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Adverse Drug Reaction News

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Risk of rare but serious skin reactions associated with the use of ustekinumab

HSA would like to bring the attention of healthcare professionals to overseas cases of rare but serious skin reactions, namely exfoliative dermatitis and erythrodermic psoriasis, which have been reported in patients receiving ustekinumab.

Ustekinumab (Stelara®, Johnson & Johnson Pte Ltd) is a fully human IgG1κ monoclonal antibody that has been registered locally since September 2009, for the treatment of adult patients with moderate to severe plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including cyclosporin, methotrexate, and psoralen combined with ultraviolet A (PUVA). It is also indicated for the treatment of adult patients with active psoriatic arthritis when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate.

Overseas cases of rare but serious skin reactions

Overseas cases of exfoliative dermatitis and erythrodermic psoriasis have been reported rarely (≥1/10,000 to <1/1,000) in psoriasis patients receiving ustekinumab.[1] These skin reactions were observed to occur within a few days of receiving ustekinumab and were severe, life-threatening reactions that could lead to hospitalisation. It is acknowledged that there could be a potential for confounding by indication in these cases. This is because ustekinumab is indicated for plaque psoriasis and patients may develop erythrodermic psoriasis as part of the natural course of their disease, presenting with symptoms that may be indistinguishable from exfoliative dermatitis.

International regulatory actions

In September 2013, the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) initiated a safety review on exfoliative dermatitis associated with ustekinumab.[2] This signal was identified through routine pharmacovigilance surveillance in the United Kingdom, where 12 cases of exfoliative dermatitis and 15 cases of erythrodermic psoriasis associated with ustekinumab treatment were received. Upon completion of their review of the initial signal detection analysis as well as clinical and post-marketing data submitted by the marketing authorisation holder, PRAC concluded that the package insert (PI) for ustekinumab should be updated to include the risk of exfoliative dermatitis and skin exfoliation.[3] A safety communication letter was issued to dermatologists in Europe to highlight this new potential risk.

In November 2014, Health Canada issued a safety review summary highlighting the possible link between exfoliative dermatitis and erythrodermic psoriasis and ustekinumab treatment.[4] In the safety review, Health Canada reported that it had received five reports of skin exfoliation (two serious and three non-serious) and one non-serious report of exfoliative dermatitis associated with the use of ustekinumab. A communication letter was issued to inform healthcare professionals about this safety concern and changes to the Canadian prescribing information were also implemented.

Local situation and HSA's advisory

HSA has not received any local reports of exfoliative dermatitis and erythrodermic psoriasis associated with the use of ustekinumab.

In view of the seriousness of these events, the local PIs of ustekinumab-containing products have been strengthened to include warnings on these skin reactions. When prescribing ustekinumab to patients, healthcare professionals are advised to take into consideration the above safety information and signs and symptoms of erythrodermic psoriasis or exfoliative dermatitis. These may manifest as redness and shedding of the skin over a large area of the body, which may be painful and/or itchy. Increasing the awareness of patients and caregivers to the possible appearance of such skin reactions, through counselling, may facilitate prompt seeking of medical attention.

HSA will continue to monitor these signals and update healthcare professionals if new information arises.

References

1 *http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2014/42613a-eng.php*
2 *http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2013/10/WC500152672.pdf*
3 *http://www.ema.europa.eu/docs/en_GB/document_library/PRAC_recommendation_on_signal/2014/02/WC500162042.pdf*
4 *http://www.hc-sc.gc.ca/dhp-mps/medeff/reviews-examens/stelara-eng.php*

CONTENTS

Analysis of adverse event reports for Year 2014

In 2014, the Vigilance and Compliance Branch of HSA captured a total of 20,176 valid[a] local adverse event (AE) reports suspected to be related to health products.[b] As of end 2014, there were approximately 170,800 AE reports in the national database since data collection started in 1993.The breakdown of the number of valid reports captured in the national AE database from 2006 to 2014 based on the date of receipt is illustrated in Figure 1. A total of 64 Dear Healthcare Professional Letters (DHCPLs) were issued last year to communicate important safety issues to healthcare professionals.

Demographics

There were more AE reports received for females (54%) than males (43%), and 3% of reports did not indicate the gender of the patients. Patients in the age group of 20-29 and 50-59 constituted the largest proportion of patients with AEs reported (15% each).

