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HSA Health Sciences Authority

ADVERSE DRUG REACTION NEWS

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ALLOPURINOL-INDUCED SERIOUS CUTANEOUS ADVERSE REACTIONS AND THE ROLE OF GENOTYPING

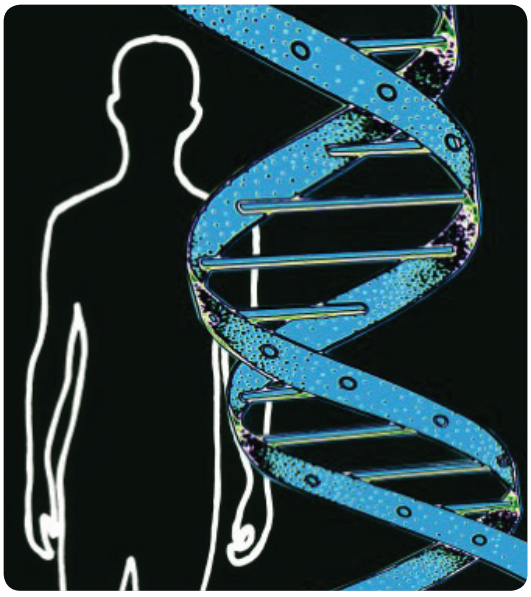
Key Points

- Allopurinol is one of the leading causes of drug-induced SCAR reported locally
- In view of the risk of SCAR, allopurinol should be used with caution, starting at a low dose, titrated and monitored accordingly, especially during the first three months of therapy
- A strong association has been observed between HLA-B*5801 allele and allopurinol-induced SCAR. Genotyping for the HLA-B*5801 allele may be considered in patients who have other pre-existing risk factors e.g., renal impairment
- Healthcare professionals are advised to educate their patients on early recognition of allergic reactions, the importance of prompt withdrawal of the drug at the first sign of rash and to seek medical advice

HSA, together with the Ministry of Health (MOH), have jointly issued a Dear Healthcare Professional Letter (DHCPL) on 23 March 2016 to remind healthcare professionals of the risk of allopurinol-induced serious cutaneous adverse reactions (SCAR), and inform on the role of genotyping prior to the initiation of allopurinol. This article shares the summary of evidence presented on allopurinol-induced SCAR, genetic associations reported and the role of genotyping prior to therapy initiation.

Allopurinol is an efficacious urate-lowering therapy (ULT) which has been registered in Singapore since 1989 and is recommended as first-line therapy for gout patients who have two or more gouty attacks per year, presence of tophus, radiographic changes of gout, or urolithiasis.[1] Globally, increasing incidence but sub-optimal management of gout has been reported.[2,3]

Allopurinol, while effective in treating chronic gout, is associated with rare and potentially fatal SCAR, such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS). Allopurinol is one of the leading causes of drug-induced SCAR reported to HSA. From 2010 to 2014, HSA received 70 cases of allopurinol-induced SCAR, seven of which were fatal. A review of local SCAR reports received by HSA and the published local and international studies found that the majority of SCAR occurred within three months, with a median onset of 3-4 weeks upon the initiation of therapy.[4-7] Risk factors of allopurinol-induced SCAR include the presence of HLA-B*5801 allele, starting dose of allopurinol and renal impairment. A low starting dose, no greater than 100mg per day, for gout has been recommended to minimise the risk of allopurinol-induced SCAR.[1]



Summary of evidence on HLA-B*5801 and allopurinol-induced SCAR

The recommendations on the use and monitoring of allopurinol and the consideration for HLA-B*5801 allele genotyping are based on the findings listed below.

- A HSA-initiated local, multi-centre, case-control study conducted at Singapore General Hospital, National University Hospital, Changi General Hospital and the National Skin Centre found a strong association between HLA-B*5801 allele and allopurinol-induced SCAR (Odds ratio=100, p=0.0004) i.e. patients carrying the HLA-B*5801 allele have higher risk of developing allopurinol-induced SCAR (100 times) compared to one who does not have the allele. This is consistent with international data which showed that HLA-B*5801 carriers have an elevated risk of developing SCAR when taking allopurinol.

- The PPV is low at 2% and the Negative Predictive Value (NPV) of the genotyping test is nearly 100%. This means that among 100 allopurinol users with positive HLA-B*5801, two patients may develop SCAR, while among 100 patients tested negative, almost all patients are unlikely to develop SCAR, provided there are no other non-genetic factors involved.

