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Adverse Drug Reaction News

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Increase in local reports of serious skin reactions related to strontium ranelate (Protos®)

The Health Sciences Authority (HSA) would like to alert healthcare professionals on its concern on the increase in the number of local reports of serious skin reactions suspected to be associated with strontium ranelate (Protos®, Servier). In view of this signal, an interim benefit-risk assessment of the drug was conducted by HSA and its Product Vigilance Advisory Committee (PVAC), which recommended closer monitoring of the drug and that a risk management plan be initiated to manage the risks of the drug. Protos® has been registered in Singapore since July 2006 for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures.

Background

HSA had earlier highlighted the risk of serious skin reactions with strontium ranelate to healthcare professionals in the March 2008 and August 2011 issues of the HSA Adverse Drug Reaction News Bulletin. The local package insert (PI) was also strengthened in 2008 and 2010 to alert healthcare professionals on the occurrence of serious skin reactions observed through post-marketing surveillance.

Local serious skin reaction reports

As of end June 2012, HSA has received a total of 59 local reports of suspected adverse reactions associated with strontium ranelate, of which 49 (83%) described skin reactions. Twelve (24%) of these reports were assessed as serious. The frequency of reporting of serious skin reactions had increased from one suspected case per year in 2007 - 2010 to four cases per year respectively in 2011 and in the first half of 2012. These include one report of generalised maculopapular rash with mucosal involvement, two reports of drug rash with eosinophilia and systemic symptoms (DRESS), two reports of exfoliative dermatitis, four reports of Stevens-Johnson syndrome (SJS) and three reports of toxic epidermal necrolysis (TEN). Of these, one report of SJS and two reports of TEN were associated with fatal outcomes.

The 12 reports all involved female patients between 53 to 83 years of age with co-morbidities such as hypertension or hyperlipidaemia. In eight of the reports, strontium ranelate was identified by the reporting physician as the only suspected drug due to its recent initiation to the patient's regular drug regimen. The time to onset ranged from eight to 122 days. Some of these patients presented with initial flu-like symptoms such as fever, cough and sore throat, followed by development of rash over trunk and limbs. Five of the patients had taken other drugs for osteoporosis before switching to strontium ranelate.

Overseas serious skin reaction reports

From 2005 to June 2012, 492 (33%) of 1,485 global adverse drug reaction (ADR) reports associated with strontium ranelate captured in World Health Organisation's (WHO's) global pharmacovigilance database (Vigibase) involved the skin and subcutaneous skin tissues, with some describing serious conditions such as exfoliative dermatitis, photosensitivity reaction, alopecia and angioedema. DRESS was more frequently reported, with a total of 28 cases captured mainly in Europe. A total of one report of SJS/TEN overlap, two reports of TEN and five reports of SJS were also reported by some European countries. Other than Singapore, Malaysia was the other Asian country with three reports of SJS.

Regulatory actions taken by the European Medicines Agency (EMA)

In November 2007, the EMA's Committee for Medicinal Products for Human Use (CHMP) had reviewed this safety concern and included a warning on DRESS in the drug's prescribing information.[1] In March 2012, a second review by the CHMP following a study in France[2] found that skin reactions accounted for 26% of all post-marketing reports associated with strontium ranelate. The CHMP concluded that the benefits of strontium ranelate continue to outweigh its risks and recommended an update of the warnings on the serious skin reactions seen with drug.[3] The recommendations by the CHMP have since been incorporated in the latest version of the local PI that was approved recently.[4]

HSA's regulatory actions and outcome of the PVAC meeting

In view of the emerging local signal of an increased incidence of serious skin reactions with strontium ranelate, HSA convened a meeting with its PVAC on 29 June 2012 to seek the committee's advice on the benefit-risk profile of Protos®, with focus on the recent increase in the number of reports of serious skin reactions. The frequencies of serious skin reactions in the local context for 2011 are estimated to be up to 1.18/1,000 patient-years for SJS/TEN and 0.39/1,000 patient-years for DRESS, based on sales data provided by the company. The review took into consideration the efficacy data of Protos® for the prevention of vertebral and hip fractures, opinions from orthopaedic and rheumatology experts, overseas safety data with regard to serious skin reactions and the estimated frequencies of serious skin reactions locally.

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Continuation of the restricted access programme for aprotinin (Trasylol®)

The Health Sciences Authority (HSA) would like to update healthcare professionals on its decision to retain the restricted access programme for aprotinin (Trasylol®, Bayer Pte Ltd). This follows a comprehensive benefit-risk assessment of the available data from the final analysis of the Canadian Blood conservation using Antifibrinolytics in a Randomised Trial (BART), literature studies as well as international regulatory actions. This regulatory decision has been made in consultation with its Product Vigilance Advisory Committee (PVAC).

Regulatory history for Trasylol®

Trasylol® has been licensed locally since July 1994 for the prophylactic use to reduce perioperative blood loss and the need for blood transfusion in patients undergoing cardiopulmonary bypass in the course of coronary artery bypass graft surgery who are at increased risk for blood loss and blood transfusion.