Reporter source and type

Majority of the AE reports were from public hospitals (52%) and polyclinics (36%), with 5% from private clinics/hospitals and 2% from drug companies. Healthcare professionals, namely doctors (85%) and pharmacists (11%), contributed to the majority of reports.

Type of health products involved

The majority of the AEs reported were associated with pharmaceuticals/biologics (98%) followed by vaccines (1%). Complementary medicines including Chinese Proprietary Medicines, health supplements and other traditional medicines accounted for 1% of the reports.

Review of AE reports

The top ten most commonly reported active ingredients suspected to cause AEs are listed in Table 1. A substantial number of AEs reported for these drugs include rash, periorbital oedema and angioedema.

AEs by System Organ Class

Most of the reports were skin-related disorders, followed by those affecting the body as a whole and respiratory disorders as shown in Table 2.

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

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

[b] *Health products include drugs, vaccines and complementary health products but exclude medical devices.*

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Figure 1. Number of AE reports captured into AE database from Year 2006 to 2014 based on date of receipt

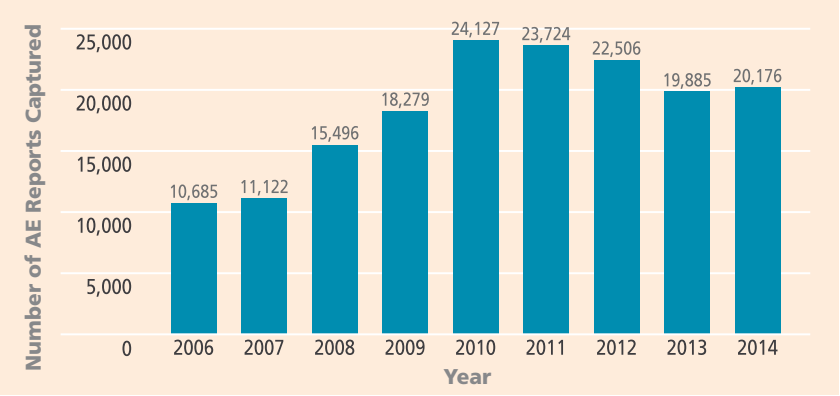

Table 1. Top 10 drugs (by active ingredients) suspected of causing AEs

Ranking	Active ingredient	No. of reports (*)
1	Coamoxiclav	1,261
2	Paracetamol	1,205
3	Amoxicillin	1,126
4	Diclofenac	1,086
5	Ibuprofen	1,079
6	Cotrimoxazole	754
7	Naproxen	748
8	Aspirin	687
9	Ciprofloxacin	440
10	Mefenamic Acid	426

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

Table 2. Top 10 AEs by System Organ Class^

Ranking	System Organ Class	Number of reports	% of total number of AE terms quoted
1	Skin and Appendages Disorders e.g., angioedema, pruritus, rash	12,261	52.3
2	Body as a Whole - General Disorders e.g., anaphylaxis, fever, oedema, pain	4,197	17.9
3	Respiratory System Disorders e.g., coughing, shortness of breath, stridor, wheezing	1,458	6.2
4	Central and Peripheral Nervous System Disorders e.g., convulsions, dizziness, headache, oculogyric crisis	1,226	5.2
5	Gastro-Intestinal System Disorders e.g., abdominal pain, diarrhoea, nausea, vomiting	1,219	5.2
6	Urinary System Disorders e.g., urinary retention, interstitial nephritis	827	3.5
7	Musculo-Skeletal System Disorders e.g., arthralgia, body aching, myalgia, rhabdomyolysis	313	1.3
8	Vascular (extra-cardiac) Disorders e.g., flushing, vasculitis, stroke	312	1.3
9	Heart Rate and Rhythm Disorders e.g., arrhythmia, bradycardia, QT prolongation, palpitation	253	1.1
10	Metabolic and Nutritional Disorders e.g., gout, azotaemia, increased creatinine kinase	219	0.9

^ *The System Organ Class refers to the adverse reaction terminology developed by the World Health Organisation (WHO).*
(NB: More than one AE term may be described in an AE report)

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■ **Analysis of adverse event reports for Year 2014** ■