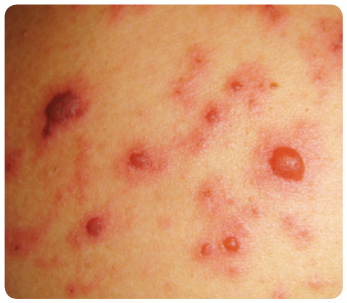
- The frequency of HLA-B*5801 prevalence is estimated at 18.5% in Singapore (approximately 1 in 5 Singaporeans or 1 in 5 Chinese, 1 in 15 Malays and 1 in 25 Indians).

- There are limited alternative ULTs available locally. Uricosuric agents such as probenecid and benzbromarone are only effective in preserved renal function (creatinine clearance > 50ml/minute for probenecid or >20ml/min for benzbromarone). Both are contraindicated in patients with a history of urolithiasis and hepatotoxicity has been reported with benzbromarone.[1] A new ULT, febuxostat, has been recently approved in Singapore in February 2016. Rare but serious cases of hypersensitivity reactions to febuxostat, including SJS and acute anaphylactic shock, have been reported overseas. In some cases, the reactions occurred in patients with a prior history of hypersensitivity to allopurinol and/or pre-existing renal disease.

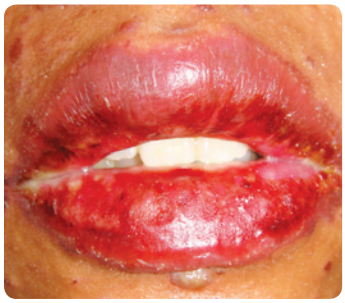
- Patients tested negative for HLA-B*5801 may still be at risk of developing allopurinol-induced SCAR. Other non-genetic risk factors associated with SCAR, such as renal impairment and starting dose of allopurinol, have been reported.[8]

- A cost-effectiveness analysis by Duke-NUS Graduate Medical School, in collaboration with HSA and National University Health System (NUHS), concluded that genotyping all gout patients prior to initiation of allopurinol is currently not cost-effective for Singapore's overall population from a health systems perspective.[9]

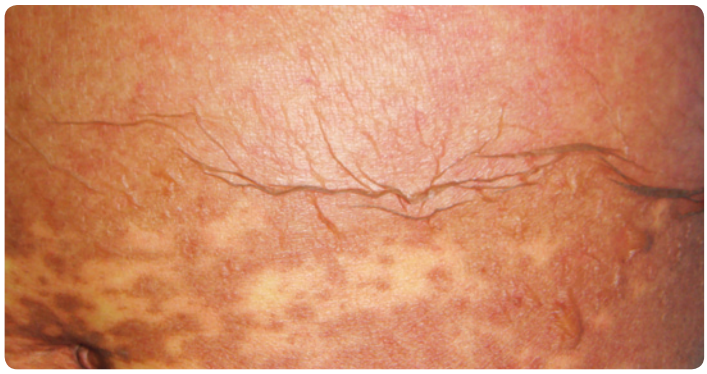
Photos of types of skin eruptions due to SCAR



Dusky and purpuric macules with vesiculation



Erosions on the lips and perioral skin



TEN-Confluent epidermal detachment

HSA's advisory

HSA has received nine allopurinol-induced SCAR reports between March to August 2016, since the issuance of the DHCPL. Majority of these cases reported the use of allopurinol for gout in Chinese patients.

In view of the seriousness and fatalities reported with allopurinol-induced SCAR, healthcare professionals are advised to use allopurinol with caution; start at a low dose, titrate and monitor accordingly based on clinical indications.

As early signs of rash and skin reactions may be indicative of a more serious reaction such as SCAR, healthcare professionals are advised to educate their patients on early recognition of allergic reactions, the importance of prompt withdrawal of the drug at the first sign of rash and the need to seek medical advice.

While genotyping is not required as standard of care for new patients starting allopurinol, doctors may consider genotyping patients who have other pre-existing risk factors for allopurinol-induced SCAR such as renal impairment and to identify the patients who are at a greater risk of allopurinol-induced SCAR. While it is likely that patients who have tested negative for this allele may not develop allopurinol-induced SCAR, the possibility of developing allopurinol-induced SCAR due to other risk factors cannot be ruled out. Genetic testing, when ordered for at-risk patients, should not substitute for appropriate clinical vigilance and patient management.

Healthcare professionals are encouraged to continue reporting suspected adverse drug reactions associated with allopurinol to the Vigilance and Compliance Branch of HSA and include information on indication of gout, renal function, starting dose and genotype status of the patient, to facilitate close monitoring of this safety issue.

Table 1. Information on DNA testing at KKH DNA Diagnostic and Research Laboratory

Where to test

The HLA-B*5801 test is available at KK Women's and Children's Hospital (KKH) DNA Diagnostic and Research Lab at $200 per test (excluding GST) and is not subsidised. The estimated turnaround time is one to two working days. For this test, 3ml of blood must be collected in an EDTA sample tube and kept at 4°C before despatch.

