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Adverse Drug Reaction News

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Contraindication of subcutaneous administration of Eprex® (epoetin alfa) in Singapore in chronic kidney disease patients

This picture is for illustrative purposes only and does not reflect all the Eprex® strengths reported in the PRCA cases.

HSA would like to update healthcare professionals that subcutaneous (SC) administration of Eprex® (epoetin alfa, Johnson & Johnson Pte Ltd) is contraindicated in Singapore in chronic kidney disease (CKD) patients, including end stage renal disease (ESRD) patients. This is due to the strong association of antibody-mediated pure red cell aplasia (Ab-mediated PRCA) with SC administration of Eprex® observed locally. This decision arose from HSA's benefit-risk assessment and its consultation with a local expert panel, comprising renal physicians and haematologists, who assessed that the benefit-risk profile of Eprex® when administered subcutaneously was no longer favourable for CKD patients in the Singapore context.[1]

Based on information available to-date, this contraindication is specific to Eprex® administered subcutaneously for CKD patients. The contraindication does not affect Eprex® administered subcutaneously in other approved indications (e.g., anaemia in patients receiving chemotherapy, anaemia in HIV-infected patients treated with zidovudine, facilitation of autologous blood collection within a predeposit programme, and augmentation of erythropoiesis in the perisurgical period of major elective orthopaedic surgery) as well as other erythropoiesis stimulating agents (ESA) approved for SC administration in CKD patients.

Summary of current local situation

Nine Ab-mediated PRCA cases were reported to HSA between 2012 and June 2013 from two local healthcare institutions. The initial signal of six local cases from one healthcare institution was first shared with healthcare professionals through a Dear Healthcare Professional Letter (DHCPL) issued on 13 June 2013.[2] Subsequently, additional cases were reported from the same healthcare institution as well as one report from another healthcare institution. While investigations were ongoing, healthcare professionals were kept updated about these cases via the August 2013 issue of the HSA Adverse Drug Reaction News bulletin.[3] All cases were reported in CKD patients with Eprex® as the only suspected ESA. In addition, all cases involved SC administration of Eprex®, except for two cases where Eprex® was administered by both the SC and intravenous (IV) routes. Since the last update in August 2013, all reported cases have been confirmed as Ab-mediated PRCA cases through bone marrow examinations and antibody testing.

HSA's assessment and regulatory decision

A comprehensive review was conducted to investigate possible causes of the unexpected increase in local Eprex®-associated Ab-mediated PRCA cases reported recently in 2012 and 2013. This included a review of past history of local cases of Eprex®-associated Ab-mediated PRCA. Locally, between 2000 to 2002 when both SC and IV routes were approved for use for Eprex®, eight cases of Ab-mediated PRCA in CKD patients were reported with Eprex® as the only suspected ESA. After the recommendation by HSA to use only IV administration of Eprex® from 2003 to March 2009 in CKD patients, Eprex®-associated Ab-mediated PRCA cases were reduced substantially, with only one case reported each in 2003 and 2006 based on loss of efficacy onset date. However, following the local reinstatement of the SC administration route of Eprex® for CKD patients in 2009, resulting in both SC and IV routes being approved for administration, there was an unexpected increase in local Eprex®-associated Ab-mediated PRCA cases reported in CKD patients in 2012 and 2013.

HSA has concluded that while root causes behind the Eprex®-associated Ab-mediated PRCA cases (such as storage/handling issues and quality/manufacturing issues) have been assessed to be inconclusive, the totality of the information available to-date indicated a strong association of Ab-mediated PRCA with SC administration of Eprex® in CKD patients.

Given the increased frequency of Eprex®-associated Ab-mediated PRCA locally, which is a serious and potentially life-threatening adverse event, a contraindication of SC administration of Eprex® in Singapore in CKD patients is warranted to minimise the risk of Ab-mediated PRCA occurring in these patients and to safeguard public health.

HSA's advisory

HSA is working with the company to strengthen the local package inserts to reflect the contraindication of the SC administration route of Eprex® in CKD patients. This contraindication does not apply to Eprex® administered intravenously, Eprex® administered subcutaneously for other approved indications, or other ESAs approved for SC administration in CKD patients.

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Safety update on hydroxyethyl starch (HES)-containing products

HSA would like to inform healthcare professionals about a new safety update regarding the use of hydroxyethyl starch (HES)-containing products, and recommends that HES-containing products should not be used in septic patients, critically ill patients and patients with renal failure and/or severe hepatic impairment. This recommendation is made in consultation with its Product Vigilance Advisory Committee (PVAC) based on information from reviews by the Cochrane Collaboration and two major regulatory agencies, which revealed increased mortality and renal injury requiring renal replacement therapy in these patients who were treated with HES-containing products.

HES-containing products are colloid solutions mainly used for fluid resuscitation in patients with hypovolaemia. There are five HES-containing products registered in Singapore: Tetraspan® Solution for Infusion 6% & 10%, HAES-Steril® Infusion 6%, Voluven® Solution for Infusion 6%, and Volulyte® Solution for Infusion 6%. Tetraspan® is marketed by B. Braun Singapore Pte Ltd, whereas the remaining three products are marketed by Fresenius Kabi (Singapore) Pte Ltd.

Background

HES solutions are known to be associated with potential safety concerns such as anaphylaxis, coagulopathy, bleeding, and renal failure. However, recent reviews by the Cochrane Collaboration, the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC), as well as the US Food and Drug Administration (FDA) triggered HSA to conduct a safety assessment of the local use of starch-based colloids in critically ill patients.

In March 2013, the Cochrane Collaboration conducted a review investigating the effects of colloids compared to crystalloids on mortality in critically ill patients when used for fluid resuscitation.[1] This updated meta-analysis of 25 studies (n=9147) showed an increased risk of death in patients treated with HES solutions. The results were primarily driven by three recent studies in septic[2,3] and critically ill[4] patients, which demonstrated a higher risk of deaths (6–17% increased risk) and renal failure requiring renal replacement therapy (20–35% increased risk) in these patients following HES treatment.