Table 3. Drugs suspected of causing serious adverse reactions

Description	WHO preferred term	Suspected active ingredient(s) *(the number in the bracket represents the number of times the drug has been implicated#)*
Skin Disorders	Stevens-Johnson Syndrome (SJS)/ Toxic Epidermal Necrolysis (TEN)/ SJS-TEN	Allopurinol (6), Phenytoin (6), Ciprofloxacin (5), Omeprazole (5), Coamoxiclav (5), Piperacillin and Tazobactam (4), Lamotrigine (4), Ceftriaxone (3), Diclofenac (3), Meropenem (3), Amoxicillin (2), Cefalexin (2), Cefazolin (2), Ceftazidime (2), Celecoxib (2), Mefenamic Acid (2), Valproate (2), Vancomycin (2)
Body as a whole	Drug Hypersensitivity Syndrome	Phenytoin (3), Allopurinol (2), Cotrimoxazole (2), Ethambutol (2), Isoniazid (2), Lamotrigine (2), Pyrazinamide (2), Rifampicin (2)
Blood disorders	Agranulocytosis/ Neutropenia/ Neutropenic sepsis	Carbimazole (4), Clozapine (3), Cyclophosphamide (3), Doxorubicin (3), Prednisolone (3), Vincristine (3), Azathioprine (2), Gemcitabine (2), Imatinib (2), Rituximab (2)
	Leucopenia	Valproate (2)
	Pancytopenia	Azathioprine (4), Cotrimoxazole (3), Cefazolin (2)
	Thrombocytopenia	Valproate (11), Piperacillin and Tazobactam (4), Heparin (2), Ruxolitinib (2)
Hepatic disorders	Hepatitis/ Hepatitis Cholestatic/ Jaundice/Hepatotoxic effect	Coamoxiclav (6), Atorvastatin (3), Isoniazid (2), Pyrazinamide (2), Rifampicin (2), Simvastatin (2)

 # More than one suspected drug may be implicated in a single AE report. Only active ingredients implicated more than once are listed here.

AE reports associated with vaccines

In 2014, HSA received a total of 249 AE reports suspected to be associated with vaccines, of which 209 reports (84%) involved children aged 12 years and below, which corresponds to the age group of vaccinees under the National Childhood Immunisation Schedule. Of these, 84% of the reports (n=176) were captured by KK Women's and Children's Hospital (KKH) active surveillance sentinel site.[1] The commonly reported AEs and the implicated vaccines in children include seizures with measles, mumps and rubella (MMR), MMR and varicella (MMRV), pneumococcal conjugate (PNC) or 5-in-1 vaccines, and suppurative lymphadenitis or injection site reactions with the *Bacillus Calmette-Guérin* (BCG) vaccine. Fever, hypersensitivity reactions, Kawasaki disease, thrombocytopenia and vaccine failure were also reported with a variety of vaccines. In the reports of seizures, more than one vaccine was implicated in 38% of the cases.

Based on trend analysis, there was a decrease in the number of reports of suppurative lymphadenitis received for the BCG vaccine from more than 70 reports in 2012 and 2013 to 18 reports in 2014. Analysis by the vaccinated cohort showed that following a peak in cases reported in the 2011 vaccinated cohort, the incidence of suppurative lymphadenitis has since returned to baseline levels.[2]

Eighteen more reports of seizures were received for MMR, MMRV, PNC and 5-in-1 vaccines combined compared to 2013. The number of reports remained consistent with the expected frequencies of occurrence listed in the package inserts of these vaccines or in literature.

Other commonly reported vaccines suspected to cause AEs in adults and children above 12 years of age were the seasonal influenza vaccine, tetanus toxoid vaccine and human papillomavirus (HPV) vaccines. Majority of these reports described non-serious events such as hypersensitivity and injection-site reactions. There were isolated reports of anaphylaxis with the tetanus toxoid vaccine, seizures with the pertussis vaccine, thrombocytopenia with the pneumococcal polysaccharide vaccine and vaccine failure with the influenza or varicella vaccine.

AE reports associated with complementary health products

There were a total of 155 AE reports involving complementary health products (CHPs) which included health supplements, complementary medicines and cosmetics. Some of the AE reports were associated with more than one suspected product.

Of the 110 reports describing hypersensitivity reactions, 70% were associated with glucosamine and included AEs such as rash, pruritus and periorbital oedema. There were 12 reports describing hepatic reactions (e.g., raised liver enzymes and jaundice) associated with CHPs. However, it was difficult to ascertain the ingredient which may have caused the hepatic reaction as CHPs are often used in various combinations, at different doses and for varying durations.