Operating hours of KKH DNA Diagnostic and Research Lab Monday to Friday: 8:30am – 6:00pm Tel: 6394 1395; 6394 1396	
Cut-off time for arrival of test sample at KKH (Note: Specimens received after cut-off time may be brought over to the next batch of testing)	12:00pm
Corresponding latest despatch time of results	6:00pm

We would like to thank Dr Bernard Thong and Dr Teng Gim Gee for their inputs to this article.

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SPECIAL FEATURE: DRUG-INDUCED LIVER ADVERSE EVENTS

Certain drugs and complementary health products can cause liver injuries. An estimated 1,000 drugs have been been found to cause liver disease, with greater propensity than others.[1] Women, older patients (> 50 years old) and those on concomitant medications are at greater risk of developing drug-induced liver injury (DILI).[2] In general, drugs may cause hepatotoxicity in one of two ways: (1) direct toxic reaction or (2) idiosyncratic reaction.[3] Immunosuppressive drugs corticosteroids, antineoplastic agents, antimetabolites, can also induce liver injuries through its inherent mechanism of action i.e. by inhibiting the body's natural immune responses and altering the production or action of cytokines; or disrupting cell metabolism and preventing cell proliferation.

Locally, drug-induced liver AEs have also been reported with the use of complementary health products. However, in many cases, it was difficult to ascertain the direct link between the suspected product and liver injury as DILI is a diagnosis based on exclusion. Furthermore, herbs are often used in various combinations, doses, and duration, making it difficult to isolate the component(s) that is/are responsible for the hepatotoxicity.

In this special feature, we present three articles on acute liver AEs. The first article is a case study on a multi-component complementary health product which was suspected to have caused jaundice in the patient. The second and third articles feature acute liver AEs suspected to be associated with the use of immunosuppressive agents in patients with a history of hepatitis B virus (HBV) infection.

HSA has developed a guide to assess and report DILI and it can be found on HSA's website: *http://www.hsa.gov.sg/content/dam/HSA/HPRG/Safety_Alerts_Product_Recalls_Enforcement/Drug%20Induced%20Liver%20Injury%20(DILI)_Guide_Web.pdf*

References

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3. *Harrison's Principles of Internal Medicine 15th Edn. McGraw Hill; 2003*

AE CASE IN FOCUS: TEST YOURSELF

A middle-aged female presented with a 2-week history of jaundice and tea-coloured urine. The patient did not have a significant medical history. She started taking a multi-component health supplement containing glucosamine HCl, green tea leaf extract, chondroitin, *Angelica gigas*, bromelain, chokeberry, *Harpagophytum procumbens*, ginger root extract, manganese, methylsulfonylmethane, papain, *Curcuma longa* and vitamin C. The patient was taking the product for joint pain. She was not known to be taking other medications. Her liver function tests showed predominantly hepatocellular derangement with initial ALT of 1480U/L and initial ALP of 273U/L. The patient is a non-smoker and a non-drinker. Laboratory investigations were negative for viral markers. Autoimmune hepatitis was also ruled out. She started taking the product 16 days prior to the onset of jaundice and tea-coloured urine. Upon discontinuation of the product and treatment, the patient's liver enzymes subsequently improved.

The patient had clinical presentation of a hepatocellular liver injury with a prolonged cholestatic phase. She was diagnosed with drug-induced liver injury (DILI) after exclusion of all possible factors as highlighted in the narrative and based on positive de-challenge of the multi-component product.

Questions:

a. Which component(s) is/are more likely to have contributed to the patient's liver injury?

b. What is your causality assessment for this AE report?

HSA would like to take this opportunity to thank Dr Tan Hiang Keat from Singapore General Hospital for his contribution to this article.

Answers can be found on page 8.

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.