In June 2013, the EMA's PRAC concluded that the benefits of infusion solutions containing HES no longer outweigh their risks and recommended the suspension of marketing authorisations of these medicines.[5] Following an appeal by the companies, the EMA conducted a re-evaluation and concluded in October 2013 that the marketing of HES-containing products can be continued, however these products should no longer be used to treat critically ill patients or patients with sepsis or burn injuries due to an increased risk of renal injury and mortality.[6]

The US FDA announced in June 2013 that HES-containing products should not be used in critically ill adult patients, including patients with sepsis and those admitted to the intensive care unit (ICU).[7] HES-containing products should also be avoided in patients with pre-existing renal disease. These recommendations were made following the FDA's analyses of available data, which showed increased mortality and renal injury requiring renal replacement therapy in these patient populations who were treated with HES-containing products.

HSA's advisory

HSA has reviewed the available information and assessments conducted by the EMA and US FDA. Although no local adverse events associated with HES-containing products have been reported to-date, HSA, in consultation with its PVAC, recommends the following in the use of these products:

- HES-containing products should not be used in patients with sepsis or critically ill patients, and in patients with renal failure and/or severe hepatic impairment.
- HES-containing products should only be used to treat hypovolaemia when crystalloids alone are not sufficient, provided appropriate measures are taken to reduce potential risk. Positive fluid responsiveness must be confirmed after the administration of HES-containing products, and the lowest possible effective dose should be used.

HSA will be working with the companies to update the above information in the local package inserts of HES-containing products.

Healthcare professionals are encouraged to report adverse events associated with the use of HES-containing products to the Vigilance Branch of HSA.

References

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Contraindication of subcutaneous administration of Eprex® (epoetin alfa) in Singapore in chronic kidney disease patients

A DHCPL was issued on 2 October 2013 to inform of the following[1]:

- **SC administration of Eprex® is contraindicated in Singapore in patients with CKD including patients with end stage renal disease.** CKD patients who are currently receiving Eprex® subcutaneously should be reviewed as soon as it is possible so that they can be switched to IV Eprex® or alternative therapeutic options be considered.
- As Ab-mediated PRCA has also been reported with other ESAs, healthcare professionals are advised to monitor their patients for possible Ab-mediated PRCA following any ESA treatment.
- ESA therapy should be discontinued immediately if Ab-mediated PRCA is suspected.
- Healthcare professionals are reminded to ensure that Eprex® and other ESAs are stored between 2°C and 8°C (as stated in their package inserts) and to advise their patients on the appropriate storage/handling of these ESAs.

Healthcare professionals are also encouraged to report any suspected reactions with the use of ESAs to the Vigilance Branch of HSA.

References

1 *http://www.hsa.gov.sg/DHCPL*
2 *Dear Healthcare Professional Letter issued by Janssen, 13 Jun 2013*
3 *HSA ADR News Bulletin 2013 Aug; 15: 7*

A good quality Adverse Event (AE) report should include details such as "Indication of drug used", "Outcome of AE" and "Time to onset of AE".

Recommendations to avoid use of glibenclamide in the elderly and renal-impaired

Glibenclamide associated with higher risk of hypoglycaemia compared with other sulfonylureas

HSA had conducted a benefit-risk assessment of glibenclamide in consultation with endocrinologists and its Product Vigilance Advisory Committee (PVAC), prompted by reports of a disproportionately higher number of hospitalisation cases due to hypoglycaemia associated with glibenclamide as compared to other sulfonylureas (SUs). Based on the review, HSA would like to advise healthcare professionals that the use of glibenclamide should be avoided in elderly patients and those with renal impairment, as these patients are more susceptible to severe and recurrent hypoglycaemia.

Background

Glibenclamide has been registered in Singapore since 1990 as Daonil® (sanofi-aventis Singapore Pte Ltd) and there are nine generic products. It is also available as a combination product with metformin, known as Glucovance® (Merck Pte Ltd).

Studies have suggested that the risk of hypoglycaemia is higher in glibenclamide compared to other SUs due to its longer half-life and the presence of active metabolites which could accumulate in patients with poor renal function.[1,2]

Furthermore, glibenclamide has greater penetration of pancreatic tissue, higher affinity for pancreatic beta-cell SU receptors,[3-6] and increased insulin sensitivity compared to some SUs.[7] It is also known to attenuate counter-regulatory actions during hypoglycaemic episodes.[8] Taken together, glibenclamide can result in sustained insulin release for protracted periods even after the drug is discontinued.[3-5] Patients with renal impairment, as well as the elderly with age-related decline in renal function, would be at a greater risk of developing severe, long-lasting hypoglycaemia.

The findings from literature are consistent with observations by local doctors, who reported that prolonged and recurrent hypoglycaemia were more common in glibenclamide users. The sustained effect of glibenclamide after drug discontinuation was also seen in some renal-impaired patients, who experienced recurrent hypoglycaemia while being treated with glucose infusion.

Evidence for comparative safety

Several studies which evaluated the safety of SUs consistently showed that glibenclamide is associated with a higher risk of hypoglycaemia when compared to other SUs, including glipizide, gliclazide and glimepiride.

- In a meta-analysis of 21 studies, glibenclamide was associated with a 83% greater risk of experiencing at least one episode of hypoglycaemia compared to other SUs.[3] In addition, two of these studies reported major hypoglycaemic episodes, and the risk was over four times higher for glibenclamide compared with other SUs, although this was not statistically significant.
- In a retrospective cohort study (n=13,963), glibenclamide had the highest rate of hypoglycaemia at 16.6 per 1000 person-years compared to other SUs.[4]
- In a retrospective cohort study (n=33,243), the relative risks for hypoglycaemia with gliclazide and glipizide compared with glibenclamide were 0.74 (95% CI 0.59, 0.92) and 0.60 (95% CI 0.40, 0.92), respectively.[9]
- In a retrospective chart review of 57 cases of glibenclamide-associated hypoglycaemia reported to the Swedish Adverse Drug Reactions Advisory Committee, 24 patients had protracted hypoglycaemia lasting 12 to 72 hours, and 10 died.[10] Death was seen even in patients who were on small doses of glibenclamide (2.5–5mg/day). Contributing factors included renal impairment, low food intake, diarrhoea, alcohol intake and interaction with other drugs.