Through the vigilance of astute clinicians, HSA detected 11 adulterated CHPs. As a result, five press releases were issued to alert the public to the dangers of the illegal health products. Most of the adulterated CHPs were marketed as capsules/pills for pain relief, slimming or sexual enhancement. Some of the adulterants detected included corticosteroids (e.g., betamethasone and dexamethasone), analgesics (e.g., paracetamol and NSAIDs, such as indomethacin, piroxicam and diclofenac) and sibutramine.

Acknowledgement

HSA would like to take this opportunity to thank all healthcare professionals for your active participation in the reporting of AEs. Your continuous vigilance and support are imperative towards our goals of detecting potential safety signals in a timely manner and taking actions promptly to safeguard public health.

Caveat for interpreting the AE figures

AE reports describe one or more AEs that have occurred in association with a health product including drug, vaccines and CHP but do not necessarily mean that the health product has been determined to be the cause of the AE. Many other factors need to be taken into account in assessing causal relationships and these include the presence of underlying diseases and medical conditions and the possible contribution of concomitant medicines.

It is worthwhile to note that the volume of AE reports for a particular health product may be influenced by the extent of use of the product, publicity, nature of reactions and other factors which vary over time. In addition, the date mentioned in each report is often the date of receipt of the report rather than the actual date of the onset of the AE. Therefore the number of reports should not be used to determine or measure the frequency of an AE.

References

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2 *HSA ADR News Bulletin 2014 Dec;16: 1-2*

MEDICAL DEVICE INFORMATION UPDATE (2)

Medical device regulations in the European Union

This article provides a brief overview on the regulation of medical devices in the European Union (EU). This is the second article in the educational series to enhance the understanding of healthcare professionals on the various issues associated with medical device regulation.

EU Directives affecting medical devices

Singapore regulates all medical devices under the Health Products (Medical Devices) Regulations. In the EU, the European Council has three separate directives for medical device regulations, namely the Active Implantable Medical Devices Directive (AIMDD) for active implantable medical devices, the In-Vitro Diagnostic Medical Devices Directive (IVDD) for in-vitro diagnostic devices and the Medical Device Directive (MDD) for general medical devices. As the EU comprises twenty-five member states, four European Free Trade Association (EFTA) countries and Turkey, these directives need to be transposed into the member states' national laws to ensure the distribution of safe medical devices within the EU. The format of the three Directives is similar and consists of a number of Articles (covering definitions, scope, free movement, harmonised standards) and Annexes (covering essential requirements, conformity assessment procedures and device classification). However, selective adoption of these directives is allowed by each member state to define the safety requirements, conformity assessments and the issuance of European Council Declaration of Conformity of medical devices.

The EU classification of medical devices

The EU classifies medical devices based on the three different EU directives and the level of risk associated with the use of the device such as if the device is active or implantable, surgically invasive, length of use, and if the device contains a medicinal substance.

a) Active implantable medical devices

Active implantable medical devices are powered by an energy source and are surgically implanted or medically introduced and left in the body to achieve their intended purposes. These include implantable cardiac pacemakers, defibrillators, leads for pacing and defibrillators, and cochlear implants. These medical devices are all considered high risk, with no further differentiation of risk within this class of medical device.

b) In-vitro diagnostic devices (IVDs)

In-vitro diagnostic devices (IVDs) are devices intended for providing information concerning a physiological or pathological state and monitoring therapeutic measures. Examples include strips for urine analysis tests, pregnancy test kits and blood glucometers. IVDs may further be classified into four different classes based on their inherent risk.

c) General medical devices

Medical devices which are neither active implantable devices nor IVDs, are termed general medical devices. These devices are classified in order of increasing risk into classes I, IIA, IIB and III according to Annex IX of the MDD. This classification is based on the Global Harmonisation Task Force (GHTF) guidance, which is also adopted by Singapore.

Summary of the EU process

Unlike the centralised system by the US Food and Drug Administration (FDA), the EU medical device control is achieved through a decentralised system of conformity assessment performed by accredited notified bodies (NBs), which are mainly private commercial organisations. There are currently 67 NBs registered in the EU. The conformity assessment performed by NBs includes review and evaluation of the risk classification, conformity assessment procedure, quality management system, the technical file or design dossiers on the design and safety of the medical device, risk management, clinical evidence and conformance to essential requirements. In some countries, government controlled or statutory bodies serve as NBs.