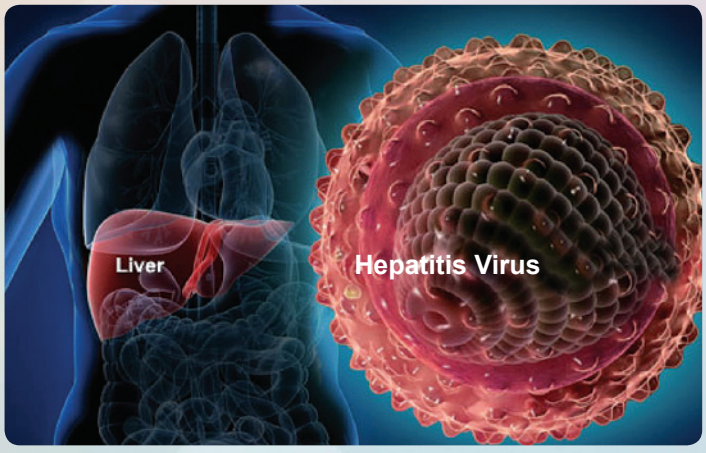
RISK OF HEPATITIS B VIRUS REACTIVATION WITH BCR-ABL TYROSINE KINASE INHIBITORS

Key Points

- Cases of HBV reactivation, associated with the use of BCR-ABL TKIs, including those with fatal outcome, have been reported overseas in patients who are chronic carriers of this virus
- Patients should be tested for HBV infection before initiating treatment with BCR-ABL TKIs. Consultation with experts in hepatic disease and in the treatment of HBV is recommended for patients with positive HBV serology prior to or during treatment
- Patients who are carriers of HBV requiring treatment with BCR-ABL TKIs should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy

Overseas cases of hepatitis B virus (HBV) reactivation have been observed following treatment with breakpoint cluster region-abelson (BCR-ABL) tyrosine kinase inhibitors (TKIs) in patients who are chronic carriers of this virus. Some of these cases had resulted in acute hepatic failure or fulminant hepatitis resulting in the need for liver transplantation or a fatal outcome.

BCR-ABL TKIs registered in Singapore include dasatinib (Sprycel®, Bristol-Myers Squibb), imatinib (Glivec®, Novartis) and nilotinib (Tasigna®, Novartis). The BCR ABL TKIs inhibit BCR-ABL tyrosine kinase and thus suppress proliferation and promotes apoptosis in leukaemic cell lines over-expressing BCR-ABL.[1] They are indicated for the treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukaemia (Ph+ CML). In addition, Sprycel® is also indicated for the treatment of Philadelphia chromosome-positive acute lymphoblastic leukaemia (Ph+ ALL) while Glivec® is also indicated for the treatment of Ph+ ALL and KIT+ gastrointestinal stromal tumours.



Background

1) European Medicines Agency (EMA)[2,3]

In February 2016, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) completed a safety review which concluded that there is convincing evidence of HBV reactivation as a class effect of BCR-ABL TKIs. PRAC's review took into consideration cumulative data from clinical trials and post-marketing experiences related to the reactivation of HBV in patients treated with BCR-ABL TKIs.

The case reports indicated that HBV reactivation may occur at any time during BCR-ABL TKIs treatment. Some of these patients had a documented history of HBV infection while in other cases, the serologic status at baseline was not known. An increase in viral load or positive serology was diagnosed upon HBV reactivation. In some of these cases, patient developed acute hepatic failure or fulminant hepatitis which required liver transplantation or resulted in a fatal outcome. The mechanism and the frequency of HBV reactivation during BCR-ABL TKIs exposure are not known at this time.

Recommendations from PRAC were to update the package inserts and to issue a safety communication to inform that patients should be tested for HBV infection before initiating treatment with BCR-ABL TKIs. It was also recommended that experts in hepatic disease and in the treatment of HBV should be consulted for patients with positive HBV serology prior to and during treatment. Patients who are carriers of HBV requiring treatment with BCR-ABL TKIs should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy.

2) UK MHRA and Health Canada

The United Kingdom Medicines & Healthcare products Regulatory Agency (UK MHRA)[4] has updated the package inserts of BCR-ABL TKIs, in line with the EMA PRAC recommendations. Health Canada (HC)[5] has also updated the respective package inserts. Both agencies have also issued safety communications to healthcare professionals to highlight this safety issue as well as recommendations for HBV screening before treatment.

Local situation and advisory

HSA has received three adverse drug reaction reports describing hepatitis B infection in patients treated with imatinib; in 2005, 2011 and 2012 respectively. In the first case, the patient had a history of chronic hepatitis B infection and developed fulminant hepatic failure about five months after initiating imatinib. In the second case, the patient was a hepatitis B carrier who developed hepatitis B and increased hepatic enzymes following seven years of treatment with imatinib. Imatinib treatment was stopped temporarily and restarted following initiation of hepatitis B treatment. In the third case, the patient developed hepatitis B infection with internal bleeding and liver cirrhosis during treatment with imatinib. However, there was insufficient information available to determine whether the condition was due to HBV reactivation or current underlying hepatitis B infection.

Novartis, in consultation with HSA, has issued two Dear Healthcare Professional Letters (DHCPL)[6] to communicate the risk of HBV reactivation associated with the use of Glivec® and Tasigna®, respectively. The letters highlighted the need to screen patients for HBV infection before treatment.

