes ■

HSA's actions

HSA oversaw the voluntary consumer level recall of the affected products. Two Dear Healthcare Professional Letters were issued on 16 November 2010 and 29 December 2010 to alert healthcare professionals on the recall. The affected companies have since completed the recall of all contaminated stocks of their products from the market.

HSA is also working with the companies to identify the root cause of *B. cepacia* contamination in the affected products to ensure that future batches of these products meet product quality standards prior to their release back on the market. The products were manufactured by different manufacturers in different countries.

Root-cause analysis is a complex process which involves detailed microbial analysis of raw materials, the water used for manufacturing, the intermediates and final product and assessing the manufacturing environment to determine the source of contamination.

HSA administers an active postmarketing surveillance programme which involves regular post-market checks and product sampling of health products in the market to ensure that they meet product quality standards. The Vigilance Branch also evaluates adverse event reports received through its spontaneous reporting system and conducts daily environmental scanning for safety issues reported by overseas regulators to ensure timely detection of product safety issues. Healthcare professionals will be kept informed of any significant findings arising from the surveillance and tests.

References

1. *http://www.cdc.gov/HAI/organisms/bCepacia.html*
2. *http://www.fda.gov/Safety/Recalls/ArchiveRecalls/2009/default.htm*
3. *http://www.fda.gov/NewsEvents/Testimony/ucm213640.htm*

Illegal product "Jianbu Huqian Wan" [健步虎潛丸] found to contain Western medicinal ingredients

In December 2010, HSA issued a press release to warn consumers of an adulterated health product labelled "Jianbu Huqian Wan" [健步虎潛丸] which was tested by HSA's Pharmaceutical Laboratory to contain two undeclared western medicinal ingredients, namely dexamethasone and chlorpheniramine. The press release is available at http://www.hsa.gov.sg/press_releases.

This product was reported to HSA's Vigilance Branch by an astute member of the public who became suspicious of the product, when her mother experienced rapid relief from body aches soon after consuming the product over a short period of time. Her mother was also reported to be experiencing adverse reactions following the use of the illegal product.

About the Product

"JianBu HuQian Wan [健步虎潛丸]" is an illegal adulterated product which was bought from overseas and is labelled to treat joint pain, muscle aches and weak limbs. The product is presented in a yellow and green outer box, which contains a white bottle with red and white capsules.

Details of reported case

The 70 year-old elderly female patient was reported to have poor diabetic control as a result of taking the product. The patient was also reported to have developed varicose veins with blood clots, rapid weight gain and increased appetite. These symptoms are similar to the adverse effects caused by the prolonged use of dexamethasone. The patient has since stopped consuming the product and has recovered.

HSA's Advisory

Healthcare professionals are encouraged to ask their patients about the use of complementary medicines while taking their medication history. The information will be useful to the doctor in making a diagnosis of the patient's medical condition and identifying potential adverse events associated with complementary medicines. Healthcare professionals are also encouraged to alert the Vigilance Branch of HSA on any suspected adverse reactions in relation to complementary health products. When such signals are reported to the Vigilance Branch of HSA, further investigations will be conducted and actions taken to protect public health and safety as necessary.

Topical ketoprofen and photosensitivity reactions

HSA would like to remind healthcare professionals of the risk of photosensitivity reactions associated with topical ketoprofen.

Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. Topical ketoprofen-containing products have been available in Singapore since 1992, and were re-classified to Pharmacy Only (P) medicines in 1997. They are indicated for treating signs and symptoms caused by conditions such as rheumatoid arthritis, tendinitis, muscular pain, and pain and swelling resulting from minor trauma.

Review by European Medicines Agency (EMA)

In July 2010, the EMA completed a review of the safety and effectiveness of topical ketoprofen-containing products.[1] The review had been initiated due to concerns over the risk of skin photosensitivity reactions, including photoallergy as well as new skin reactions reported in people using topical ketoprofen together with products containing octocrylene (a chemical sunscreen found in several cosmetics and care products such as shampoo, skin creams, anti-ageing creams, make-up removers and hair sprays). These concerns were initially raised by the French medicines regulatory agency (Afssaps), which decided to suspend the marketing authorisation of all topical medicines containing ketoprofen in France in December 2009.