Recommendations from WHO and other guidelines

In 2012, the World Health Organisation (WHO) reviewed the comparative safety and efficacy of glibenclamide in the elderly. The authors found that there was an increased relative risk of hypoglycaemia and resulting harm from the use of glibenclamide versus any of the other second-generation SUs, particularly gliclazide and glipizide.[11] They concluded that the evidence "unequivocally recommends against the use of glibenclamide in elderly patients", and recommended that it should not be used for those older than 60 years of age.

In 2013, the Canadian Diabetes Association's guidelines on Pharmacologic Management of Type 2 Diabetes recommended that classes of antihyperglycaemic agents other than SUs should first be considered in patients at high risk of hypoglycaemia, such as the elderly and those with renal failure.[12] If a SU had to be used in such individuals, gliclazide and glimepiride were associated with less hypoglycaemia than glibenclamide.

The Kidney Disease Outcomes Quality Initiative (KDOQI) 2012 Diabetes Guidelines also stated that glibenclamide should be avoided in patients with chronic kidney disease (CKD) stages 3, 4 and 5 (i.e. glomerular filtration rate (GFR) <60ml/min/1.73m^2).[13] The KDOQI Guidelines recommended glipizide as the preferred second-generation SU, as it did not have active metabolites and did not increase the risk of hypoglycaemia.

HSA's advisory

After in-depth review and consultation with endocrinologists and its PVAC, HSA's assessment and recommendations are as follows:

- Glibenclamide should be **avoided**:
  - In patients older than 60 years old, or
  - In patients with estimated glomerular filtration rate (eGFR) less than 60ml/min/1.73m^2, or
  - In patients with serum creatinine above the upper limit of normal

The local package inserts of glibenclamide-containing medicines will be strengthened to reflect these recommendations. A Dear Healthcare Professional Letter was issued on 4 December 2013 to healthcare professionals to advise them on these new recommendations.

Healthcare professionals are advised to take into consideration the above recommendations when prescribing glibenclamide or Glucovance®. They are also encouraged to report adverse reactions associated with the use of glibenclamide or other SUs to the Vigilance Branch of HSA.

References

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4 *J Am Geriatr Soc 1996; 44: 751-5*
5 *Metabolism 2006; 55: 78-83*
6 *Acta Endocrinol (Copenh) 1984; 105: 385-90*
7 *Diabet Med 1994; 11: 974-80*
8 *Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th edn*
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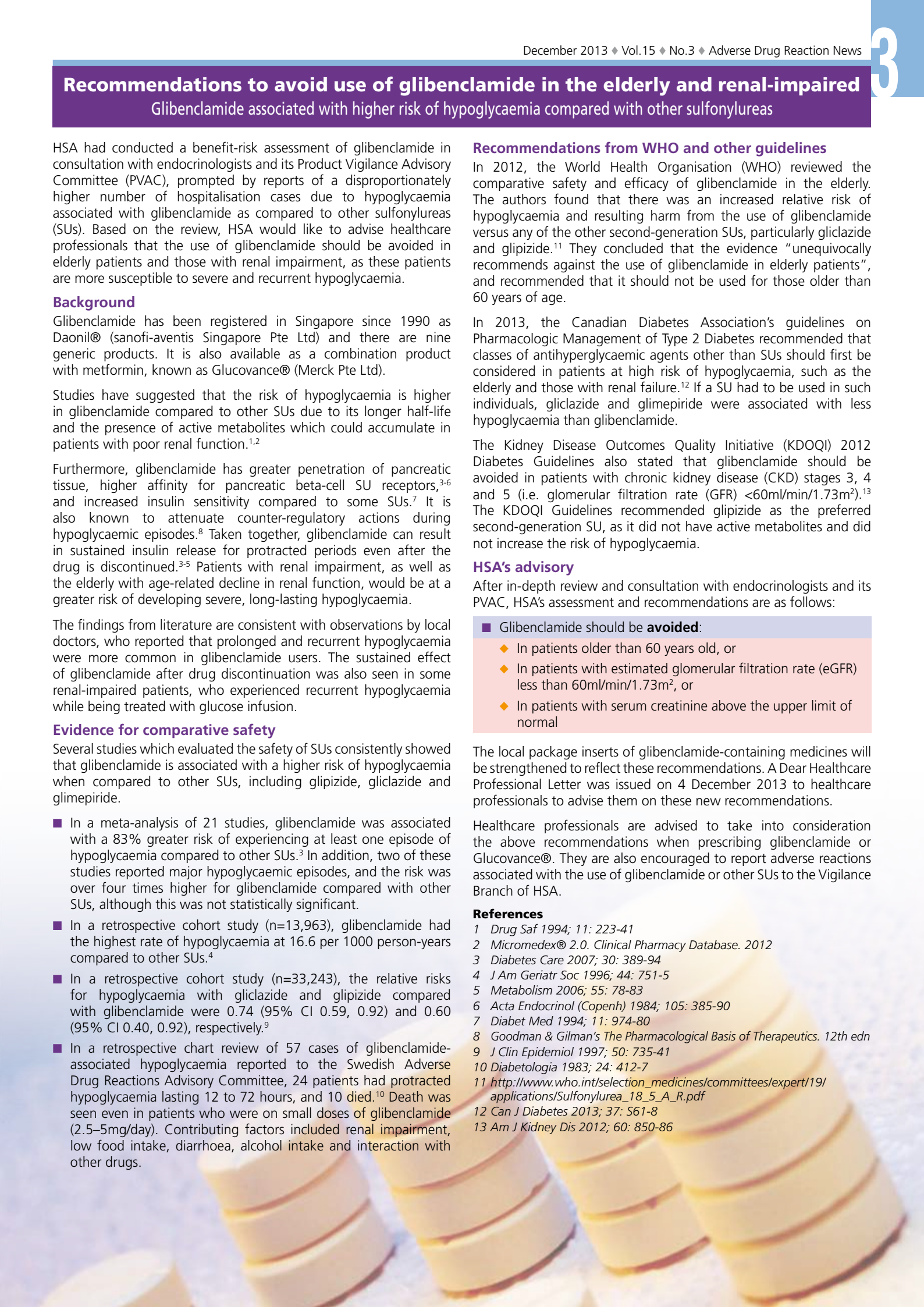

