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HSA Health Sciences Authority

ADVERSE DRUG REACTION NEWS

Contents

NEW RECOMMENDATIONS ON THE USE OF DOMPERIDONE

Key Points

- The use of domperidone for treatment of dyspepsia, nausea and vomiting is associated with a potential risk of serious cardiovascular events
- Precautionary measures to mitigate the risk include contraindicating the use in patients with high risk of cardiotoxicity and use of lowest possible dose for the shortest possible duration

Background

Domperidone is a pro-kinetic and anti-emetic drug registered in Singapore for the treatment of dyspepsia, as well as nausea and vomiting due to various conditions.

HSA has recently completed a re-assessment to determine if additional measures are necessary to further mitigate the cardiovascular (CV) risk associated with the use of domperidone. This follows an earlier assessment in 2012, which resulted in the strengthening of the package inserts (PIs) of domperidone to include warnings of increased risk of ventricular arrhythmia (VA) and sudden cardiac death (SCD), especially in patients older than 60 years old or those taking oral doses of more than 30 mg daily.

International regulatory actions

Several other drug regulatory agencies have also carried out assessments on domperidone and issued recommendations on its use. The European Medicines Agency (EMA) removed the indication for dyspepsia due to insufficient long-term efficacy data supporting this indication, and restricted the maximum oral daily dose to 30 mg for its use to treat nausea and vomiting.[1] Health Canada retained the use in gastritis and nausea and vomiting at a maximum daily dose of 30 mg as well as strengthened the safety warnings in the PI to highlight the risk of CV events.[2]

HSA's benefit-risk re-assessment

Domperidone is a well-established pro-kinetic drug used in the treatment of nausea, vomiting and dyspepsia. HSA has reassessed its risk-benefit following a review of five epidemiology studies, which suggested an association with increased risk of VA and SCD.[3-4]

The identified cardiotoxicity risk factors included advanced age (>60 years old), underlying CV conditions, high domperidone dose (>30 mg/day) and concomitant use with QT prolongation drugs and CYP3A4 inhibitors. Local reports of cardiotoxicity associated with domperidone use were found to be isolated. From 2006 to 2016, HSA received two cases of QT prolongation associated with domperidone. Considering the long history of use in local clinical setting and the relatively low incidence of locally reported cardiac-related adverse events, HSA, in consultation with its Medicines Advisory Committee, concluded that the benefit-risk profile of domperidone remains favourable when used appropriately for the above indications. Additional measures were recommended to mitigate the risk of cardiotoxicity, which included restricting its use in high risk patients and strengthening the CV warnings in the PI.

HSA's advisory

Healthcare professionals are advised of the following, when considering the use of domperidone:

- Domperidone is contraindicated in patients with existing prolongation of cardiac conduction intervals, particularly QTc, patients with significant electrolyte disturbances or underlying cardiac disease and when co-administrated with QT-prolonging medicines or potent CYP3A4 inhibitors.
- An increased risk of cardiotoxicity was observed in patients older than 60 years.
- Domperidone should be used at the lowest effective dose for the shortest possible duration.
- In adults and children aged ≥ 12 years old weighing ≥ 35 kg, the recommended maximum oral daily dose is 30 mg, given in doses of 10 mg up to three times daily. Taking into account the pharmacokinetic studies and bioavailability of rectal suppositories, the recommended rectal suppository dose is 30 mg twice daily.
- In children aged < 12 years old and those aged ≥ 12 years old weighing < 35 kg, the recommended dose is 0.25 mg/kg orally up to three times daily. For rectal administration, these patients may also be given 0.75 mg/kg twice daily as suppositories.

HSA is working with the product registrants to update the local PIs of products containing domperidone. These include new recommendations on the dosing regimen, treatment duration and relevant safety information and contraindications.

Healthcare professionals are encouraged to take into consideration the above recommendations when prescribing domperidone. They are also encouraged to report any suspected serious adverse reactions related to domperidone to the Vigilance and Compliance Branch of HSA.

References

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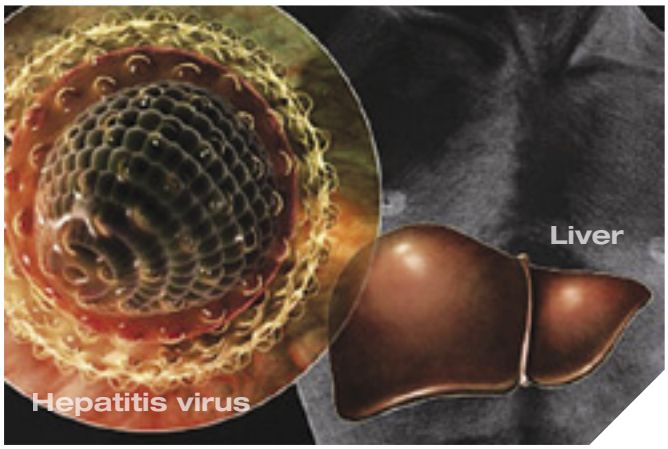
RISK OF HEPATITIS B VIRUS REACTIVATION WITH DIRECT-ACTING ANTIVIRALS