In November 2007, the sale of Trasylol® was suspended worldwide in response to the results from an interim analysis of the BART study, suggesting that Trasylol® was associated with an increased risk of mortality when used in high risk cardiac surgeries as compared to lysine analogues, namely tranexamic acid and aminocaproic acid. Since then, Trasylol® has been made available locally via the restricted access programme.[1] Under this restricted access programme, doctors are required to provide a written undertaking that they have understood the risks associated with the use of Trasylol®, will discuss the risks involved with patients and obtain their written consent before prescribing Trasylol®.

HSA's benefit-risk assessment

HSA has completed its benefit-risk assessment which, besides the final analysis of the BART study and data from scientific literature, also took into consideration the local experience of the Trasylol® restricted access programme as well as advice from its PVAC. The outcome of the review concluded that Trasylol® continues to have a place in therapy in preventing blood loss in patients undergoing cardiopulmonary bypass who are at increased risk for blood loss and blood transfusion.

HSA's regulatory decision

HSA has assessed that the aprotinin restricted access programme has served its purpose of ensuring the safe use of Trasylol® locally and will be continued.

References

1 *http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/safety_information/product_safety_alerts/safety_alerts_2007/sales_of_aprotinin.html*

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■ **Increase in local reports of serious skin reactions related to strontium ranelate (Protos®)** ■

The PVAC's interim conclusion was that strontium ranelate has a role in the treatment of postmenopausal osteoporosis and its benefits continue to outweigh the risks when used appropriately. As an increased risk of serious skin reactions has been detected locally, the committee recommended the quantification of the risk by capturing the actual number of patients taking the product. As serious skin reactions are unpredictable, a strong risk management plan was to be in place to minimise the risk and close surveillance of the drug implemented.

Following the meeting, HSA issued a Dear Healthcare Professional Letter (DHCPL) on 13 July 2012 to alert healthcare professionals on the increase in the number of local reports of serious skin reactions and the outcome of the PVAC meeting. HSA is currently working with the company on the details of the risk management plan which would include a close monitoring programme for strontium ranelate with the cooperation of healthcare professionals. The warnings on DRESS, SJS and TEN in the local PI will be strengthened to include information that the incidence of SJS and TEN may be higher in Asians. Healthcare professionals will be updated on the details of the risk management plan for strontium ranelate once they are finalised.

HSA's advisory

Doctors are strongly advised to prescribe strontium ranelate according to its approved indication, keeping in mind the MOH Clinical Practice Guidelines for Osteoporosis when selecting the appropriate choice of pharmacotherapy. The choice of therapy for osteoporosis should be based on the benefits and risks of treatment and must carefully be weighed for each individual patient.

Healthcare professionals are advised to monitor their patients closely for serious skin reactions. In managing the risk of serious skin reactions, healthcare professionals are reminded that the highest risk of occurrence of DRESS, SJS and TEN is within the first eight weeks of treatment, with poorer prognosis in the elderly. Patients who are prescribed strontium ranelate should be advised of the likely time to onset and signs and symptoms of DRESS, SJS and TEN and monitored closely for skin reactions.

Patients should also be educated on early recognition of these serious skin reactions. As early withdrawal of any suspect drug is associated with a better prognosis, patients should be advised to stop treatment immediately and permanently if symptoms of serious allergic skin reactions occur and to seek medical advice. These include extended skin rashes, blisters and sores, accompanied with flu-like symptoms in some cases. Treatment should not be re-started at any time in these patients.

As HSA continues to monitor the issue closely, healthcare professionals are encouraged to report any serious adverse events suspected to be associated with strontium ranelate to the Vigilance Branch of HSA.

References

1 *http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/11/WC500015595.pdf*
2 *http://www.ncbi.nlm.nih.gov/pubmed/21885232*
3 *http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/public_health_alerts/2012/03/human_pha_detail_000057.jsp&mid=WC0b01ac058001d12*
4 *Singapore package insert for Protos®. Approved 2 July 2012.*

Safety update on statins

Important product safety information and risk of rhabdomyolysis with high dose simvastatin

HSA would like to draw the attention of healthcare professionals to important new safety information related to the class of statin products, in particular the safety product label changes initiated by the US Food and Drug Administration (FDA) as well as its re-analysis results from the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial.

Statins are indicated for the treatment of hypercholesterolaemia in addition to diet and exercise. There are six different types of statins licensed in Singapore, namely atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin. These statins are marketed as single-ingredient products under both proprietary and generic brands. They are also marketed as combination products, such as Vytorin® by MSD containing simvastatin/ezetimibe and Caduet® by Pfizer containing amlodipine/atorvastatin.

Safety updates by the US FDA

a) All statins

In February 2012, the US FDA announced several safety updates to the product labels of statin-containing products, including warnings on cognitive side effects and reports of increased blood glucose and glycosylated haemoglobin (HbA1c) levels.[1] Despite these new safety concerns, FDA has assessed that the cardiovascular benefits of statins outweigh the small increased risks.