The local package inserts for BCR-ABL TKIs have been updated regarding this safety issue. Healthcare professionals are encouraged to be vigilant for HBV reactivation when prescribing BCR-ABL TKIs for their patients and to report any cases of HBV reactivation associated with the use of BCR-ABL TKIs to HSA.

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6. *http://www.hsa.gov.sg/DHCPL*

RISK OF HEPATITIS B VIRUS REACTIVATION WITH POMALIDOMIDE

Key Points

- Overseas cases of hepatitis B virus (HBV) reactivation, some of which progressed to acute hepatic failure, have been reported rarely following treatment with pomalidomide in combination with dexamethasone in patients previously infected with HBV
- Healthcare professionals are advised to establish the HBV status of patients before initiating treatment with pomalidomide
- Caution should be exercised when using pomalidomide in combination with dexamethasone in patients previously infected with HBV, including patients who are hepatitis B core antibody (anti-HBc) positive but hepatitis B surface antigen (HBsAg) negative

Pomalidomide (Pomalyst®, Celgene Pte Ltd) is an immunomodulating agent that is structurally related to thalidomide. It has been licensed locally since December 2014 for use, in combination with dexamethasone, for the treatment of adult patients with relapsed and refractory multiple myeloma (MM), who have received at least two prior treatment regimens (including lenalidomide and bortezomib) and have demonstrated disease progression in the last therapy. As a structural analogue of thalidomide, a known human teratogen, a teratogenic effect cannot be ruled out when Pomalyst® is taken during pregnancy. In order to minimise the risk of teratogenicity associated with its use, Pomalyst® is currently available locally under the Pregnancy Prevention Programme (i-access® programme) where healthcare professionals who wish to prescribe or dispense Pomalyst® to their patients will need to be enrolled.

Overseas cases of HBV reactivation with pomalidomide

Cases of HBV reactivation have been reported rarely (incidence less than 0.1%) following treatment with pomalidomide in combination with dexamethasone. In some of these cases, HBV reactivation was reported to have progressed to hepatic failure.[1]

The cases of HBV reactivation generally occurred during early phase of treatment with pomalidomide, with most reports received within the first treatment cycle. Patients treated with pomalidomide usually have existing risk factors for viral reactivation including old age, underlying progressive MM and prior treatment with multiple immunosuppressive treatments. The immunosuppressive effect of pomalidomide, in combination with dexamethasone, may further increase the risk of viral reactivation in these patients.

Review by the European Medicines Agency (EMA)

In March 2016, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) completed a safety review on the association of HBV reactivation with pomalidomide use. The review assessed clinical studies and cases of suspected adverse drug reactions reported by healthcare professionals and in literature.[2]

As of 7 August 2015, five patients were identified to have developed HBV reactivation while receiving treatment with pomalidomide. Two cases resulted in acute hepatic failure, one of which had a fatal outcome. Four cases occurred within a month of initiating pomalidomide therapy. Two of the cases of HBV reactivation reviewed by PRAC were reported from the literature.[3,4] The first case was a 56-year old man diagnosed with IgG kappa MM who had received multiple chemotherapies after stem cell transplants and was started on monotherapy with pomalidomide when he experienced jaundice with abnormal liver function tests. His laboratory test results showed positive HBsAg, hepatitis B envelope antigen (HBeAg) and HBV DNA >8.2 log10 IU/ml. He was previously tested to be anti-HBc positive and HBsAg negative. The second case was a 68-year old woman with refractory MM who received pomalidomide and dexamethasone together with multiple drugs including anthracyclines, alkylators and proteasome inhibitors. She initially suffered from major hematological toxicities and infectious complications including HBV reactivation, but later experienced long-term disease control upon careful dose adjustments and selection of combination drugs.

Based on the assessment results, recommendations were made by PRAC to update the product information of pomalidomide with warnings on infections and HBV reactivation, as well as to distribute a safety communication to healthcare professionals to inform on the need to establish the HBV status of patients before initiating treatment with pomalidomide.[5]

Local situation and HSA's advisory

To date, HSA has not received any local reports of HBV reactivation with pomalidomide use.

The Singapore package insert of Pomalyst® currently warns of the risk of hepatitis and HSA is working with the company to strengthen the warnings on the risk of HBV reactivation.

Healthcare professionals are encouraged to exercise caution when prescribing pomalidomide in patients previously infected with HBV and to establish the HBV status of their patients before initiating treatment with pomalidomide.