Key Points

- There have been overseas reports of hepatitis B virus (HBV) reactivation in patients who received treatment with direct-acting antivirals (DAAs) for hepatitis C virus (HCV) infection
- Healthcare professionals are encouraged to be vigilant for HBV reactivation in patients who have a past or current HBV infection, and who are prescribed DAA-containing products for the treatment of HCV infection

Overseas cases of hepatitis B virus (HBV) reactivation have been reported in patients who were treated with direct-acting antivirals (DAAs) for hepatitis C virus (HCV) infection. In some cases, the HBV reactivation had led to serious outcomes such as hepatic failure and death. This risk has been observed with the use of DAA regimens that are interferon-free.

DAAs are a class of drugs used for the treatment of HCV infection. They inhibit viral replication, thus reducing the amount of HCV in the body. DAAs not requiring use in combination with interferon are registered in Singapore either as single-ingredient or combination products. They include asunaprevir (Sunvepra™, Bristol-Myers Squibb (Singapore) Pte Ltd), daclatasvir (Daklinza™, Bristol-Myers Squibb (Singapore) Pte Ltd), sofosbuvir (Sovaldi®, Gilead Sciences Singapore Pte Ltd), simeprevir (Olysio®, Johnson & Johnson Pte Ltd), sofosbuvir/ledipasvir (Harvoni®, Gilead Sciences Singapore Pte Ltd), and dasabuvir/ombitasvir/paritaprevir/ritonavir (Viekira Pak™, Abbvie Pte Ltd).



International regulatory actions

a) European Medicines Agency (EMA)[1]

In March 2016, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) initiated a review to assess the extent of HBV reactivation in patients treated with DAAs for HCV infection. The review was triggered by reports of HBV reactivation in patients co-infected with HBV and HCV, and who were receiving treatment with DAAs for HCV infection. Approximately 30 cases of HBV reactivation were identified by the PRAC during its review. As co-infection with HCV is known to suppress HBV replication, it was suggested that reactivation of HBV could be a consequence of the rapid treatment-induced reduction in HCV and the DAAs' lack of activity against HBV.

The PRAC concluded its review in December 2016, and recommended for all patients to be screened for HBV before starting treatment with DAAs for HCV infection. It also recommended that patients co-infected with HBV and HCV should be monitored and managed according to current clinical guidelines.

b) US Food & Drug Administration (FDA)[2]

The US FDA also conducted a review on this safety issue, and issued a safety communication in October 2016 to warn about the risk of HBV reactivation in patients co-infected with HCV, while

receiving treatment with DAAs for HCV infection. FDA's review of the FDA Adverse Event Reporting System (FAERS) database and the medical literature for cases reported or published between 22 November 2013 and 18 July 2016 had identified 24 cases of HBV reactivation in patients receiving DAAs for the treatment of HCV. The cases of HBV reactivation had generally occurred within four to eight weeks of starting HCV treatment, and were heterogeneous in terms of the HCV genotype and status of baseline HBV disease. Of the 24 cases with HBV reactivation, two had a fatal outcome, while one patient had required a liver transplant.

The US FDA has since recommended for the package inserts (PIs) of DAAs to be updated with warnings about the risk of HBV reactivation. Healthcare professionals were also advised to screen patients for evidence of current or prior HBV infection before starting treatment with DAAs, and to monitor patients for hepatitis flare or HBV reactivation during DAA treatment and post-treatment follow-up.

c) Other international regulatory agencies[3-5]

Besides the EMA and US FDA, several other international regulatory agencies had similarly conducted safety reviews to assess the risk of HBV reactivation associated with the use of DAAs for the treatment of HCV infection. In September 2016, the New Zealand Medicines Adverse Reactions Committee (MARC) concluded from its review that there was insufficient evidence to confirm a causal association. However, considering that HBV reactivation could lead to potentially life-threatening events, the MARC recommended that the risk of HBV reactivation and the need for screening and monitoring for HBV in patients who are prescribed DAAs be updated in the PIs of DAA-containing products.

In December 2016, both the Australian Therapeutic Goods Administration (TGA) and Health Canada concluded from their safety reviews that there is a potential risk of HBV reactivation in patients co-infected with HBV and HCV who were receiving treatment with DAAs for HCV infection. Consequentially, both agencies have also requested for additional safety information regarding the risk for HBV reactivation to be updated to the PIs of DAA-containing products.

Local situation and HSA's advisory

To date, HSA has not received any local adverse reaction report of HBV reactivation in patients receiving treatment with DAAs for HCV infection. The Singapore PIs for DAA-containing products that are approved for the treatment of HCV infection in interferon-free regimens are in the process of being updated to include safety information regarding the risk of HBV reactivation. Healthcare professionals are encouraged to be vigilant for HBV reactivation in patients who have a past or current HBV infection, and who have been prescribed DAA-containing products for the treatment of HCV infection.