Update on strontium ranelate (Protos®): Risk of cardiac events and enhancing awareness of the local risk management plan to mitigate the risk of serious skin reactions

HSA would like to update healthcare professionals on two issues related to strontium ranelate (Protos®, Servier (S) Pte Ltd): (1) Risk of cardiac events raised by the European Medicines Agency (EMA); and (2) Enhancing awareness of the local risk management plan (RMP) to mitigate the risk of serious skin reactions.

Protos® is indicated locally for the treatment of severe osteoporosis in postmenopausal women at high risk for fracture to reduce the risk of vertebral and hip fractures.

(1) Risk of cardiac events

Background

In April 2013, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) conducted a review of strontium ranelate as part of a routine benefit-risk assessment of the drug and concluded that there was an increased risk of myocardial infarction and other cardiac events in patients taking strontium ranelate.[1] This was in addition to the earlier recognised risk of venous thromboembolism that had been previously identified from Phase III clinical trials.[2]

A review of the pooled data from randomised studies in around 7,500 post-menopausal women with osteoporosis showed an increase in the risk of myocardial infarction with strontium ranelate (1.7%) as compared with placebo (1.1%), with a relative risk of 1.6 (95% CI 1.07, 2.38). There was also an imbalance in the number of serious cardiac events seen with the drug in two other studies, one in men with osteoporosis and another in patients with osteoarthritis. However, no increased risk in mortality was observed.[3]

The PRAC concluded that certain restrictions in the use of the drug should be put in place to ensure that its benefit-risk balance remains favourable. The Committee recommended the use of strontium ranelate be restricted to severe osteoporosis in postmenopausal women at high risk of fracture and severe osteoporosis in men at increased risk of fracture.[3] In addition, several measures were taken in the European Union to minimise the risk of cardiac events until a full evaluation is completed by the EMA, such as contraindicating the use of strontium ranelate in patients with current or past history of cardiovascular diseases and closely monitoring patients for such events during treatment.

Local situation and actions taken

As of end-September 2013, HSA has received 97 adverse event reports associated with strontium ranelate, none of which was related to cardiac events. The majority of the reports (90%) described hypersensitivity reactions. The local safety concern was primarily related to serious skin reactions.

Following the review by EMA, HSA had strengthened the local package insert (PI) to restrict the use of strontium ranelate to postmenopausal women with **severe** osteoporosis who were at high risk of fracture. The use of strontium ranelate in men is not an approved indication in Singapore.

The local PI had also been updated with measures to mitigate the risk of cardiac events. These measures included[3]:

- Treatment with strontium ranelate should only be started by a physician experienced in the treatment of osteoporosis.
- Strontium ranelate is contraindicated in patients with a current or past history of ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease, or in patients with uncontrolled hypertension.
- Physicians should base their decisions to prescribe strontium ranelate on an assessment of the individual patient's risks. The patient's risk of developing cardiovascular disease should be evaluated before and at regular intervals during treatment.
- Treatment should be stopped if the patient develops ischaemic heart disease, peripheral arterial disease or cerebrovascular disease, or if hypertension becomes uncontrolled.

In addition, the local Patient Medication Guide (PMG) had been updated with information on cardiac events. A Dear Healthcare Professional Letter (DHCPL) dated 1 August 2013 was issued by Servier to update healthcare professionals about the latest safety development and changes to the local PI.

(2) Enhancing awareness of the local RMP to mitigate the risk of serious skin reactions

Background

Following an increase in number of local reports of serious skin reactions observed with strontium ranelate, HSA, in consultation with its Product Vigilance Advisory Committee (PVAC), implemented a RMP to mitigate the risk of occurrence of serious skin reactions locally.[4] The components of the RMP included strengthening of the local PI to include information on the higher risk of serious skin reactions in the Asian population, the development of a PMG to alert patients to the signs and symptoms of serious skin reactions, and collection of data to allow an estimate of the number of patients newly started on Protos®. For the latter, Servier regularly provides HSA with an estimated number of new patients on strontium ranelate collected through a "Patient Care Program (PCP)"* initiated by the company in March 2013.

* *The PCP is managed by the company to support new patients in the close monitoring of adverse reactions following Protos® treatment. Enrolment of patients into this programme is on a voluntary basis.*

Additional requirement for company to obtain signed acknowledgment from doctors before supply to clinics

As HSA continued to receive reports of Stevens-Johnson syndrome (SJS) and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) (1 case of each) from April to May 2013, bringing the total number of cumulative reports to eight for SJS or toxic epidermal necrolysis (TEN) and four for DRESS since 2006, a second review on the benefit-risk profile of strontium ranelate was initiated in August 2013 in consultation with its PVAC and experts from endocrinology, rheumatology and orthopaedics. The review concluded that strontium ranelate continues to have a role in therapy and the measures to address the risk of cardiac events are adequate. However, there is a need to further enhance the awareness of healthcare professionals and patients regarding the risk of serious skin reactions associated with strontium ranelate.