Conformity assessment

A manufacturer is able to select different conformity assessment procedures (also known as Route of Conformity Assessment) under the New Approach Directive introduced in 1985. Under this directive, the manufacturer may use combinations of modules with different complexity for conformity assessment covering different phases of product design and manufacturing.

Upon satisfactory assessment by NBs, the device is "CE marked". This is where the manufacturer affixes the "CE" *(Conformité Européene)* mark to its device or labels as an indication that the device conforms to the requirement of the respective medical device directives, allowing the device to be marketed across all member states including EFTA.

The low-risk devices in General Medical Device Class I (self-notified), which are non-sterile and/or do not have a measuring function*, do not require NB's certification and the manufacturers can self-certify and affix the CE mark. Similarly, general IVDs which are IVDs with the lowest risk among the IVDs also do not need NB approval. All other medical devices are required to have conformity assessments performed by NBs.

** Medical devices with measuring function are devices used for quantitatively measuring a physiological or anatomical parameter, e.g., thermometers and blood pressure monitoring devices.*

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■ **Medical device regulations in the European Union** ■

Review of EU's process

In 2010, an EU-wide product withdrawal of the Poly Implant Prosthèse (PIP) breast implants was made following evidence that the PIP devices, which were produced in France, were found to be deliberately filled with industrial grade silicone since 2001. The incidence of PIP breast implant ruptures was also reported to be higher than those of other silicone breast implants due to the inferior quality of the shell of the implant. An estimated 400,000 women had received this defective implant which could expose them to non-medical grade silicone.[1] As a result of this safety concern over the PIP breast implants, a review of the regulatory process recommended that evidence other than those from manufacturers, such as detailed data from clinicians, should be considered in the regulation of medical devices.

Comparisons have also been made between a pre-market approval (PMA) system in the US and the decentralised system of conformity assessment performed by NBs in the EU. It was stated that the PMA system has greater transparency of approval decisions and post approval reporting requirements which may address the current challenges of decentralised approval by NBs. However, the counter argument against the PMA system was the unnecessary additional cost and delay to approval.[2] A Boston Consulting Group's study reported that medical devices are generally available three years sooner in the EU than device registered through the US FDA PMA process.

Future development

The current Medical Device Directives was proposed to be replaced by the draft Medical Device Regulations.[3,4] The proposed Regulations, in contrast to Directives, would require member states to adopt the Medical Device Regulations in totality rather than selective adoption into their national laws. The Regulations will strengthen the oversight of NBs by the regulators and at the same time increase the power of NBs over the manufacturers. The number of NBs will be reduced from the current 67 to about 20. Other proposals include the establishment of an expert group Medical Device Co-ordination Group (MDCG) and clinical experts so that the regulators can manage a system of "scrutiny" and improve co-ordination between member states.[5]

Conclusion

In conclusion, the EU decentralised regulatory system of relying on NBs operates very differently from a pre-market approval/notification system. The decentralised regulatory system in EU allows selective adoption of the three Directives into the member states' legal frameworks. A medical device once approved by any EU member state, will be approved throughout the EU.

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2 *http://www.eucomed.org/newsroom/115/187/17-5-billion-for-unnecessary-measures-will-be-a-blow-to-medical-device-innovation-in-Europe?cntnt01template=detail-pr*
3 *http://ec.europa.eu/health/medical-devices/files/revision_docs/proposal_2012_542_en.pdf*
4 *http://europa.eu/rapid/press-release_MEMO-12-710_en.htm*
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AE case in focus: Test yourself

HSA AE Adverse Events Watch

A teenage female presented to the hospital's children emergency department after she exhibited acute behavioural changes for two days. Her mood was labile as she switched between smiling to being afraid. She also started having auditory hallucinations and persecutory delusions. She has neither medical/psychiatric history nor family history of note and the attending physician's diagnosis was acute psychosis. Her clinical findings were negative and organic causes were ruled out.

Three months earlier, the patient had been trying to lose weight and started taking a slimming product which she purchased online. The product was a health supplement labelled to contain the following ingredients: Grapefruit 150mg, Raspberry ketone 30mg, Hawthorn berry 30mg, Green tea 25mg and Pomegranate 20mg.

a) What would you suspect?

b) What would be your next course of action?