Having reviewed all available safety data, including data from EU member states' databases and data provided by the manufacturers, the EMA's Committee for Medicinal Products for Human Use (CHMP) concluded that the risk of serious photoallergic reactions was very low (one case per one million patients treated) and that the benefits of topical ketoprofen-containing products continue to outweigh their risks. However, the CHMP recommended that doctors should inform patients on how to use these medicines appropriately to prevent the occurrence of serious skin photosensitivity reactions.[2]

Local situation and HSA's advisory

Between 1993 and 2010, HSA received 45 reports of adverse drug reactions associated with the use of topical ketoprofen-containing products, of which 25 involved skin reactions such as dermatitis, rash, urticaria, and skin blistering. The majority (77%) of these skin reactions were assessed to be non-serious. No information was available as to whether these skin reactions were a result of photosensitivity reactions to these products.

Healthcare professionals are reminded to inform patients on how to use these products appropriately so as to prevent the occurrence of serious skin photosensitivity reactions. Advice to patients should include:

1) To ensure that treated areas are protected from sunlight during the whole period of topical ketoprofen treatment and for 2 weeks after stopping treatment
2) To stop treatment immediately if they develop any skin reaction after application of these medicines and seek their doctor's advice

Healthcare professionals are also strongly encouraged to report any adverse reactions suspected to be associated with topical ketoprofen-containing products to the Vigilance Branch of HSA.

References

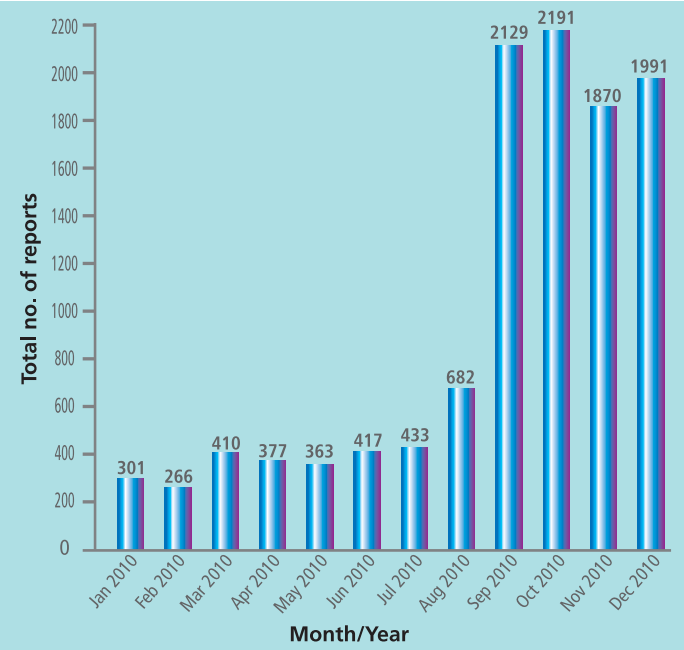
1. *http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/07/WC500094975.pdf*
2. *http://www.ema.europa.eu/docs/en_GB/document_libraryReferrals_document/Ketaprofen_107/WC500094971.pdf*

Analysis of adverse event (AE) reports for year 2010

In the year 2010, the Vigilance Branch (VB) of HSA received a total of 29,769 local reports of adverse events (AE) suspected to be related to health products. These reports were further screened[1] and a total of 11,267 reports were captured into the national AE database.

With effect from September 2010, all electronic reports with non-serious AE terms (eg, rash, watery eyes) received from the national electronic medical record exchange, known as the Critical Medical Information Store (CMIS) have been included in the AE database. The objective of this initiative is to facilitate the incorporation of quantitative signal detection and data mining tools. Chart A provides a breakdown of the reports received over the year 2010. The inclusion of reports with non-serious AE terms accounts for the significant increase in the number of reports from September 2010.

Chart A: No. of AE reports reviewed from Jan to Dec 2010 based on date of receipt



Types of health products involved

Majority of the reports analysed were associated with pharmaceuticals/biologics (97.6%) followed by vaccines (1.9%), complementary medicines including Chinese Proprietary Medicines (0.3%) and health supplements (0.2%).

Ethnic group, gender and age

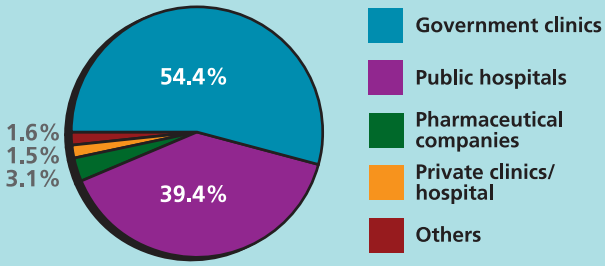
An analysis of the reports according to ethnic groups showed that Chinese patients constituted the highest proportion (69.5%) of AE reports, followed by Malays (8.6%) and Indians (6.0%). Majority of AEs were reported in patients between 50 and 69 years of age. There were more reports of AEs occurring in females (57.5%) than in males.