References

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3. *http://www.medsafe.govt.nz/profs/adverse/Minutes167.htm#3.2.4*
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5. *http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2016/61274a-eng.php*

ANALYSIS OF ADVERSE EVENT (AE) REPORTS FOR YEAR 2016

Key Points

- In 2016, NSAIDs and antibiotics were the two highest reported pharmacotherapeutic groups of western drugs suspected to cause AEs. The two major classes of AEs were skin-related disorders and those affecting the body as a whole
- The most commonly reported vaccine AE in children under 12 years was seizure (febrile and afebrile) with the measles, mumps and rubella (MMR), MMR and varicella, varicella, 5-in-1 and pneumococcal conjugate vaccines
- No reports of vaccine-associated anaphylaxis were received in the paediatric population, consistent with the trend in the last preceding seven years
- Healthcare professionals are encouraged to stay vigilant for AEs from adulterated complementary health products as the average number of detected cases has been 15 per year in the past five years

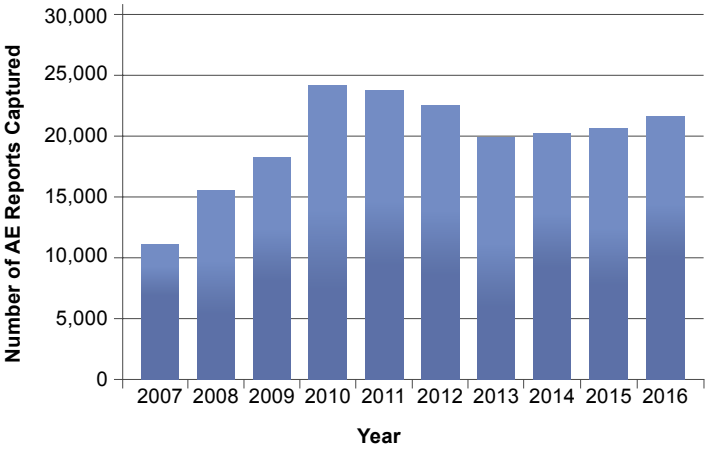
This review provides an analysis of the adverse events (AEs) associated with health products (namely western drugs, vaccines and complementary health products) that were reported to HSA in 2016.

Report analysis for 2016

(a) Volume of reports

In 2016, HSA reviewed 21,637 valid+ local AE reports suspected to be associated with health products, an increase of 4.9% over preceding year. The breakdown of the number of valid reports captured in the national AE database for the past 10 years based on the date of receipt is illustrated in Figure 1.

Figure 1. Number of valid reports captured in the AE database from year 2007 to 2016 based on date of receipt



+ Reports lacking important details such as names of suspected drugs and AE descriptions were regarded as invalid reports and were not captured into the national AE database as they could not be assessed for causality.

(b) Source and types of reports

As in previous years, the majority of the reports analysed were associated with pharmaceutical drugs (96.6%). The other reports were associated with vaccines (1.6%), biologics (1.1%), and complementary health products (CHPs) (0.7%), which included Chinese Proprietary Medicines (CPM), health supplements, traditional medicines, and cosmetics. Most of the reports were contributed by the public hospitals/healthcare organisations (57.3%) and polyclinics (39.6%), while the rest were from private hospitals/clinics, retail pharmacies (1.2%) and pharmaceutical companies (1.9%). Doctors (83.2%) contributed most to the number of reports in 2016, followed by pharmacists (12.2%). The other contributors were dentists, nurses, research coordinators and drug companies (4.6%).

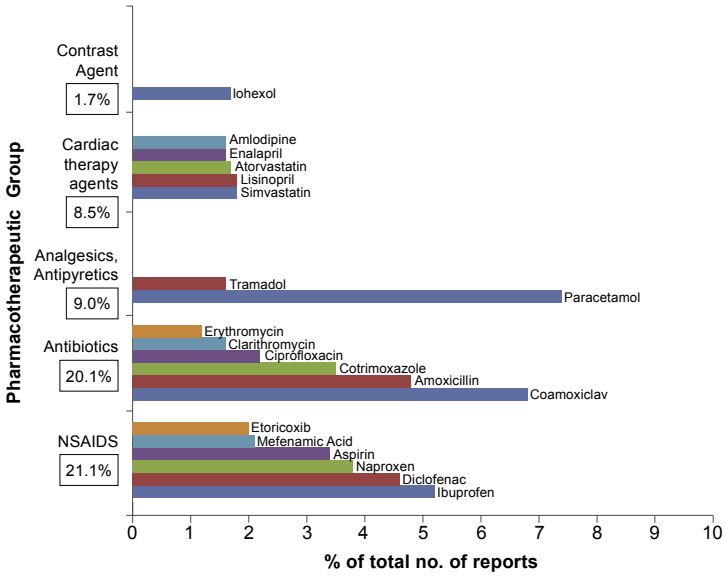
(c) Demographics

Chinese patients constituted the highest proportion (59.0%) of AE reports, followed by Malays (11.0%) and Indians (7.5%). There were more reports of AEs occurring in females (57.0%) than in males. The age range of the patients with the highest frequency reported was 50 to 59 years of age (15.6%), followed by 60 to 69 years (14.8%).