This case is based on an actual adverse event report submitted to HSA, but with minor changes to protect patient confidentiality. We would like to take this opportunity to thank Dr Joshi Abhinav, Medical Officer, Department of Psychiatry, National University Hospital for his contributions in partnering with us in our vigilance work to safeguard public health.

Answers to the case study can be found on page 6.

Answers to AE case in focus: Test yourself

a) Since clinical findings were negative and organic causes were ruled out, possible adulteration to this product is to be suspected.

Common pharmaceutical ingredients often used as adulterants in slimming products include appetite suppressants, diuretics, laxatives and lipase inhibitors.

1 Appetite suppressants

e.g., Sibutramine, Sibutramine analogues, Phentermine

Centrally-acting appetite suppressants exert their effects via various neurotransmitter pathways (i.e., norepinephrine, serotonin and dopamine) to reduce appetite or increase satiety. These substances increase neurotransmitter levels by either blocking the neuronal reuptake of neurotransmitters or enhancing their release.[1]

Sibutramine has been withdrawn from Singapore (since October 2010) and other global markets because of safety concerns on cardiovascular events, such as heart attacks and strokes, which outweighed its modest efficacy in weight loss. Fenfluramine and phentermine have been associated with valvular heart disease and the rare but serious risk of pulmonary hypertension.[2] Psychosis is also listed as a possible side effect for this class of drugs.

2 Diuretics

e.g., Bumetanide, Furosemide

The effects of diuretics in causing rapid weight loss are temporary. Diuretics have high potential to cause dehydration and electrolyte imbalances such as hyponatremia or hypokalaemia when used in excessive amounts.

3 Laxatives

e.g., Phenolphthalein, Senna

Long-term and overuse of laxatives may lead to dependency and tolerance in patients. This in turn may also result in fluid and electrolyte imbalances. In addition, a review of animal studies found that phenolphthalein was associated with carcinogenicity after repeated oral exposure in mice for 26 weeks.[3]

4 Lipase inhibitor

e.g., Orlistat

Orlistat is an inhibitor of gastrointestinal lipase and reduces the absorption of dietary fat. It is recommended for patients with BMI greater or equal to 30kg/m^2 or overweight patients with BMI greater or equal to 28kg/m^2 with associated risk factors. Adverse reactions of orlistat are largely gastrointestinal in nature, such as abdominal pain and oily spotting. Other adverse reactions include headaches and upper respiratory tract infections.[4]

b) Notify HSA if you suspect a possible causal association between the health product taken and the adverse event experienced by the patient. Reporting an adverse event does not mean that there is a definite link between the event and the drug.

The presence of common adulterants can only be detected and confirmed by laboratory testing. In this case study, the attending doctor had suspected possible adulterants in the health supplement that could have caused the symptoms and submitted an ADR report to HSA. The product was subsequently sent to the laboratory for testing and was found to contain potent undeclared ingredients namely sibutramine, benzyl sibutramine and phenolphthalein. The amount of sibutramine detected in the product exceeded the maximum recommended dosage. Psychosis is listed as one of the possible side effects of sibutramine. A press release regarding this product was issued by HSA to members of the public to alert them not to purchase it.[5]

From 2009 to 2014, the Vigilance and Compliance Branch of HSA received 33 ADR reports associated with slimming products, describing adverse events such as hepatotoxicity, renal toxicity, abnormal thyroid function and psychosis. Of these, 15 ADR reports involved registered western pharmaceuticals and another 13 ADR reports involved complementary health products. The remaining five ADR reports involved illegal slimming products including one fatal case.

HSA strongly encourages healthcare professionals to report any adverse reactions suspected to be related to the use of health products to the Vigilance and Compliance Branch. Your support towards the national safety monitoring programme is invaluable in safeguarding public health.

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2 *British National Formulary (59th edition) 2010*
3 *http://ntp.niehs.nih.gov/ntp/roc/content/profiles/phenolphthalein.pdf*
4 *Singapore package insert for Xenical®. Approved Nov 2009*
5 *http://www.hsa.gov.sg/content/hsa/en/News_Events/Press_Releases/2014/TwoIllegalWeightLossProducts.html*

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

HSA encourages the reporting of all suspected adverse events 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 *http://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 and Compliance Branch* (refer to full address on page 8)
- By fax to *(65) 6478 9069*
- By email to *HSA_productsafety@hsa.gov.sg*

List of Dear Healthcare Professional Letters (DHCPL) issued by HSA, pharmaceutical and medical device companies between 29 November 2014 and 1st April 2015

For details, please log on to MOHAlert via your professional board's website.