As part of a new licensing condition to the company, HSA has required that with effect from 1 January 2014, Servier will need to obtain the signed acknowledgement from doctors that they are aware of the risk of serious skin reactions and that they have received the PMG for distribution to their patients before the company can supply strontium ranelate to the respective clinics and hospitals. Of note is that the enrolment of patients into the PCP is an initiative by the company and it is a voluntary participation

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■ ***A good quality Adverse Event (AE) report should include details such as "Indication of drug used", "Outcome of AE" and "Time to onset of AE".*** ■

HLA-B*1502 genotype testing: Towards safer use of carbamazepine

On 30 April 2013, a Dear Healthcare Professional Letter (DHCPL) was jointly issued by the Ministry of Health (MOH) and HSA to highly recommend genotyping for HLA-B*1502 allele prior to initiation of carbamazepine (CBZ) therapy in new patients of Asian ancestry, as genotyping for this group of patients is now considered the standard of care.[1] This recommendation was based on both local and international data supporting a strong association between HLA-B*1502 and CBZ-induced Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN).

A HSA-initiated multi-centre study at Changi General Hospital, Singapore General Hospital and National University Hospital (NUH) found a strong association between the HLA-B*1502 allele and CBZ-induced SJS/TEN (Odds ratio 181, p<0.0001). The results were consistent with international data that HLA-B*1502 carriers have an elevated risk of developing SJS/TEN when taking CBZ.

As of 1 November 2013, a total of 307 blood samples were sent to the NUH Molecular Diagnostic Centre for HLA-B*1502 genotype testing, and 30 (9.8%) of these samples tested positive for the presence of the HLA-B*1502 allele. Over the past 10 years, HSA received an average of 15 reports of CBZ-induced SJS/TEN per year. After the implementation of HLA-B*1502 genotype screening, HSA has not received any reports of SJS/TEN associated with the use of CBZ in patients screened for the HLA-B*1502 allele.

Healthcare professionals are reminded to take note of the following:

- CBZ is indicated for the treatment of epilepsy and other conditions such as bipolar disorders, alcohol-withdrawal syndrome, trigeminal neuralgia, diabetic neuropathy and diabetes insipidus centralis. Testing for the presence of HLA-B*1502 allele is highly recommended in new patients of Asian ancestry, regardless of the indication for which the drug is used.
- CBZ should not be prescribed prior to the return of HLA-B*1502 test results. This is because of the possibility of development and progression of SJS/TEN in susceptible patients even after prompt discontinuation of the drug.
- The use of CBZ should be avoided and treatment alternatives are recommended in patients who are found to be positive for HLA-B*1502. Preliminary data have shown a suspected association between this allele and phenytoin-induced SJS/TEN, although the effect size is not as large.[2,3] As a precaution, patients who are identified to be positive for the HLA-B*1502 allele should also not be prescribed phenytoin.
- Genetic testing should not substitute for appropriate clinical vigilance and patient management. Although rare, patients negative for HLA-B*1502 could still develop SJS/TEN as the role of other factors such as drug dose, concomitant medications and co-morbidities have not been studied.

Healthcare professionals are also encouraged to report any adverse reactions suspected to be associated with the use of CBZ to the Vigilance Branch of HSA.

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1 *http://www.hsa.gov.sg/DHCPL*
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■ **Update on strontium ranelate (Protos®)** ■

on the part of doctors to enrol their patients into the programme. A HSA DHCPL will be disseminated to healthcare professionals who have yet to provide acknowledgement of their awareness of the RMP and receipt of the PMG.

HSA's advisory

As a risk management measure to minimise the risk of serious skin reactions associated with the use of strontium ranelate, HSA strongly encourages doctors who have yet to sign the acknowledgement form to follow up accordingly with Servier. No further action is required of the doctors who have already signed the letter of acknowledgement.

Healthcare professionals are advised to continue close monitoring of their patients for serious adverse events such as cardiac events and early signs of serious skin reactions. In addition, healthcare professionals are reminded of the new restricted indication and recommendations outlined above to mitigate the risk of cardiac events. As HSA continues to monitor the safety of the drug closely, healthcare professionals are encouraged to report any adverse events associated with strontium ranelate to the Vigilance Branch of HSA.

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

Reports of febrile seizures with measles, mumps, rubella and varicella (MMRV) combination vaccine

From January to October 2013, HSA received 13 reports of seizures following MMRV vaccination, as compared to six in 2012. Of these reports in 2013, 85% concerned febrile seizures occurring within three weeks of vaccination with Priorix-Tetra™ (GlaxoSmithKline Pte Ltd), which is the MMRV vaccine used predominantly in Singapore. Seven and five children received the first and second dose of the MMRV vaccine, respectively. The dose given to the remaining child was not specified. Four children were reported to have personal or family history of seizures. All recovered shortly after the seizure episode.

The risks of febrile seizures with MMR and MMRV vaccines are well established. The number of febrile seizures attributable to MMR vaccines was estimated at 2.5 to 3.4 per 10,000 children vaccinated.[1] The attributable risk of febrile seizures in the main risk period of 5 to 12 days following the first dose of Priorix-Tetra™ was 3.64 per 10,000 (95% CI –6.11, 8.30).[2] There was no indication of an increased risk after the second dose.

Whilst the number of reports of febrile seizures remained within the expected incidence, healthcare professionals are recommended to provide counselling to parents/caregivers about the possible risk of febrile seizures post-MMRV vaccination and the management of such events.

References

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2 *Singapore package insert for Priorix-Tetra™, approved April 2013*

Safety advisory on cyproterone acetate/ethinylestradiol

HSA, in consultation with its Product Vigilance Advisory Committee (PVAC), has completed its benefit-risk assessment on cyproterone acetate/ethinylestradiol (CPA/EE). New restrictions will be imposed to limit the use of this product so as to mitigate the risks of venous and arterial thromboembolism in view of the modest benefit derived from treatment with CPA/EE for conditions such as androgenetic alopecia and mild acne.