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LIST OF DEAR HEALTHCARE PROFESSIONAL LETTERS ON SAFETY CONCERNS ISSUED BY HSA, PHARMACEUTICAL AND MEDICAL DEVICE COMPANIES (1 APRIL 2016 TO 31 JULY 2016)

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

Therapeutic products

13 Apr 2016	**Zydelig® (idelalisib)** Advisory on decreased overall survival and increased rate of serious adverse events such as infections
18 Apr 2016	**Roaccutane® (Isotretinoin)** Voluntary recall of selected lots due to insertion of incorrect package insert
25 Apr 2016	**Taxotere® (Docetaxel)** Voluntary recall of selected lots due to a failure in the filling process which led to a low number of potentially over-concentrated Taxotere ® Concentrate vials
23 May 2016	**Invokana™ (canagliflozin)** Advisory on the risk of lower limb amputations (primarily of the toes)
31 May 2016	**DBL Carboplatin Injection 10mg/ml** Potential risk of methotrexate being present on the exterior surface of one batch of Carboplatin 10mg/ml vials due to methotrexate vial breakage/spill during packing process at the manufacturing site
31 May 2016	**Ventolin® Solution for Intravenous Infusion 5mg/5ml (salbutamol sulphate)** Notification on a temporary and voluntary hold on the manufacturing and release of affected product at GSK's Parma manufacturing site as a precautionary measure due to data inconsistencies at this facility
31 May 2016	**Ultiva® For Injection 1mg/vial (remifentanil hydrochloride), Tracrium® Injection 10mg/ml (5ml ampoule) (atracurium besylate), Mivacron® Injection 2mg/ml (10ml ampoule) (mivacurium chloride)** Notification on a temporary and voluntary hold on manufacturing and release of affected product at GSK's Parma manufacturing site as a precautionary measure due to data inconsistencies at this facility
16 Jun 2016	**Risperidone** Revised licensed indication to short-term treatment of persistent aggression in patients with Alzheimer's dementia (AD) only due to higher risk of cerebrovascular adverse events in patients with mixed/vascular dementia versus AD
22 Jun 2016	**Vismodegib (Erivedge®)** Advisory on the risk of premature epiphyseal fusion
4 Jul 2016	**Codeine-containing products** Recommendations for use in the treatment of pain and the relief of cough and cold in children and adolescents

Medical devices

4 Apr 2016	**Biomet Endobon® Xenograft Granules** Voluntary recall of selected lots as limited results indicated that the product's cytotoxicity tests did not pass at 36 months (real-time) aging
20 Apr 2016	**Stardrive® and Hex Drive Self-tapping 3.5mm Locking Screws** Voluntary recall of selected lots as the affected packages include incorrect screws with incorrect labels, and part and lot numbers etchings
17 May 2016	**Cortex Screw Ø 4.5mm, Self-tapping, Length 20mm, Pure Titanium, Sterile and Non-sterile** Voluntary recall of selected lots as the affected packages may incorrectly contain a 4.5mm Cortex Screw that is 22mm in length
20 May 2016	**Cordis PRECISE® PRO RX Nitinol Stent System (Carotid)** Voluntary recall of selected lots due to an increased frequency of users reporting difficulty with stent deployment and/or separation of the bond between sections of the device outer member
26 May 2016	**Nipro Diagnostics TRUEresult Blood Glucose Test Strips** Voluntary recall of selected lots as the affected products may give incorrect low blood glucose results
30 May 2016	**TIGR® Matrix Surgical Mesh** Advisory that the outside of the inner pouch is non-sterile and product packaging has to be handled according to the 'Instructions for Use'
9 Jun 2016	**Baxter Healthcare COSEAL Surgical Sealant** Voluntary recall of selected lots due to the potential for incomplete dissolution of the polyethylene glycol component during the reconstitution of the product, which may affect the consistency of the hydrogel formation during use
10 Jun 2016	**Heartware® Controllers** Hazard alert on the possibility of loose power and data connectors arising from reports received during ongoing product performance monitoring
17 Jun 2016	**Flexible Shaft Ø 8.0mm, L 360 mm for Extraction System for Solid Medullary Nails** Voluntary recall of affected lots due to failure to pass the biological safety evaluation for cytotoxicity following exposure to test conditions
28 Jun 2016	**Medtronic RestoreSensor® Implantable Neurostimulators, Models 37714 and 97714** Advisory on the risk of disruption in therapy due to insufficient recharging of affected models
7 Jul 2016	**Medtronic Tunneling Tool Model 3755 and DBS Extensions Models 7483 and 37086** Label updates on reported events related to Medtronic Deep Brain Stimulation tunneling procedure
11 Jul 2016	**Synthes® Mandible Distractor, Monoaxial and Proximal Foot Plate** Voluntary recall of affected products as the fastener on the Mandible Distractor may become prematurely separated from the Proximal Foot Plate
15 Jul 2016	**Stryker Neurovascular Target Detachable coils** Voluntary recall of affected products due to damaged sutures in the coil which may lead to increased occurrence of coil stretching
15 Jul 2016	**Medtronic Deep Brain Stimulation Therapy-ACTIVA®PC, ACTIVA® SC, ACTIVA® RC AND ACTIVA® PC+S** Label updates on reported events of loss of coordination related to Medtronic Deep Brain Stimulation Therapy