Source of AE reports

The majority of the reports received by VB was from healthcare professionals working in the government clinics (54.4%) followed by public hospitals (39.4%), pharmaceutical companies (3.1%) and private clinics/hospitals (1.5%). Please refer to Chart B for the source of the AE reports.

[1] *Reports lacking important details such as names of suspected drugs and AE descriptions will not be captured into the national AE database as they cannot be assessed for causality.*

Chart B: Source of AE Reports in 2010



Review of AE reports

Approximately 45% of all the reports analysed 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 AEs reported, based on system-organ classification, were skin-related disorders (43.8%), followed by body as a whole (i.e. general disorders such as pain, fever, oedema) (17.1%), and respiratory disorders (7.8%). Please refer to Table 2 for the full listing.

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

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

Ranking	Active ingredient	No. of reports (*)
1	Amoxicillin	940
2	Paracetamol	607
3	Diclofenac	535
4	Cotrimoxazole	506
5	Aspirin	388
6	Simvastatin	384
7	Ibuprofen	379
8	Naproxen	330
9	Enalapril	312
10	Hydrochlorothiazide	308

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

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

Ranking	System organ class	No. of reports (% #)
1	Skin & appendages	6,258 (43.8)
2	Body as a whole	2,451 (17.1)
3	Respiratory	1,119 (7.8)
4	Gastrointestinal	849 (5.9)
5	Nervous	759 (5.3)
6	Urinary	518 (3.6)
7	Metabolic & nutritional	419 (2.9)
8	Musculoskeletal	312 (2.2)
9	Heart	311 (2.2)
10	Psychiatric	236 (1.7)

*** 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

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■ Analysis of adverse event (AE) reports for year 2010 ■