HSA, together with its PVAC, concluded that there remains a place in therapy for CPA/EE, particularly for moderate to severe acne where conventional treatment (e.g., systemic antibiotics, topical therapy) has failed, as well as in the treatment of mild hirsutism. However, there was insufficient data to demonstrate its benefit in treating androgenetic alopecia compared with the risk of thromboembolism. In view of the increased risks of VTE and ATE associated with CPA/EE, additional warnings and restrictions will be put in place in the labelling to mitigate the risks of such events.

CPA/EE has been licensed in Singapore since 1990 for the treatment of androgen-dependent diseases in women, such as acne (especially pronounced forms and those which are accompanied by seborrhoea or by inflammation or formation of nodes), androgenetic alopecia, and mild forms of hirsutism (Diane-35®, Bayer (South East Asia) Pte Ltd). It is also available as generic products Estelle-35® or Estelle-35ED® (Apex Pharma Marketing Pte Ltd).

Background

In January 2013, the French health authority (ANSM) initiated a suspension of the marketing authorisations of CPA/EE in France.[1] This decision followed its review which found that the effectiveness of these products in treating acne was only moderate. Furthermore, the ANSM took the view that these products were being widely used off-label for contraception although their efficacy as a contraceptive had not been established. The ANSM considered that the benefit-risk ratio of CPA/EE was unfavourable since its modest efficacy did not outweigh the risk of thromboembolic events and unwanted pregnancies.

At the request of ANSM, the European Medicines Agency (EMA) conducted a review on the risk of venous thromboembolism (VTE) and arterial thromboembolism (ATE) associated with CPA/EE. In May 2013, the EMA concluded that the benefits of CPA/EE continue to outweigh its risks, provided that several measures were taken to minimise the risk of thromboembolism.[2] These included stipulating that CPA/EE should only be used for the treatment of acne when alternative treatments (such as topical therapy or systemic antibiotic treatment) have failed, the removal of indication for the treatment of alopecia, and strengthening of the safety information in the package inserts (PI) of CPA/EE-containing products.

Similarly, Health Canada and the Australian Therapeutic Goods Administration (TGA) also concluded that the benefits of CPA/EE continue to outweigh its risks when used as authorised for acne and hirsutism.[3,4]

HSA's benefit-risk assessment

HSA's review took into consideration the efficacy of CPA/EE in its locally authorised indications, expert opinions from dermatologists, O&G specialists and family physicians, local ADR reports associated with the use of CPA/EE, related scientific literature on VTE and ATE, and actions taken by other regulatory agencies.

HSA's regulatory decision and advisory

The indications for CPA/EE will be restricted and its safety information in the local PIs will be strengthened as follows:

- CPA/EE is indicated for the treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhoea) and/or mild forms of hirsutism in women of reproductive age
- When used for the treatment of acne, CPA/EE should only be used after topical therapy or systemic antibiotic treatments have failed
- CPA/EE is no longer indicated for the treatment of androgenetic alopecia
- CPA/EE should not be prescribed for the purpose of contraception alone
- The need to continue treatment should be evaluated periodically by the treating physician
- The use of CPA/EE carries an increased risk of VTE compared with no use. The excess risk of VTE is highest during the first year a women starts CPA/EE or when restarting or switching after a pill-free interval of at least a month

In addition, the contraindications and warnings will be strengthened to increase awareness of the risk and risk factors of thromboembolism in relation to the use of CPA/EE.

Although no local cases of thromboembolic events associated with CPA/EE have been reported, healthcare professionals are reminded to screen patients for risk factors, such as increasing age, smoking and obesity, as well as counsel them on the signs and symptoms of VTE and ATE. Patient selection and counselling are vital in ensuring that the benefit-risk profile of CPA/EE remains positive.

Healthcare professionals are also encouraged to report adverse reactions suspected to be associated with the use of CPA/EE to the Vigilance Branch of HSA.

References

1 *http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/01/news_detail_001703.jsp&mid=WC0b01ac058004d5c1*
2 *http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Cyproterone_and_ethinylestradiol_containing_medicinal_products/human_referral_prac_000017.jsp&mid=WC0b01ac05805c516f*
3 *http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/29283a-eng.php*
4 *http://www.tga.gov.au/safety/alerts-medicine-diane-35-130205.htm*

■ ***A good quality Adverse Event (AE) report should include details such as "Indication of drug used", "Outcome of AE" and "Time to onset of AE".*** ■

List of Dear Healthcare Professional Letters (DHCPL) issued by HSA, pharmaceutical and medical device companies

Summary of Dear Healthcare Professional Letters issued by HSA and/or pharmaceutical and medical device companies from December 2012 to November 2013. For details, please log on to MOHAlert via your professional board's website.

3 Dec 2012 – Zofran® (ondansetron) causes dose-dependent QT prolongation [GSK]

27 Dec 2012 – Recommendation not to start new patients on Tredaptive™ (ER niacin/laropiprant) in light of results of HPS2-THRIVE cardiovascular outcomes study [MSD]

7 Jan 2013 – Update on AMO AR40e Intraocular Lens (IOL) Field Safety [AMO]

9 Jan 2013 – Urgent Field Safety Notice on Birmingham Hip™ Modular Heads (Monoblock and Sleeved) [Smith and Nephew]

9 Jan 2013 – Hypersensitivity and infusion reactions related to Benlysta™ (Belimumab) [GSK]

21 Jan 2013 – Treatment with TREDAPTIVE® (extended-release niacin/laropiprant) should be discontinued [MSD]

23 Jan 2013 – Calcitonin — association with malignancy and new restrictions on use [Novartis]

28 Jan 2013 – Pradaxa® (dabigatran etexilate) contraindicated in patients with prosthetic heart valve replacement [Boehringer Ingelheim]