RESTRICTIONS ON THE USE OF METOCLOPRAMIDE-CONTAINING PRODUCTS

Key Points

- Benefit-risk assessments of metoclopramide-containing products by international regulatory agencies and HSA confirmed the relationship between the use of high doses or long-term use of metoclopramide and the increased risks of neurological adverse reactions
- Restrictions on the indication, dose and duration of use of metoclopramide-containing products have been recommended
- Healthcare professionals are advised to take them into consideration when prescribing metoclopramide-containing products

HSA had issued a Dear Healthcare Professional Letter in July 2015 and its amendment in March 2016 to healthcare professionals regarding new restrictions on the use of metoclopramide-containing products in order to reduce the risk of neurological and other dose-related adverse reactions. This article serves as a consolidation of the two letters and a reminder on the restrictions and revised indications for its use.

Metoclopramide is a pro-kinetic drug that has been licensed in Singapore since 1989 for the prevention and treatment of nausea and vomiting due to various conditions. Locally, there are 12 registered metoclopramide-containing products, which are available in various dosage forms such as tablet, syrup and injection.

Background

In December 2011, a benefit-risk assessment of metoclopramide use in different age groups in the European Union (EU) was initiated by the European Medicines Agency (EMA), following concerns from the French National Agency for the Safety of Medicine and Health Products (ANSM) regarding the benefit-risk balance of metoclopramide. ANSM expressed that despite its long use for a wide range of indications, there was limited evidence of efficacy for approved indications of metoclopramide, while the risks of neurological and cardiovascular adverse events are known.[2] The review, completed in December 2013, confirmed the relationship between the use of high doses or long-term use of metoclopramide and the increased risks of neurological adverse reactions, such as acute extrapyramidal symptoms and irreversible tardive dyskinesia. In addition, there were also very rare reports of serious cardiovascular reactions, particularly if metoclopramide was administered intravenously. Patients at risk of cardiovascular reactions include the elderly population, patients with cardiac conduction disturbances (including QT prolongation), uncorrected electrolyte balance, bradycardia, and those taking other medicinal products known to prolong the QT interval.

In order to minimise the risk of potentially serious neurological adverse reactions, the EMA's Committee for Medicinal Products for Human Use (CHMP) recommended restrictions on the indications, dose and duration of use of metoclopramide-containing products in the EU.[2] It was recommended that the use of metoclopramide should be restricted to the short term (i.e. up to 5 days). Indications involving long-term treatment (e.g., gastroparesis, dyspepsia) were no longer supported. As it is indicative that adverse events increased with dose, the dose should be restricted to the minimum effective dose with a recommended maximum daily dose of 30 mg and 0.5mg/kg, in adults and children, respectively. In addition, metoclopramide should be contraindicated in children below one year of age due to increased risks of extrapyramidal disorders and methaemoglobinaemia.

Other international regulatory actions

The United States Food and Drug Administration (US FDA) and Health Canada have reported the increased risk of irreversible tardive dyskinesia beyond 12 weeks of metoclopramide treatment in 2009 and 2011.[3,4] Both agencies retained the indications involving long-term treatment but recommended that the maximum treatment duration for metoclopramide should not exceed 12 weeks. The Australian Therapeutic Goods Administration (TGA) adopted the CHMP's recommendations in February 2015, including restricting the use to short-term indications with a maximum treatment duration of 5 days.[5] In addition, both Health Canada and TGA have recommended that the maximum daily dose of metoclopramide should not exceed 30 mg in adults and 0.5 mg/kg in children, and that the product should be contraindicated in children below one year of age.[5,6]

HSA's benefit-risk assessment and advisory

Locally, nearly 1 in 5 neurological adverse events reports associated with metoclopramide received by HSA from 1993 to August 2014 were reported in children. Overall, the local incidence rate of neurological side effects in adults and children did not exceed those reported overseas.

Taking into consideration the current available scientific evidence, the local incidence of adverse drug reactions, the input from local clinical experts and international regulatory actions, HSA has reviewed the benefits versus the risks of metoclopramide. The recommendations are:

- In adults, metoclopramide will be indicated for the following:
  - the prevention of nausea and vomiting associated with chemotherapy and radiotherapy with low and minimal emetogenicity
  - the prevention of post-operative nausea and vomiting (only via the parenteral route)
  - the symptomatic treatment of acute migraine-induced nausea and vomiting
  - the adjunct treatment of gastroparesis
  - the management of dyspepsia and gastroesophageal reflux disorder when other treatment options are unsuitable (only via the oral route)
  - as an adjuvant to surgical and radiological procedures.