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

Description	WHO preferred term	Suspected active ingredient≠ (the number in the bracket represents the number of times the drug has been implicated)
Blood disorders	Agranulocytosis/ neutropenia	Azathioprine (2), Benzathine Benzylpenicillin (1), Carbimazole (1), Clindamycin (1), Clopidogrel (1), Clozapine (1), Hydroxychloroquine (1), Levofloxacin (1), Naproxen (1), Omeprazole (1), Ticlopidine (1), Chlorpromazine (1), Cyclophosphamide (1), Gabapentin (1), Lamotrigine (1), Linezolid (1), Mycophenolate (2), Olanzapine (1), Omeprazole (1), Piperacillin And Tazobactam (1), Prednisolone (2), Tacrolimus (1), Valproic Acid (Valproate) (1), Vancomycin (2)
	Haemolytic anaemia	Anti-Thymocyte Immunoglobulin (1), Benzylpenicillin (1), Ceftriaxone (1), Clopidogrel, Dapsone (1), Sulfasalazine (1)
	Leucopenia	Azathioprine (1), Cefazolin (1), Cotrimoxazole (3), Codeine (1), Quetiapine (1), Valganciclovir (1)
	Pancytopenia	Azathioprine (2), Carboplatin (1), Ceftriaxone (1), Cotrimoxazole (3), Diclofenac (1), Lenalidomide (2), Orphenadrine (1), Paracetamol (1), Pemetrexed (1), Zidovudine (1)
	Thrombocytopenia	Abciximab (1), BCG (1), Carbamazepine (4), Cefazolin (1), Chlorpheniramine (1), Clopidogrel (1), Clozapine (1), Diclofenac (1), Diltiazem (1), Ethambutol (1), Everolimus (1), Heparin (8), Hepatitis B (2), Ibuprofen (1), Isoniazid (1), Laropiprant, Niacin (1), Linezolid (2), Mefloquine (1), Piperacillin And Tazobactam (2), Pyrazinamide (1), Rifampicin (1), Sorafenib (1), Sunitinib (1), Trabectedin (1), Valproate (5), Vancomycin (1)
Hepatic disorders	Cholestatic hepatitis	Carbimazole (2), Celecoxib (1), Ticlopidine (1)
	Hepatitis/hepatitis with jaundice	Allopurinol (8), Azathioprine (4), Carbamazepine (5), Celecoxib (1), Chlorpromazine (2), Ciprofloxacin (1), Cloxacillin (1), Colchicine (1), Cotrimoxazole (6), Dapsone (5), Diclofenac (5), Erythromycin (2), Ethambutol (2), Ethambutol (2), Isoniazid (2), Fenofibrate (1), Heparin (1), Herbal Extracts (1), Ibuprofen (1), Indometacin (2), Isoniazid (2), Itraconazole (1), Ketoconazole (1), Lamotrigine (1), Lovastatin (1), Metronidazole (1), Mirtazapine (1), Moxifloxacin (1), Naproxen (1), Nevirapine (1), Nifedipine (1), Paracetamol (2), Phentermine (1), Phenytoin (1), Piperacillin And Tazobactam (2), Pyrazinamide (1), Pyridoxine (Vit B6) (1), Pyrimethamine (4), Rifampicin (2), Simvastatin (5), Sulfasalazine (1), Ticlopidine (1), Tolterodine (1), Valproic Acid (2)
Skin disorders	Stevens-Johnson syndrome (SJS)/ toxic epidermal necrolysis (TEN)/SJS-TEN	Allopurinol (6), Amlodipine (1), Aspirin (1), Amoxicillin (3), Ampicillin (1), Benzylpenicillin (1), Carvedilol (2), Cefepime (1), Ceftriaxone (1), Celecoxib (2), Ciprofloxacin (2), Clopidogrel (1), Cloxacillin (1), Coamoxiclav (5), Cotrimoxazole (9), Carbamazepine (21), Carbimazole (2), Cefalexin (2), Ceftazidime (1), Chlormezanone (1), Chlorpromazine (1), Ciprofloxacin (2), Cloxacillin (1), Diclofenac (2), Enalapril (4), Esomeprazole (2), Etoricoxib (5), Fenofibrate (1), Foscarnet (1), Gimeracil (1), Glipizide (1), Hydroxychloroquine (2), Ibuprofen (1), Isosorbide Mononitrate (1), Lamotrigine (2), Meropenem (2), Metronidazole (1), Mefenamic Acid (1), Metronidazole (1), Midecamycin (1), Naproxen (2), Neomycin (1), Nevirapine (3), Nicotinic Acid (1), Oteracil Potassium (1), Omeprazole (6), Phenytoin (10), Piperacillin And Tazobactam (1), Pantoprazole (1), Phenobarbitone (1), Phenoxymethylpenicillin (1), Probenecid (1), Propylthiouracil (1), Simvastatin (3), Strontium Ranelate (2), Sulfadiazine (1), Tegafur (1), Tetracycline (1), Vancomycin (2)

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

Table 4: Top 5 vaccines, number of reports received and examples of serious VAEs

Ranking	Vaccine received	Total no. of reports events	Examples of some serious adverse reported
1	Bacillus Calmette-Guerin (BCG)	28	Lymphadenitis (12), injection site abscess (4)
2	Pneumococcal	25	Kawasaki disease (2), seizures with or without fever (2)
3	Hepatitis B	18	Thrombocytopenia (2), persistent or abnormal crying (3)
4	5- in- 1^	15	Seizures with or without fever (4), injection site abscess (2), celluitis (2)
5	6- in- 1+	14	Seizures with or without fever (3)

^ *5-in-1 includes Diphtheria, Pertussis, Tetanus, inactivated Polio and Haemophilius influenza type B vaccines*

\+ *6-in-1 includes 5-in-1 and Hepatitis B vaccines*

Analysis of Vaccine adverse event (VAE) reports

A total of 191 suspected VAE reports were received, of which 105 reports (55%) were classified as serious. 120 reports (65%) involved children less than 12 years of age which corresponds with the age-group of vaccinees under the National Childhood Immunisation Schedule. Out of the 120 reports, 23 (19%) reports involved more than one vaccine. The top five suspected vaccines commonly reported to cause AE in children are listed in table 4.