(d) Suspected drugs

The top 20 suspected drugs commonly reported to cause AEs were from the following pharmacotherapeutic groups: nonsteroidal anti-inflammatory agents (NSAIDs) (21.1%), antibiotics (20.1%), analgesics and antipyretics (9.0%), cardiac therapy agents (8.5%), and contrast agent (1.7%) (Figure 2). This constituted more than half of the total volume of reports received. The most commonly reported AEs were related to allergic reactions such as rash, angioedema and face oedema.

Figure 2. Top 20 drugs (by active ingredients) suspected of causing AEs



(e) Adverse events

The top System Organ Classes (SOC*) reported were skin-related disorders, followed by those affecting the body as a whole and respiratory system as shown in Table 1, a consistent trend observed in the past 5 years.

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

*Table 1. Top AEs by System Organ Class**

Ranking	System Organ Class	No. of reports	% of reports
1	Skin And Appendages Disorders e.g., angioedema, rash, urticaria	11,949	48.6
2	Body As A Whole - General Disorders e.g., anaphylactic reaction, fever, oedema, pain	4,399	17.9
3	Respiratory System Disorders e.g., coughing, shortness of breath, wheezing	1,473	6.0
4	Central & Peripheral Nervous System Disorders e.g., convulsions, giddiness, headache, oculogyric crisis	1,292	5.3
5	Gastro-Intestinal System Disorders e.g., abdominal pain, diarrhoea, vomiting	1,289	5.2
6	Urinary System Disorders e.g., abnormal renal function, interstitial nephritis, urinary retention	826	3.4
7	Vascular Disorders e.g., flushing, stroke, vasculitis	412	1.7
8	Musculo-Skeletal System Disorders e.g., arthralgia, myalgia, rhabdomyolysis	377	1.5
9	Heart Rate And Rhythm Disorders e.g., bradycardia, chest pain, palpitation	321	1.3
10	Psychiatric Disorders e.g., agitation, confusion, hallucination	220	0.9

(f) Serious AEs of interest

The drugs suspected to cause serious skin, body as a whole, renal and hepatic adverse reactions are listed in Table 2.

Vaccine adverse event (VAE) reports

There were 315 AE reports suspected to be associated with vaccines, of which 273 reports (86.7%) involved children aged 12 years and below, which corresponded to the age group of vaccinees under the National Childhood Immunisation Schedule. Of these, 87.5% of the reports (n=239) were captured by KK Women's and Children's Hospital (KKH) active surveillance sentinel site, which screens all paediatric hospital admissions for possible relationship to vaccination.[1]

The most commonly reported AE in children aged 12 years and below was seizures (febrile and afebrile seizures) with the measles, mumps and rubella (MMR), MMR and varicella, varicella, 5-in-1** and pneumococcal conjugate vaccines. Other more commonly reported AEs included rash, fever, Kawasaki disease and thrombocytopenia involving a variety of vaccines, injection-site reactions with 5-in-1 and *Bacillus Calmette-Guérin* (BCG) vaccines, lymphadenitis with the BCG vaccine and gastrointestinal events with the rotavirus vaccine.

Based on yearly trend analysis, there were more reports of febrile seizures with the 5-in-1 vaccine and aseptic or viral meningitis with the hepatitis B vaccine received in 2016. All patients recovered without sequelae. Overall, the number of AE reports received remained consistent with the expected frequencies of AE occurrence listed in the package inserts of the vaccines or in literature.