The recommended maximum daily dose is 30mg by the oral, intravenous or intramuscular route.

- In children (aged one to 18 years old), metoclopramide should be restricted to the second-line treatment of established post-operative nausea and vomiting (only via the intravenous route). The recommended maximum daily dose is 0.5 mg/kg.
- Metoclopramide is contraindicated in infants less than one year of age.
- Treatment should be kept as short as possible, in accordance to one's clinical judgement. Treatment duration beyond 12 weeks should be avoided unless the therapeutic benefit is judged to outweigh the risk to the patient.
- Intravenous doses should be administered as a slow bolus (over a period of at least three minutes).

HSA is working with the companies of metoclopramide-containing products to update their local package inserts with the new restrictions.

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

References
1. *http://www.hsa.gov.sg/DHCPL*
2. *http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Metoclopramide_31/WC500146610.pdf*
3. *http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2009/ucm149533.htm*
4. *http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2011/13627a-eng.php*
5. *http://www.tga.gov.au/publication-issue/medicines-safety-update-volume-6-number-1-february-2015 (Metoclopramide and neurological adverse events)*
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ANSWERS TO AE CASE IN FOCUS: TEST YOURSELF

a) This is a multiple-component health supplement which was labelled with 13 ingredients. Assessing causality and determining the exact component/s which caused the patient's liver injury is challenging, given the multiple components within the health supplement.

There is some published case reports of hepatotoxicity possibly associated with glucosamine with or without chondroitin.[1,2]

In the LiverTox* monograph for 'glucosamine and chondroitin', it was stated that in controlled trials, glucosamine and its combination with chondroitin have not been linked to serum enzyme elevations or to instances of clinically apparent liver injury. However, several isolated case reports of clinically apparent liver injury attributed to glucosamine (with or without chondroitin) have been published lately, but the relationship of glucosamine itself as opposed to other herbals in the implicated products or to potential contaminants, remains unclear and some cases were considered only 'possibly' related to glucosamine. The onset of the adverse event is typically one to four weeks after starting the preparation and the liver injury is typically hepatocellular or mixed.[3]

Another likely component associated with liver injury would be the green tea leaf extract. According to the LiverTox monograph for 'green tea', the association with high doses of green tea *(Camellia sinesis)* with liver injury suggests a component of direct hepatotoxicity, and some degree of host susceptibility exacerbated by environmental features such as obesity, fasting or glutathione depletion. Liver injury usually occurs within three months, with latency. The onset of the symptoms of liver injury can range from ten days to seven months. Given the wide use of green tea and its extract in health supplements, liver injury from green tea is considered rare. Patients who present with acute liver injury particularly with a hepatocellular pattern without an obvious cause should be asked about the use of health supplements containing green tea extract, and should be advised to stop all herbal medications.[4]

The published documentation of liver injuries associated with herbal components is a growing field. Currently, there is a lack of published documentation of liver injury with the other components contained in this product.

b) The patient had no significant medical history and there was a clear temporal relationship between her intake of a multi-component product and the onset of liver injury. Onset of jaundice in the patient occurred within 16 days of taking the product. The patient also experienced a positive de-challenge upon withdrawal of the product.

Based on the information provided by the reporting doctors, causality assessment of the liver injury was done using Roussel Uclaf Causality Assessment Method (RUCAM) scale. The causality of the liver injury in this patient associated with the use of the product was assessed as 'probable'.

* LiverTox is a clinical and research information resource on drug-induced liver injury. This resource is provided by the Liver Disease Research Branch of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Division of Specialized Information Services of the National Library of Medicines (NLM), National Institute of Health of the United States of America: http://livertox.nih.gov/index.html

Reporting of AEs for complementary health products

From January to June 2016, HSA received six liver injury reports suspected to be associated with use of complementary health products containing multiple components.

HSA encourages healthcare professionals to report suspected adverse events with complementary health products.

Spontaneous adverse event (AE) reporting by healthcare professionals forms the cornerstone of post-marketing health product safety surveillance. It remains one of the most important ways of monitoring the safety of a health product throughout its marketed life. Reporting an AE does not necessarily mean that there is a definite link between the event and the product.

References
1. *World J Gastroenterol. 2013; 19: 5381-4*
2. *BMJ Case Rep. 2009; doi: 10.1136/bcr.02.2009.1603*
3. *http://livertox.nlm.nih.gov/Glucosamine.htm*
4. *http://livertox.nih.gov/GreenTea.htm*

Please send your enquiries, comments and suggestions to:

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