Reports on adulterated products

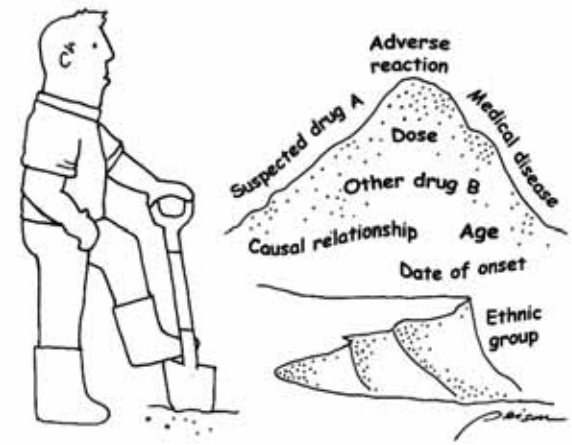
Through reports submitted by healthcare professionals and feedback from alert members of the public, the Vigilance Branch has detected drug safety problems associated with three adulterated products and taken actions to safeguard public health. The products are Te Xiao Huo Luo Jing Dan [特效活络金丹], JianBu HuQian Wan [健步虎潜丸] detected in November 2010 and Horkut Chooi Foong Hor Lok Tan [虎骨追风活络丹] in December 2010.

The adulterants found in these products were dexamethasone, chlorpheniramine, paracetamol, dextromethorphan and indomethacin.

Conclusion

Singapore has maintained a good reporting rate of over 500 reports per million inhabitants per year for the past five years. According to a recent report published by WHO's Uppsala Monitoring Centre, Singapore was ranked third in terms of the number of valid reports per million inhabitants that was submitted to the WHO global database. Singapore has moved up from the eighth position in 2009 to the third position this year. The Vigilance Branch would like to take this opportunity to thank healthcare professionals for your active participation in the national AE monitoring programme of health products. Your invaluable support and contribution in submitting good quality AE reports is imperative so that we can continue to work in partnership to promptly detect potential safety signals related to health products and take actions to safeguard public health.

Call for quality adverse event (AE) reports



Each year, a substantial number of reports received from the Critical Medical Information Store (CMIS) are not included in the national database as they lack certain essential information for causality assessment, such as the name of the suspected drug and description of the adverse event (AE). We recognise that complete information for a case report may not be readily available at the time of reporting. Nevertheless, a minimum criteria is needed for a report to qualify for causality assessment. This includes the name of the suspected drug, date of administration of the suspected drug, description of the AE, and date of onset of the AE. Where possible, information such as the indication and dosage of the suspected drug, administration of concomitant drugs, presence of co-morbidities and outcome of the patient will greatly facilitate our internal review and provides a more conclusive assessment. Please refer to table 1 for the list of information required on an AE report.

Table 1 : List of information required on an AE report

Information required	Details required	Rationale
Patient's details	Initials, gender, age/date of birth	To identify duplicate reports
Reporter's details	Name, place of practice, contact number)	For /Verification of reports
Details of adverse event	Date of onset/latency, concise description (e.g. type of rash).	For causality assessment
Suspect health product	Brand name or active ingredient(s), dose, therapy dates	Brand name preferred in case of brand specific AEs.
Concomitant health product(s)	Complementary medicines, interaction between two medicines	To identify confounders
Other relevant information	Pre-existing conditions, known allergies, test done and results	
Outcome	Recovery status, Sequelae	
Seriousness of event	Should only be serious based on criteria below: ■ Patient died due to reaction ■ Congenital anomaly ■ Involved or prolonged in-patient hospitalisation ■ Involved persistent or significant disability or incapacity ■ Medically significant ■ Life threatening	
Treatment given to patient	Yes /No. If yes, specify.	

Reports of unintended pregnancies related to etonorgestrel implant (Implanon®)

Implanon® (SOL limited) is a sub-dermal contraceptive implant which contains 68mg of etonogestrel and has been licensed in Singapore since May 2002.

Background

Recently, the UK Medicines and Healthcare products Regulatory Agency (MHRA) has announced that there have been reports of problems with inserting and removing Implanon® and that in some women who have had an unintended pregnancy, Implanon® was found not to have been inserted at all.

Based on statistics provided by the company, the distribution of Implanon® in Singapore is estimated to be 6,597 implants between May 2002 to September 2010. During this period, the company has received 4 medically confirmed spontaneously reported unintended pregnancies (0.06 unintended pregnancies per 100 implants distributed).

The correct technique of Implanon® insertion

Implanon® should be inserted subdermally using a sterile disposable applicator at the inner side of the non-dominant upper arm about 8-10cm above the medial epicondyle of the humerus. There is a possibility of the implant falling out of the needle prior to insertion. The applicator should therefore always be held in the upward position until the time of insertion. To ensure proper insertion, the doctor must first visually verify the presence of the implant in the applicator while keeping the shield on the needle and then confirm the successful insertion by palpation of the implant. The presence of the implant should be verified by palpation and women should be shown how to feel its location at the time of fitting.