** *5-in-1 refers to Diphtheria, Pertussis, Tetanus, Inactivated Polio and Haemophilus influenza type B vaccine*

Table 2. Drugs suspected of causing serious AEs

Description	WHO preferred terms	Suspected active ingredient(s) (2016) (number in bracket denotes the number of times the drug has been implicated#)	Top 10 suspected active ingredient(s) (2011 to 2015) (number in bracket denotes the cumulative number of times the drug has been implicated^)
Skin disorders	Stevens Johnson Syndrome (SJS) / Toxic Epidermal Necrolysis (TEN) / SJS-TEN	Cotrimoxazole (7), Allopurinol (4), Omeprazole (4), Pembrolizumab (3), Carbamazepine (2), Diclofenac (2), Etoricoxib (2)	Carbamazepine (35), Omeprazole (27), Allopurinol (25), Coamoxiclav (25), Cotrimoxazole (23), Phenytoin (22), Lamotrigine (16), Amoxicillin (15), Ceftriaxone (15), Etoricoxib (15)
Body as a whole	Anaphylactic reaction/ Anaphylaxis	Diclofenac (17), Paracetamol (12), Ibuprofen (10), Ceftriaxone (8), Naproxen (8), Aspirin (7), Coamoxiclav (7), Amoxicillin (4), Benzylpenicillin/ Penicillin G (4), Cefazolin (4), Atracurium (3), Etoricoxib (3), Fentanyl (3), Omeprazole (3)	Diclofenac (64), Ibuprofen (52), Paracetamol (42), Aspirin (37), Coamoxiclav (35), Naproxen (34), Ceftriaxone (31), Amoxicillin (27), Ciprofloxacin (23), Iohexol (18)
Renal disorders	Acute renal failure/Interstitial nephritis/Renal impairment	Cotrimoxazole (4), Omeprazole (4), Ciprofloxacin (3), Coamoxiclav (3), Naproxen (3), Lisinopril (2)	Ciprofloxacin (14), Diclofenac (11), Enalapril (7), Cotrimoxazole (6), Losartan (5), Omeprazole (5), Coamoxiclav (4), Mefenamic Acid (4), Vancomycin (4), Metformin (3), Sitagliptin (3), Sulfadiazine (3)
Hepatic disorders	Hepatic failure/ Hepatitis/ Hepatitis cholestatic/ Hepatoxicity/ Jaundice	Coamoxiclav (3), Efavirenz (2), Regorafenib (2)	Cotrimoxazole (8), Coamoxiclav (5), Carbimazole (5), Amiodarone (4), Regorafenib (4), Ketoconazole (4), Simvastatin (4), Allopurinol (3), Azathioprine (3), Fenofibrate (3), Gabapentin (3), Piperacillin-Tazobactam (3)

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

^ Based on onset date of the AE

The commonly reported vaccines suspected to cause AEs in adults and children above 12 years of age were the human papillomavirus (HPV), pneumococcal, seasonal influenza and tetanus toxoid vaccines. The commonly reported AEs included rash, angioedema and injection-site reactions associated with a variety of vaccines. Serious AEs included an isolated report of *Guillain-Barré* syndrome with the influenza vaccine (with another suspected drug, pembrolizumab) and reports of tonic-clonic movements with the HPV vaccine and vaccine failure with the influenza vaccine.

VAE of interest: anaphylaxis

Anaphylaxis is a potentially life-threatening allergic reaction which can occur after different exposures to substances e.g., food, venom, drugs or vaccines. A study in the US using data collected on more than nine million subjects found the risk of anaphylaxis following vaccination to be rare, with a rate of 1.3 per million vaccine doses administered.[2] The incidence did not vary significantly by age.

Analysis of the local VAE reports for the past ten years found six cases of anaphylaxis, three associated with the tetanus toxoid vaccine, two with the influenza vaccine and one with the typhoid vaccine. The age of the patients ranged between 34 to 43 years old.

There have been no cases of anaphylaxis in children reported to HSA related to vaccines. KKH's active surveillance of VAEs at the inpatient setting for close to seven years did not report any cases of anaphylaxis following vaccination. This observation was also noted by a study of anaphylaxis in children seen at the paediatric emergency department in the same hospital from 2007 to 2014.[3] Based on more than one million patient attendances where 485 episodes of anaphylaxis were picked up, none was associated with vaccines.

Despite its rarity, anaphylaxis is a potentially life-threatening medical emergency that healthcare professionals should be prepared to treat. It is also important to recognise anaphylaxis and distinguish it from a vasovagal reaction for the purpose of clinical management. HSA had developed a guide for recognising anaphylaxis, in consultation with Prof Chng Hiok Hee, Clinical Professor in Rheumatology, Allergy and Immunology. Healthcare professionals may wish to refer to the guide which contains a questionnaire to aid reporting of anaphylaxis as an AE.[4]

Complementary health products (CHP) AE reports

In 2016, there were 161 suspected AE reports involving CHPs, an increase of 15% over the preceding year. Of these, 99 reports (61%) were associated with glucosamine-containing products, describing mostly non-serious hypersensitivity reactions (e.g., rash, pruritus and periorbital oedema).

There were ten reports (6.2%) of hepatic reactions (e.g., transaminitis and jaundice) associated with CHPs, of which seven patients were hospitalised. One of the implicated products, 'Snake Powder Capsules', was found to be adulterated with western medicines, namely, chloramphenicol, chlorpheniramine, dexamethasone, ibuprofen and tetracycline.[5]

With the help of astute clinicians, HSA detected 11 adulterated CHPs and issued five press releases.[5] Common adulterants included corticosteroids (e.g., dexamethasone), antihistamines (e.g., chlorpheniramine) and analgesics (e.g., ibuprofen, diclofenac).

Acknowledgement

The Vigilance and Compliance Branch would like to take this opportunity to thank you, our healthcare professionals for your active participation in the reporting of AEs. This has helped HSA in the early detection of potential safety signals and enabled the relevant regulatory actions to be taken to safeguard public health.

With your vigilance in reporting AEs to HSA, Singapore has retained its first position globally in 2016 in terms of the number of valid ADR reports per million inhabitants submitted to the World Health Organisation global pharmacovigilance database for five consecutive years since 2011.