29 Jan 2013 – Voluntary Recall of CONFIDENCE™ Spinal Cement System 5cc Kit, CONFIDENCE™ Spinal Cement System 7cc Kit, CONFIDENCE™ Spinal Cement system 11cc Plus Kit and CONFIDENCE™ Spinal Cement System Kit [Johnson & Johnson Medical]

4 Feb 2013 – Voluntary Recall of Iliadin® Solution 0.025%, Iliadin® Solution 0.05%, Iliadin® Spray 0.05%, Iliadin® Solution for Nose 0.01% [Merck]

8 Feb 2013 – Communications on the association of MabThera® (Rituximab) with Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome [Roche]

1 Mar 2013 – Urgent Voluntary Recall of Certain HOYA One-Piece Intraocular Lenses [HOYA Medical Singapore]

6 Mar 2013 – TYKERB© (lapatinib ditosylate monohydrate) — Comparative data have shown that Lapatinib based regimens are less effective than Herceptin© (trastuzumab) based regimens in certain settings [GSK]

7 Mar 2013 – Update on the risk management plan for strontium ranelate (Protos®) to mitigate the risks of serious skin reactions [HSA]

8 Mar 2013 – Local Risk Management Plan for Strontium Ranelate (Protos®) [Servier]

14 Mar 2013 – Decrease in the potency of Tuberculin PPD RT 23 SSI 2TU [SSI]

18 Mar 2013 – Prolia® (denosumab 60 mg) — Risk of anaphylactic reaction and new contraindication in patients with clinically significant hypersensitivity to Prolia® [GSK]

8 Apr 2013 – Xgeva® (denosumab 120 mg) — Risk of atypical femoral fracture [GSK]

9 Apr 2013 – Communication on cases of necrotising fasciitis reported with Avastin® (Bevacizumab) [Roche]

9 Apr 2013 – The sales suspension of the Alcon AcrySof® CACHET® Phakic Lens due to risks of accelerated corneal endothelial cell loss (ECL) [Alcon]

9 Apr 2013 – Recommendations for Clinical Use OPTEASE® Retrievable Vena Cava Filter [Johnson & Johnson Medical]

25 Apr 2013 – VOTRIENT® (pazopanib) — Important Change to Frequency of Serum Liver Test Monitoring for Hepatotoxicity [GSK]

30 Apr 2013 – Recommendations for HLA-B*1502 genotype testing prior to initiation of carbamazepine in new patients [HSA]

30 Apr 2013 – Update on B:2367047 Rovacor Tablets 20mg (Lovastatin) SIN 10531P [Ranbaxy]

3 May 2013 – Voluntary Recall of CONFIDENCE™ Spinal Cement System 7cc Kit, CONFIDENCE™ Spinal Cement system 11cc Plus Kit and CONFIDENCE™ Spinal Cement System Kit [Johnson & Johnson Medical]

10 May 2013 – Voluntary Recall of LIGACLIP® 10mm M/L Endoscopic Rotating Multiple Clip Applier [EES]

23 May 2013 – ADVAGRAF® prolonged-release tacrolimus and PROGRAF® tacrolimus — Potential risk of medication errors [Janssen]

29 May 2013 – Communication on risk of hepatotoxicity with concurrent use of Zelboraf® (vemurafenib) and ipilimumab [Roche]

4 Jun 2013 – Urgent Voluntary Recall of Integra LifeSciences DuraGen Plus Adhesion Barrier Matrix, DuraGen Dural Graft Matrix and Suturable DuraGen Dural Regeneration Matrix [Integra LifeSciences]

7 Jun 2013 – Potential for Over or Under Delivery of Insulin if Insulin or Other Fluids Contact the Inside of Medtronic Paradigm Tubing Connectors [Medtronic International]

10 Jun 2013 – Advisory on the CoaguChek® XS System, CoaguChek® XS Plus System and CoaguChek® XS Pro System [Roche Diagnostics]

13 Jun 2013 – Antibody-Mediated Pure Red Cell Aplasia (PRCA) case cluster observed with subcutaneous administration of erythropoietin (EPO) Eprex® at a Singapore Institution [Janssen]

13 Jun 2013 – Voluntary Recall of Synthes 3.7mm and 5.0mm Dynamic Locking Screws (DLS) [Synthes Singapore]

26 Jun 2013 – Voluntary Recall of Zimmer NexGen® Micro Implants (Femur, Patella, Articular Surface) and Provisionals [Zimmer]

1 Jul 2013 – Information on Potential Vitamin K Interaction with Warfarin [Pfizer]

10 Jul 2013 – Communication on updated recommendations for management of hepatitis B reactivation in patients treated with MabThera® (rituximab) [Roche]

23 Jul 2013 – Voluntary Consumer Level Recall of LOT: L930 ACET-650 (Acetaminophen) Suppositories Mislabelled as ACET-325 [Medicell Pharmaceutical]

25 Jul 2013 – Communication on Risk of Eye Disorders with Use of Lariam® (mefloquine) [Roche]

31 Jul 2013 – Risk of RAS-Mutant Malignancy Progression and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS Syndrome) associated with Zelboraf® (vemurafenib) [Roche]

1 Aug 2013 – Important new recommendations for the use of Protos® (strontium ranelate) following new data showing an increased risk of non-fatal myocardial infarction [Servier]

19 Aug 2013 – ETHICON SECURESTRAP™ 5mm Absorbable Strap Fixation Device (Product Codes: STRAP12, STRAP25, STRAP25R) [Johnson & Johnson Medical]

28 Aug 2013 – Change in shelf-life, storage conditions and manufacturing site for Tegretol 200 Tablet 200mg (SIN00352P) [Novartis]

25 Sep 2013 – Introduction of New Warning to Durogesic® (fentanyl) Transdermal System and Fentanyl Injection 0.1mg/2ml (fentanyl citrate): Serotonin syndrome may occur under co-administration with serotonergic drugs [Janssen]