Therapeutic products

3 Dec 2014 **Euthyrox® (levothyroxine):**
Change of primary packaging, storage condition and manufacturing site to improve product stability

14 Jan 2015 **Motilium® (domperidone) Oral Suspension (1mg/mL) and Tablet (10mg):**
Important update on recent changes to the dosage recommendation to minimise cardiac risks including serious arrhythmia and sudden cardiac death

Medical devices

16 Dec 2014 **Zimmer Trilogy Bone Screws - 6.5mm X 35mm & 6.5mm X 25mm:**
Voluntary recall of selected lots of Zimmer Trilogy Bone Screws of 25mm and 35mm length due to fracture during insertion

13 Jan 2015 **InterStim® and InterStim® II Neurostimulators:**
Labelling update related to the impact of cycling feature on device battery longevity

13 Jan 2015 **Gunther Tulip and Cook Celect retrievable inferior vena cava (IVC) filter sets:**
Updated product information on optimal retrieval period of Gunther Tulip and Cook Celect retrievable inferior vena cava (IVC) filter sets

16 Jan 2015 **Medpor Surgical Implant Contoured Two Piece Chin, Medpor Barrier Implant and Medpor Titan Max Orbital Floor and Wall Implant:**
Recall of selected lots due to higher occurrence rate of implant damage during intra-operative handling for MEDPOR Surgical Implant (Part 86001), and MEDPOR BARRIER Sheets (Part 9305 and 9312); For the TITAN MAX OFW MTB Right (Part 81036), the barrier location is situated on the incorrect surface of the implant

21 Jan 2015 **Medtronic INSYNC III Protect 7285 Dual Chamber Implantable Cardioverter Defibrillator with Cardiac Resynchronisation Therapy (CRT-D):**
Important notification on the need to maintain frequent and timely follow-up interrogation schedules with patients implanted with the device

30 Jan 2015 **HeartWare® Ventricular Assist System Controllers:**
Voluntary recall of selected controllers due to identified risks associated with electrostatic discharge (ESD)

2 Feb 2015 **Sterile packaged femoral heads and tapers:**
Voluntary recall of various unconsumed sterile packaged femoral heads and tapers as configuration had failed a packaging test due to potential compromise in the inner sterile tray barrier

17 Feb 2015 **BIRMINGHAM HIP™ Resurfacing (BHR) system:**
Update to the Instruction For Use of the BIRMINGHAM HIP™ Resurfacing system to include warnings of greater risk for early revision surgery for certain population sub-groups

24 Feb 2015 **LENTIS HydroSmart foldable Intraocular Lenses (IOL):**
Voluntary recall of all LENTIS HydroSmart foldable IOL in glass vials due to the potential for postoperative opacification

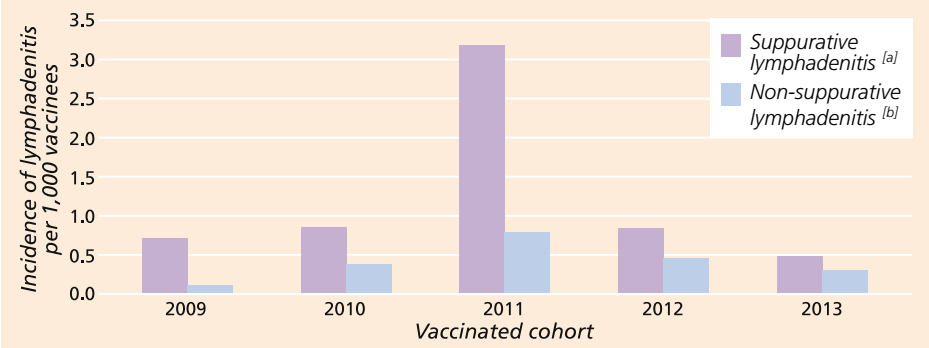
1 Apr 2015 **PFNA and PFNA-II Femoral Nails and PFNA-II Endcaps (R2014081)**
Voluntary recall of specific part and lot numbers of Proximal Femoral Nail Antirotation (PFNA) and PFNA-II Femoral Nails and PFNA-II Endcaps (R2014081) due to incorrect anodised colour coding