References

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4. *http://www.hsa.gov.sg/content/dam/HSA/HPRG/Safety_Alerts_Product_Recalls_Enforcement/Anaphylaxis_guide.pdf*
5. *http://www.hsa.gov.sg/press_releases*

HIGHLIGHTS ON LOCAL SAFETY SIGNALS FOR THE YEAR 2016

The Health Sciences Authority (HSA) conducts regular individual and aggregated reviews of all adverse event (AE) reports. This is to identify serious, unexpected AEs that were not included in the drug's package insert (PI) or higher than expected reporting frequency of established AEs from clinical trials or global post-marketing experience. Any local safety signals and significant drug-AE pair of interest relevant to the local context will be published in this bulletin to raise the awareness of our healthcare professionals.

In 2016, the following local safety signals were identified by HSA:

Gemeprost and uterine rupture

Gemeprost (Cervagem®, Sanofi-Aventis Singapore Pte Ltd) is a prostaglandin analogue indicated for the softening and dilatation of the uterine cervix prior to transcervical intrauterine operative procedures in pregnant patients in the first trimester of gestation, therapeutic termination of pregnancy in patients in the second trimester of gestation and induction of abortion of second trimester pregnancies complicated by intrauterine foetal death.

HSA was alerted by one healthcare institution which observed a cluster of seven reports over a period of nine months of uterine rupture associated with gemeprost indicated for the termination of mid-trimester pregnancy. Patients' age ranged from 25 to 38 years old and gemeprost was the only suspected drug listed in the reports. The diagnosis of uterine rupture was confirmed in all the patients through scans and repair of the uterus was done in which all patients recovered. Six out of the seven patients had past history of uterine surgery where lower segment caesarean section was performed.

HSA investigated this issue and the product quality report by the company did not show any product quality issues for the affected batch. Further investigations carried out by the healthcare institution identified a group of patients at risk for uterine rupture (e.g., two or more previous uterine scars) and a risk mitigation protocol for gemeprost was implemented. Following this, no further cases of uterine rupture associated with gemeprost were reported to-date.

Uterine rupture is a rare AE reported with gemeprost, most commonly in multiparous women and in those women with a history of uterine surgery.[1] Healthcare professionals are advised to monitor patients' cervical dilatation and uterine contractions when using this drug in the termination of pregnancy especially in patients at higher risk of uterine rupture or during the second trimester or the second course of the therapy.

Dinoprostone Vaginal Delivery System 10mg and placental abruption

Dinoprostone Vaginal Delivery System (VDS) 10mg (Cervidil®, Ferring Pharmaceuticals Pte Ltd) is indicated for the initiation of cervical ripening in patients, at- or near-term, who have favourable induction features and in whom there is a medical or obstetrical indication for induction of labour.

In 2016, HSA received two reports of placental abruption with dinoprostone VDS 10mg. The patients were reported to experience severe vaginal bleeding and one neonate died in connection with placental abruption during labour. Cardiotocography monitoring was done before and after dinoprostone VDS 10mg insertion. The company's review of the manufacturing records and analyses of samples from the implicated batch did not show any deviations.

Placental abruption is a complication of pregnancy, with a background incidence of between 0.2 to 1% of pregnancies.[2,3] Risk factors for placental abruption include chronic hypertension, eclampsia, premature rupture of membranes, previous abruption, maternal age and smoking during pregnancy.[4]

Placental abruption as an AE is currently not listed in the PI of Cervidil®.[5] The company recently submitted an application to update the PI to reflect the uncommon occurrence of placental abruption, based on observations from clinical studies. Healthcare professionals are advised to take into consideration the reports of placental abruption following the use of dinoprostone-containing preparation in the routine monitoring of patients for the induction of labour.

Pembrolizumab and Stevens Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN)

Pembrolizumab (Keytruda®, MSD Pharma (Singapore) Pte Ltd) is indicated for the treatment of patients with unresectable or metastatic melanoma, and those with locally advanced or metastatic non-small cell lung carcinoma whose tumours express PD-L1 as determined by a validated test and who have received platinum-containing chemotherapy.

From June 2016 to November 2016, HSA received three reports of SJS/TEN associated with pembrolizumab. The patients' ages ranged from 45 to 81 years old. In one case, SJS developed after 19 weeks of therapy, given once every three weeks. The second and third patient developed SJS and TEN, 10 and 14 days, respectively after their first dose. Pembrolizumab was the only suspected drug in all three cases. Two patients recovered and one died.

At least one case of pembrolizumab-associated SJS has been described in published literature, with onset of rash beginning one week after the first dose. The patient first developed maculopapular rash and diagnosis of SJS was made following four skin biopsies as the reaction progressed.[6] In the WHO global pharmacovigilance database (as of 31 March 2017), three other cases of pembrolizumab-associated SJS/TEN were reported in the United States and France. Two of them had co-suspected drugs, and in one case the patient died.

The company will be issuing a Dear Healthcare Professional Letter (DHCPL) and HSA is currently working with them to update the local PI to reflect this new safety information, and will continue to monitor this signal closely.

Healthcare professionals are encouraged to report any suspected serious AEs related to health products to the Vigilance and Compliance Branch of HSA. With your continuous vigilance in identifying these serious AEs, regulatory or clinical actions may be taken to mitigate the risks and help protect public health.