In cases where the implant cannot be palpated or when the presence of the implant is doubtful, it is recommended that other suitable methods such as ultrasound or magnetic resonance imaging be used to confirm its presence. If imaging methods also fail, it is advisable to verify the presence of the implant by measuring the etonogestrel level in a blood sample of the women.

Advisory and call for reports of unintended pregnancies

The proper insertion of Implanon® is crucial for its efficacy. An implant that is not inserted on the correct day or not inserted properly can result in an unintended pregnancy. Pregnancy should also be excluded before the insertion of Implanon®.

Implanon® should be inserted by someone who is familiar or trained with the proper technique of insertion. Healthcare professionals are advised to follow the instructions on the package insert on proper insertion of Implanon® and to attend training sessions organised by the manufacturer (MSD) on the proper technique of Implanon® insertion.

You are also strongly encouraged to promptly report any cases of unintended pregnancies in patients using Implanon® to the Vigilance Branch of HSA.

Recall of Affected Lots of 1•DAY ACUVUE® TruEye™ Contact Lenses

The Health Sciences Authority would like to update healthcare professionals on the two voluntary recalls of limited lots of 1•DAY ACUVUE® TruEye™ Contact Lenses in August and October 2010 that were conducted by Johnson & Johnson Vision Care. The recalls were initiated due to reports in Japan of eye irritation or discomfort resulting from the use of this product.

Background

1•DAY ACUVUE® TruEye™ Contact Lenses is indicated for daily wear single-use only for the correction of refractive ametropia in phakic or aphakic persons with non-diseased eyes who may have 1.00D or less of astigmatism. In August 2010, Johnson & Johnson Vision Care reported that they had received a limited number of complaints in Japan associated with the use of this 1•DAY ACUVUE® TruEye™ Contact Lens. These complaints describe an unusual stinging or pain upon the insertion of the lens from certain lots of the product.

Investigations conducted by Johnson & Johnson Vision Care revealed that a manufacturing issue in the lens rinsing process during a certain timeframe on one of the manufacturing lines had led to some of the lenses not being properly rinsed. The 1•DAY ACUVUE® TruEye™ Contact Lenses were manufactured in Ireland, and the company had assessed that this was an isolated incident.

Regulatory Actions

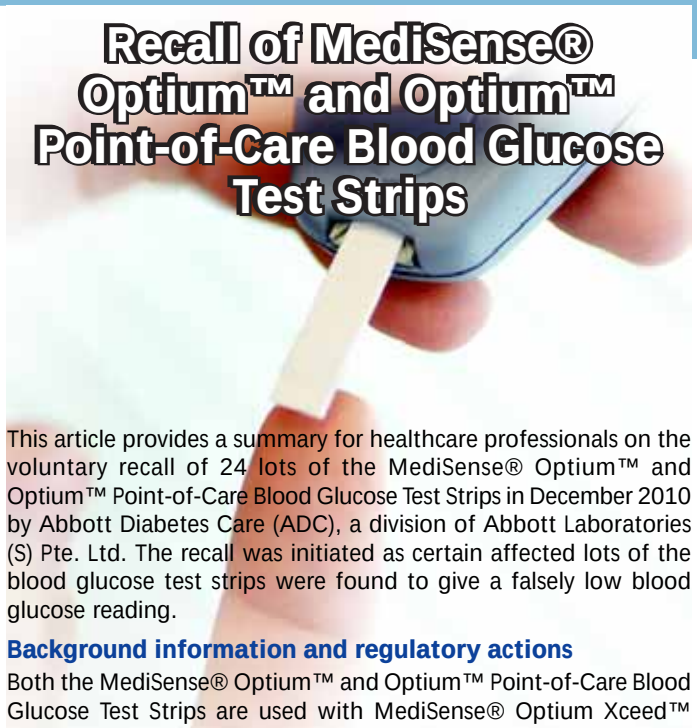
Johnson & Johnson Vision Care had distributed 1,557 boxes of the affected lots, each containing 30 lenses to various optical outlets in Singapore in 2010. In August 2010, Johnson & Johnson Vision Care ceased the supply and initiated an immediate recall of these affected lots of contact lenses. All retailers, including optometrists and optical outlets were also informed of this regulatory action. The first recall of the affected lots was completed by 23 August 2010. The second recall, including the full destruction of affected lenses, was completed by 10 January 2011.