Erratum: Incorrect legend for figure

In the article "Update on the trend of lymphadenitis and injection-site reactions with the BCG vaccine SSI®" published in the December 2014 issue of the HSA Adverse Drug Reaction News, there was an error in the legend for Figure 1 where 'Suppurative lymphadenitis' and 'Non-suppurative lymphadenitis' were interchanged. The corrected graph is provided here and the updated article can be downloaded from

http://www.hsa.gov.sg/content/hsa/en/Health_Products_Regulation/Safety_Information_and_Product_Recalls/Adverse_Drug_Reaction_News_Bulletin/2014/2014-december-volume16number3.html

Figure 1. Incidence of lymphadenitis for the 2009 to 2013 vaccinated cohorts



[a] Suppurative lymphadenitis is defined as the presence of fluctuation on palpation or pus on aspiration, the presence of a sinus, or large lymph nodes adherent to skin with caseous lesions on excision.[3]

[b] The estimates for non-suppurative cases are likely to be underestimates as these cases are usually not reported to HSA given that it is a common and expected reaction post-BCG vaccination.

Risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) associated with ziprasidone

HSA would like to inform healthcare professionals about overseas cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) that have been reported with the use of ziprasidone.

Ziprasidone (Zeldox®, Pfizer Private Limited) is an antipsychotic drug that has been registered in Singapore since 2002. It is indicated for the treatment of schizophrenia, related psychoses, prevention of relapse and for maintenance of clinical improvement during continuation therapy. It is also indicated for the treatment of manic or mixed episodes associated with bipolar disorder, with or without psychotic features.

About DRESS[1,2]

DRESS is a serious adverse drug-induced reaction that is potentially life-threatening. It has a delayed onset, usually appearing two to six weeks after initiation of the causative drug. Manifestations of DRESS may include cutaneous reactions such as rash or exfoliative dermatitis, fever, lymphadenopathy, eosinophilia and other systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, pericarditis and pancreatitis. The estimated incidence of this syndrome ranges from 1 in 1,000 to 1 in 10,000 drug exposures, with a mortality rate of up to 10%. The pathogenesis of DRESS is unclear and there is no specific treatment for DRESS. Early recognition of the syndrome, prompt discontinuation of the offending agent and supportive care are important in the management of DRESS. Treatment with corticosteroids may also be considered in cases with extensive organ involvement.

Review by the US Food and Drug Administration (FDA)[2]

In December 2014, the US FDA issued a drug safety communication informing that ziprasidone was associated with DRESS. This safety communication followed the review of six worldwide cases of DRESS associated with the use of ziprasidone that were reported to the FDA Adverse Event Reporting System (FAERS).

In all six cases, the signs and symptoms of DRESS appeared between 11 and 30 days after ziprasidone treatment was initiated. Of these, a recurrence of symptoms following the discontinuation and re-initiation of ziprasidone was reported for three cases, where a faster time to onset of the symptoms was observed following the re-initiation. Three cases were reported to have concomitant therapy with drugs associated with the occurrence of DRESS. While none of the cases reported death, serious outcomes including hospitalisation had been reported.

In view of the consistency of the case characteristics to the signs and symptoms of DRESS, the temporal relationship between ziprasidone initiation and the onset of symptoms, and the reported cases of positive re-challenge, FDA's assessment concluded that an association between ziprasidone use and the occurrence of DRESS was supported. Based on the available evidence, the FDA had requested for the package inserts (PI) of ziprasidone-containing products to be updated to include warnings on the risk of DRESS.

Local situation and HSA's advisory

HSA has not received any adverse drug reaction reports of DRESS associated with ziprasidone use. The local PI for Zeldox® has been strengthened to include warnings on the risk of DRESS.

Healthcare professionals are advised to be vigilant to possible signs and symptoms of DRESS, such as skin rash, fever, lymphadenopathy and eosinophilia, in patients prescribed ziprasidone.

References

1 *Am J Med 2011; 124: 588-97*
2 *http://www.fda.gov/Drugs/DrugSafety/ucm426391.htm*

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All website references were last accessed on 24 April 2015.