References

1. *Singapore package insert for Cervagem®. Approved June 2016*
2. *PLoS One 2015; 10:e0125246*
3. *Am J Obstet Gynecol 2015; 213:573.e1*
4. *http://www.uptodate.com/contents/placental-abruption-clinical-features-and-diagnosis*
5. *Singapore package insert for Cervidil®. Approved July 2013*
6. *Reactions Weekly 2016; 1621:203*

LIST OF DEAR HEALTHCARE PROFESSIONAL LETTERS ON SAFETY CONCERNS ISSUED BY HSA, PHARMACEUTICAL AND MEDICAL DEVICE COMPANIES (1 DECEMBER 2016 TO 30 APRIL 2017)

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

Therapeutic products

22 Sep 2016*	**Technescan DTPA for Injection** Change of representation of active ingredient in the labelling
12 Dec 2016	**Dilantin® (phenytoin sodium) 20mg and 100mg capsules** Potential non-engagement/securing of the Child Resistant Closure for certain batches
3 Jan 2017	**Mirena® (levonorgestrel) Intrauterine Delivery System** Affected product may have an incorrectly mounted insertion tube which may result in the inversion of the insertion depth scale
25 Jan 2017	**Bayer Aspirin 500mg tablets** Notification of drug shortage and advisory to switch patients taking affected product to alternative therapies/ treatments
2 Feb 2017	**Zelboraf® (vemurafenib)** Potential risk of Dupuytren's contracture and plantar fascial fibromatosis associated with use
20 Mar 2017	**Solu-Medrol® 500 mg/8ml injection (methylprednisolone)** Selected batches do not contain Singapore Approved Packaging
5 Apr 2017	**Cotellic™ (cobimetinib)** Risk of severe haemorrhage associated with use of cobimetinib

Medical devices

8 Nov 2016*	**SynchroMed® II Implantable Drug Infusion Pump** Updated information on the issue of overinfusion
10 Nov 2016*	**8840 N'Vision® Clinician Programmer and SynchroMed® II Infusion System** Update of the Model 8870 software application card to mitigate the potential for clinical effects of drug over-delivery during the SynchroMed® II full system priming bolus procedure
6 Dec 2016	**Exactech Equinoxe Reverse Shoulder Fixed Angle Torque Defining Screwdriver** Potential non-retention of screw head in the affected device
15 Dec 2016	**Claria MRI™ CRT-D SureScan™ and Amplia MRI™ CRT-D SureScan™ devices** Loss of LV pacing that may occur for all models
10 Jan 2017	**Synthes Radial Head Prosthesis** Voluntary recall due to possible loosening post-operatively at the stem bone interface for the radial stem
21 Feb 2017	**Medtronic Strata™ II/Strata™ NSC Valves** Update to the Instruction For Use due to possible reverse polarity of the valve magnet that can lead to inaccurate pressure level reading on the Strata™ Indicator Tool or StrataVarius™ system
24 Feb 2017	**Starclose SE Vascular Closure System** Voluntary recall of selected lots due to difficulty or failure in deploying the StarClose SE Clips
27 Feb 2017	**MiniMed™ 640G Insulin Infusion Pump** Software issue that could prevent the internal battery of the pump from charging
1 Mar 2017	**Endurant™/Endurant II™ 23mm and 25mm Bifurcated Stent Graft Systems** Voluntary recall of specific lots due to greater susceptibility to fabric permeability variations that may be associated with endoleaks observed during the initial implant procedure
3 Mar 2017	**Cordis® S.M.A.R.T® Flex Vascular Stent System sizes 5x200mm and 6x200mm** Voluntary recall of all unexpired lots due to higher frequency of deployment issues compared to other sizes
22 Mar 2017	**Medtronic StrataMR™ Adjustable Valves & Shunts** Voluntary recall of all unused units due to the potential for underdrainage of cerebrospinal fluid
31 Mar 2017	**Lotus™ Valve System** Voluntary recall of all units due to a higher than anticipated number of reports of early pin release prior to locking the valve in its final position
11 Apr 2017	**Zenith Alpha™ Thoracic Endovascular Graft** Update to the Instructions for Use due to new information including recommendations on patient selection, device planning and sizing, and patient monitoring for blunt thoracic aortic injury

* *DHCPLs not published in Dec 2016 issue*

Useful Information

Doctors, dentists and pharmacists can claim continuing education points for reading each issue of the HSA ADR News Bulletin. Doctors can apply for one non-core Continuing Medical Education (CME) point under category 3A, dentists can apply for one Continuing Professional Education (CPE) point under category 3A and pharmacists can apply for one patient-care Continuing Professional Education (CPE) point under category 3A per issue of the bulletin.