2 Oct 2013 – Contraindication of the Subcutaneous Administration of Eprex® in Chronic Kidney Disease Patients [HSA]

8 Oct 2013 – Voluntary recall of rHead and uHead stem implants [Small Bone Innovations]

11 Oct 2013 – Medical Device Labelling Correction of the TomoFix Medial High Tibia Plate Surgical Technique Guide and the TomoFix Application Notes [Synthes Singapore]

21 Oct 2013 – Voluntary Recall of Versys® Hip System Cemented Revision/Calcar Femoral Stem and Versys Heritage® Hip Prosthesis Femoral Revision Stem [Zimmer]

24 Oct 2013 – Medical Device Field Safety Notification on SynFix-LR Implant Holder [Synthes Singapore]

28 Oct 2013 – Voluntary Recall of TISSUE-GUARD Family of Products-DURA-GUARD, SUPPLE PERI-GUARD [Baxter Healthcare]

6 Nov 2013 – Voluntary Recall of Cordis OPTEASE® Retrievable Vena Cava Filter [Johnson & Johnson Medical]

7 Nov 2013 – Zimmer Low Density Polyethylene (LDPE) Bag Adhesion [Zimmer]

19 Nov 2013 – Recall of the IN.PACT® AMPHIRION Paclitaxel-eluting Percutaneous Transluminal Angioplasty (PTA) Balloon Catheter (IN.PACT Amphirion Drug – Eluting Balloon) [Medtronic International]

29 Nov 2013 – Voluntary Recall of Zimmer Periarticular Distal Lateral Femoral Plate (All non-expired lots manufactured prior to July 24, 2013) [Zimmer]

Neurologic and psychiatric adverse reactions associated with mefloquine

HSA would like to update healthcare professionals regarding serious neurologic and psychiatric adverse reactions associated with the use of mefloquine. Although these adverse reactions are not new, more global post-marketing information has emerged showing that these symptoms may persist for months to years after mefloquine is discontinued. In addition, there are also isolated reports of recurrence of neurologic and psychiatric symptoms when mefloquine was taken a second time.

Mefloquine is indicated for chemoprophylaxis and treatment of malaria. It is available locally as Lariam® (Roche Singapore Pte Ltd), Meflotas® (Apotheca Marketing Pte Ltd) and Mephaquin Lactab® (LF Asia Distribution).

Published case reports of neuropsychiatric adverse events

There have been published case reports describing neuropsychiatric adverse reactions to mefloquine, some of which presented with a prodromal phase of moderate symptoms such as dizziness, insomnia and generalised anxiety which progressed to worsening of symptoms.[1-4]

In one report, a healthy 24-year-old male with no significant medical history or known drug allergies developed severe and prolonged neuropsychiatric adverse reactions to mefloquine that was prescribed for malaria chemoprophylaxis.[1] The patient developed prodromal symptoms of anxiety which progressed to the development of psychosis, short-term memory impairment, confusion and personality changes accompanied with vertigo and disequilibrium. His psychiatric symptoms and sleep disturbances persisted for two weeks following the discontinuation of mefloquine and gradually decreased in frequency and severity over the subsequent weeks. In contrast, other symptoms such as palpitations, tinnitus, vertigo and disequilibrium became relatively more prominent. It was reported that the episodes of vertigo and disequilibrium continued to persist for 10 months following the onset of these symptoms.

Review by the US Food and Drug Administration (FDA)

In July 2013, the US FDA issued a safety communication informing the public about the strengthened and updated warnings to the US package insert (PI) for mefloquine regarding neurologic and psychiatric adverse reactions.[5] This followed the safety assessment conducted by FDA which took into consideration data obtained from the FDA Adverse Event Reporting System and published literature.

The safety assessment identified patients who developed neurologic symptoms such as dizziness, loss of balance, tinnitus and vertigo with the use of mefloquine for malaria prophylaxis. Patients who reported neurologic symptoms were healthy with no known major medical problems prior to taking mefloquine. Some of the patients did not suspect their symptoms were due to mefloquine and continued to take the drug despite experiencing the symptoms.

These neurologic symptoms developed early in the course of treatment for many of the cases. Patients who developed neurologic symptoms usually had concomitant psychiatric symptoms such as anxiety, confusion, paranoia and depression. There were cases where the neurologic and psychiatric symptoms persisted for months to years after mefloquine was discontinued. Abnormal neurologic function tests have been reported in patients, along with a diagnosis of permanent vestibular damage. In some cases, there was a recurrence of neurologic and psychiatric symptoms when mefloquine was taken a second time.

Local situation

As of 20 November 2013, HSA has received nine reports describing neurologic and psychiatric adverse reactions such as confusion, anxiety, depression, delusion, hallucination, insomnia, manic reaction, dizziness, agitation and convulsions in patients taking mefloquine. These adverse reactions are consistent with the known safety profile for mefloquine.

The PI for Lariam® currently states that mefloquine should not be prescribed for prophylaxis of malaria in persons with active depression or with a history of major psychiatric disorders or convulsions. In view of the latest information, HSA is working with the companies to strengthen existing neurologic and psychiatric warnings and precautions in the PI for mefloquine products, including information regarding the persistence of symptoms months after discontinuation of the drug.

HSA's advisory

Healthcare professionals are advised to take into consideration the possibility of development of neurologic and psychiatric adverse reactions in patients taking mefloquine. If the patient develops neurologic and psychiatric symptoms during prophylactic treatment, mefloquine should be stopped and an alternative antimalarial medicine be considered.

Healthcare professionals are also encouraged to report neurologic and psychiatric adverse reactions associated with the use of mefloquine to the Vigilance Branch of HSA.

References

1 *Travel Med Infect Dis 2012; 10: 144-51*
2 *Encephale 2011; 37: 393-6*
3 *Encephale 2000; 26: 67-70*
4 *Malar J 2006; 5:74*
5 *http://www.fda.gov/Drugs/DrugSafety/ucm362227.htm*

Please send your enquiries, comments and suggestions to:

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All website references were last accessed on 29 November 2013.