HSA has also issued a press release in August 2010 followed by an update on the HSA website to advise members of the public to stop using the affected lots of 1•DAY ACUVUE® TruEye™ Brand Contact Lenses. Consumers who are in doubt of the product lot number should consult a doctor if they experience symptoms of eye irritation or feel unwell after using this product. The press release is available at http://www.hsa.gov.sg/press_releases.

Advisory

To date, HSA and Johnson & Johnson Vision Care Singapore have not received any adverse reaction reports associated with the use of 1•DAY ACUVUE® TruEye™ Contact Lenses. Healthcare professionals are advised to report any adverse reactions associated with the use of 1•DAY ACUVUE® TruEye™ Contact Lenses to the Medical Device Branch of HSA.

Recall of MediSense® Optium™ and Optium™ Point-of-Care Blood Glucose Test Strips



This article provides a summary for healthcare professionals on the voluntary recall of 24 lots of the MediSense® Optium™ and Optium™ Point-of-Care Blood Glucose Test Strips in December 2010 by Abbott Diabetes Care (ADC), a division of Abbott Laboratories (S) Pte. Ltd. The recall was initiated as certain affected lots of the blood glucose test strips were found to give a falsely low blood glucose reading.

Background information and regulatory actions

Both the MediSense® Optium™ and Optium™ Point-of-Care Blood Glucose Test Strips are used with MediSense® Optium Xceed™ Blood Glucose Monitoring System, for the purpose of monitoring blood glucose levels. The MediSense® Optium™ and Optium™ Point-of-Care Blood Glucose Test Strips are available in four pack sizes; 10, 25, 50 or 100 test strips per box.

ADC initiated the recall of certain lots of MediSense® Optium™ and Optium™ Point-of-Care Blood Glucose Test Strips following a routine internal quality review that showed blood glucose test strips from these affected lots may give falsely low blood glucose readings. The falsely low blood glucose readings were due to a longer than normal blood fill times. The normal blood fill time for the blood glucose strips should be no longer than five seconds. In the case of these recalled lots, the fill time may be affected by the age of the test strips and whether the strips have been exposed to temperatures exceeding 30°C for an extended period of time.

As a result of these inaccurate blood glucose readings, falsely low blood glucose readings may result in users trying to raise their blood glucose unnecessarily and those with normal to high readings not treating their elevated blood glucose adequately.

Regulatory actions and advisory

All affected lots of the Abbott MediSense Optium™ Blood Glucose Test Strips distributed locally have been voluntarily recalled by ADC in December 2010.

HSA has issued a press release on 24 December 2010 to advise members of the public to stop using the affected lots of the glucose test strips, to consult a doctor if they experience symptoms of hyper- or hypoglycaemia due to treatment based on readings obtained from the affected test strips and to contact their healthcare providers for other glucose testing options if they need to adjust their insulin therapy. The press release is available at http://www.hsa.gov.sg/press_releases

In a Dear Healthcare Professional Letter (DHCPL) issued by ADC on 30 December 2010, healthcare professionals were advised to immediately stop the supply and to return the affected lots of both MediSense® Optium™ and Optium™ Point-of-Care Blood Glucose Test Strips to the company.

The blood glucose meter, MediSense® Optium Xceed™ Blood Glucose Monitoring System, that uses the affected blood glucose test strips are not being recalled and can continue to be used. To date, HSA has not received any adverse reaction reports related to the use of MediSense® Optium™ and Optium™ Point-of-Care Blood Glucose Test Strips. Healthcare professionals are encouraged to report any adverse reactions suspected to be related to the use of the affected blood glucose test strips to the Medical Device Branch of HSA.

HRT Safety Update

Combined oestrogen plus progestogen therapy found to increase breast cancer risk

The HSA Vigilance Branch would like to update healthcare professionals on the recent findings of an 11-year follow-up of post-menopausal women in the Women's Health Initiative (WHI) study and remind healthcare professionals of the importance of appropriate use of hormone replacement therapy (HRT).

Background to the WHI study

The WHI study is a randomised, placebo-controlled trial conducted in postmenopausal women aged 50 to 79 years with an intact uterus. The objective was to assess the major health benefits and risks of the most commonly used combined HRT in the United States - oestrogen plus progestogen therapy (0.625mg conjugated oestrogen plus 2.5mg medroxyprogesterone).[1] The trial, with a planned duration of 8.5 years, ended prematurely in 2002 after a mean of 5.6 years because an increased risk for breast cancer and an overall negative benefit-risk ratio was seen in the HRT group.