RISK OF FALSELY ELEVATED OESTRADIOL LEVELS DUE TO CROSS-REACTIVITY OF FULVESTRANT WITH OESTRADIOL IMMUNOASSAYS

Key Points

- Medical and scientific literature as well as rare international post-marketing reports suggest that fulvestrant can cross-react with oestradiol (E2) immunoassays due to its structural similarity with E2. This can result in falsely elevated E2 levels, which may in turn lead to misinterpretation of the menopausal status of women
- Healthcare professionals are advised to indicate if their patient is on fulvestrant when requesting for blood tests that include E2, and to consider the need to review the previously reported test results
- Healthcare professionals may wish to consider alternative methods for E2 measurements (e.g., liquid chromatography-mass spectrometry) in patients on fulvestrant

HSA would like to highlight to healthcare professionals about the risk of falsely elevated oestradiol (E2) levels due to cross-reactivity of fulvestrant with E2 immunoassays, which can result in unnecessary therapy modification.

Fulvestrant (Faslodex®, AstraZeneca Singapore Pte Ltd) has been registered in Singapore since 2006. It is indicated for the treatment of post-menopausal women with oestrogen receptor (ER)-positive, locally advanced or metastatic breast cancer for disease relapse on or after adjuvant anti-oestrogen therapy, or disease progression on therapy with an anti-oestrogen. Fulvestrant is a competitive ER antagonist with an affinity comparable to E2. Its mechanism of action is associated with down-regulation of ER protein levels.

Background[1]

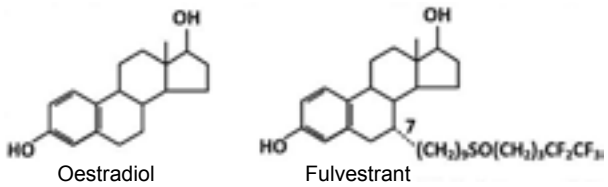
Medical and scientific literature as well as rare international post-marketing reports suggest that fulvestrant can cross-react with E2 immunoassays due to its structural similarity with E2. This can result in falsely elevated E2 levels, which could potentially lead to unnecessary surgery or endocrine therapy modification due to misinterpretation of menopausal women as being premenopausal.

Case report on falsely elevated E2 levels in a postmenopausal patient[2]

A 36-year-old woman with ER-positive breast cancer underwent bilateral oophorectomy, followed by treatment with letrozole and fulvestrant. The patient was later found to have an unexpected increase in E2 level which was inconsistent with the menopausal symptoms she experienced, such as hot flushes. A pelvic ultrasound revealed a possible small soft tissue density in the left adnexal region that was suspected to be residual ovarian tissue persisting after oophorectomy (a rare condition known as ovarian remnant syndrome). The patient subsequently underwent additional imaging and surgical intervention with diagnostic laparoscopy to remove the possible remnant. Pathology however, revealed no ovarian tissue, thus ruling out ovarian remnant syndrome as the cause of her increased E2 levels.

Testing of the patient's serum E2 levels using a more sensitive and specific liquid chromatography-tandem mass spectrometry (LC-MS/MS) method showed the patient's serum E2 levels to be undetectable, hence confirming that an exogenous agent was likely to be cross-reacting with the immunoassay and producing falsely elevated serum E2 readings. Fulvestrant possesses the basic structure of E2 with the exception of an aliphatic chain of 14 carbons at position 7α (Figure 1). This allows the drug to bind anti-E2 antibodies in the immunoassay and cause false positive results. Based on this structural similarity, fulvestrant was deemed the most likely culprit that led to the falsely elevated E2 reading in this patient.

Figure 1. Chemical structure of oestradiol and fulvestrant[2]



Oestradiol Fulvestrant

Actions by other regulatory agencies

Health Canada has published an advisory regarding the risk of unnecessary therapy modification due to falsely elevated E2 levels in patients taking fulvestrant.[2] Apart from issuing a Dear Healthcare Professional Letter in Canada, AstraZeneca has also updated the Faslodex® product monograph to include warnings about this safety issue.

The Australian Therapeutic Goods Administration (TGA),[3] European Medicines Agency (EMA)[4] and United States Food and Drug Administration (US FDA)[5] have also updated the product labelling of Faslodex® with warnings that fulvestrant can interfere with E2 measurement by immunoassays, resulting in falsely elevated E2 levels.

Local situation

To date, HSA has not received any local ADR reports of falsely elevated E2 levels associated with the use of fulvestrant. HSA is working with AstraZeneca to update the local Faslodex® package insert to reflect information on the drug-mediated cross-reactivity of fulvestrant with E2 immunoassays.

HSA's advisory

Healthcare professionals are advised to indicate if their patient is on fulvestrant when requesting blood tests that include E2 levels and to consider alternative methods such as liquid chromatography-mass spectrometry instead of immunoassays to detect E2. Healthcare professionals may also consider the need to carry out a review of the previously reported E2 test results in patients on fulvestrant.

References

1. *http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2016/60590a-eng.php*
2. *Clin Breast Cancer 2016; 16: e11-3*
3. *Faslodex® Australian Product information, updated on 8 August 2016*
4. *Faslodex® Summary of Product Characteristics, updated on 9 November 2016*
5. *Faslodex® US Product label, updated on 7 December 2016*

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