In response to the earlier findings from the trial, HSA had published a series of bulletin articles in 2002 and 2004 to update healthcare professionals on the benefits and risks of oral combined HRT in women with an intact uterus.[2,3] HSA requested that product licence holders of the relevant oral combined HRT preparations in Singapore update the study findings in the package inserts of these products. A public advisory was also issued by HSA, in consultation with medical experts in the management of HRT, to advise physicians not to use HRT for the prevention of coronary heart disease.[4]

Latest findings from the WHI study[5]

Following termination of the study intervention phase in 2002, clinical visits and follow-up continued throughout the post-intervention and study extension phases to investigate the long-term effects of combined HRT on cumulative breast cancer incidence and mortality. Continued follow-up for breast cancer incidence was carried out in 12,788 (83%) of the surviving participants from the original trial for a mean of 11 (SD 2.7) years. Results from this continual follow-up of participants showed that oestrogen plus progestogen was associated with a greater incidence of breast cancer compared to placebo (385 cases [0.42% per year] versus 293 cases [0.34% per year]; hazard ratio [HR], 1.25; 95% CI, 1.07-1.46; p=0.004). In addition, this current analysis found breast cancers in the combined HRT group more likely to be node-positive (81 [23.7%] versus 43 [16.2%], respectively; HR, 1.78; 95% CI, 1.23-2.58; p=0.03).

Breast cancer mortality also appeared to be increased with combined use of oestrogen plus progestogen. There were more deaths directly attributed to breast cancer (25 deaths [0.026% per year] versus 12 deaths [0.013% per year]; HR, 1.96; 95%CI, 1.00-4.04; p=0.049) among women in the combined HRT group compared with women in the placebo group. However, it should be noted that in terms of absolute rates, the risk of breast cancer mortality was low, representing an additional 1.3 deaths from breast cancer per 10,000 women per year attributable to combined HRT. The wide confidence intervals with lower limits close to 1.0 also imply that these results should be interpreted with caution. Similar results were obtained for all-cause mortality after breast cancer diagnosis with 51 deaths (0.053% per year) in the combined HRT group compared to 31 deaths (0.034% per year) in the placebo group (HR, 1.57; 95% CI, 1.01-2.48; p=0.045). Additional secondary analyses conducted to examine the potential effect of excluding data from women who did not re-consent to follow-up supported the primary analyses.

Similar findings from the Million Women Study

The findings from the WHI study were consistent with those from the Million Women Study (MWS), a cohort study investigating the effects of specific types of HRT on incident and fatal breast cancer.[6] Approximately 1.08 million women aged 50 to 64 years were recruited into the MWS and half of them had used HRT. In the MWS, higher breast cancer mortality was observed in current users of HRT at recruitment compared to those with no prior use (HR, 1.22; 95% CI, 1.00-1.48; p=0.05). In current users of each type of HRT, the risk of breast cancer increased with increasing total duration, with an estimated 6 and 19 additional cancers per 1000 users of oestrogen-progestogen combinations after 5 and 10 years of HRT use, respectively.

Local situation

There are eight oral combination oestrogen plus progestogen preparations registered locally. All eight products contain estradiol as the oestrogen component instead of conjugated oestrogens (which was used in the WHI study). These products are contraindicated for use in patients with known, past or suspected breast cancer. To date, HSA has not received reports of breast cancer associated with the use of combined HRT.

HSA's advisory

HSA would like to remind healthcare professionals that HRT does not protect postmenopausal women against cardiovascular events and that HRT should not be initiated or continued for the purpose of reducing cardiovascular risk or preventing coronary heart disease. For the treatment of menopausal symptoms, HRT is beneficial in the short term and should be used at the lowest effective dose, for the shortest duration of treatment. Women on HRT should have their therapy and health reviewed regularly. As the potential harm may outweigh the potential benefits for women who are using HRT solely for the long-term prevention of osteoporosis, it is recommended that patients are made aware of other non-HRT therapies for the treatment and prevention of osteoporosis. Any serious adverse reactions suspected to be related to HRT should be reported to HSA's Vigilance Branch.

References

1. *JAMA 2002;288:321-333*
2. *HSA Adverse Drug Reaction News. August 2002, Vol 4 No. 2*
3. *HSA Adverse Drug Reaction News. July 2004, Vol 6 No. 2*
4. *http://www.hsa.gov.sg/press_releases.html*
5. *JAMA 2010;304:1684-16*
6. *Lancet 2003;362:419-427*

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All website references were last accessed on 30 Mar 2011.