Cognitive impairment

FDA's review took into consideration information from the Adverse Events Reporting System database, published medical literature (case reports and observational studies) and randomised clinical trials investigating the effects of statins on cognition. In general, cognitive side effects (eg, memory loss, confusion) observed were non-serious and were reversible within a few weeks after discontinuation of the statin therapy. The time to onset of the event was highly variable, ranging from one day to several years after statin exposure. The cases did not appear to be associated with fixed or progressive dementia, such as Alzheimer's disease. Further assessment also did not reveal an association between the adverse event and any specific statin, the age of the patient, the statin dose, or concomitant medication use. Nevertheless, the US product labels for statins were updated to provide healthcare professionals with this information for consideration when prescribing statins.

Increased fasting glucose and HbA1c

FDA's class labelling on increased fasting glucose and HbA1c stemmed from the review of clinical trial meta-analyses and epidemiological data from published literature, including the Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study, which reported a 27% increase in investigator-reported diabetes mellitus in rosuvastatin-treated patients versus placebo-treated patients. Data from these studies suggest the possibility of a class effect of statins in increasing fasting plasma glucose and HbA1c.

b) Simvastatin

Rhabdomyolysis and dose restrictions

In June 2011, FDA confirmed an increased risk of myopathy and rhabdomyolysis with high dose simvastatin (80mg) following a re-analysis of the SEARCH trial.[2] In this trial, the incidence of myopathy increased from 0.02% (one patient) among patients taking 20mg simvastatin daily to 0.9% (52 patients) among those taking simvastatin 80mg daily. In addition, 22 patients (0.4%) in the simvastatin 80mg group developed rhabdomyolysis vis-à-vis no cases of rhabdomyolysis in patients from the simvastatin 20mg group.

Local situation

To date, HSA has not received any local adverse reaction report on cognitive impairment and abnormal blood glucose levels associated with the use of statins. HSA has received one report of rhabdomyolysis in a patient taking high dose simvastatin (80mg). This patient was also on other concomitant medications such as aspirin, atenolol, clopidogrel, enalapril and omeprazole.

HSA has reviewed the information present on cognitive impairment, increased fasting glucose and HbA1c and rhabdomyolysis and is currently working with the companies of the various statin-containing products to strengthen the local package inserts (PIs) to include precautions and warnings on these safety issues.

Healthcare professionals are advised to take into consideration the above safety issues when prescribing statins and are encouraged to report adverse drug reactions associated with the use of statin-containing products to the Vigilance Branch of HSA.

Summary of important safety label updates

Updates to all statins PI

- Post-marketing reports of cognitive impairment (eg, memory loss, forgetfulness, amnesia, memory impairment, confusion) have been associated with statins. The reports are generally non-serious and reversible upon statin discontinuation.
- Increases in HbA1c and fasting serum glucose levels have been reported with statins

Updates to simvastatin PI

- Increased risk of myopathy and rhabdomyolysis with high dose simvastatin (80mg)

References

1 *http://www.fda.gov/Drugs/DrugSafety/ucm293101.htm*
2 *http://www.fda.gov/Drugs/DrugSafety/ucm256581.htm*

Latest updates on the risk of lymphoma with topical calcineurin inhibitors (TCIs)

Summary of findings from the US Food and Drug Administration's Paediatric Advisory Committee review

HSA has been monitoring the developments of the risk of lymphoma related to topical calcineurin inhibitors (TCIs) and would like to provide healthcare professionals with new safety updates on this topic.

Tacrolimus (Protopic® ointment, J&J) and pimecrolimus (Elidel® cream, Novartis), are the two TCIs licensed in Singapore since March 2004 and January 2003, respectively. Protopic® was approved as second-line therapy for the treatment of moderate to severe atopic dermatitis (AD) while Elidel® was approved as second-line therapy for the short-term and intermittent long-term treatment of mild to moderate AD in patients two years of age and older.

Summary of previous regulatory actions and clinical findings

This safety issue dates back to 2005 when the US Food and Drug Administration (FDA) issued a public health advisory and implemented a boxed warning for both tacrolimus and pimecrolimus on risk of malignancy. This arose due to increasing concern over the use of TCIs as first-line and off-label therapy, post-marketing reports of malignancy in children and adults, and carcinogenicity findings from animal studies.[1] In May 2011, the US FDA held a Paediatric Advisory Committee (PAC) meeting to discuss the findings from epidemiologic association studies.[2-4] The studies reviewed suggest that there is an increased risk of lymphoma, particularly T-cell lymphoma, in TCI-treated AD patients compared to untreated AD patients.

In one of the reviewed studies, Hui *et al* (n = 953,064) observed a significantly higher risk of cutaneous T-cell lymphoma in topical tacrolimus-exposed AD patients (hazard ratio (HR) = 3.13, 95% CI 1.41 – 6.94); topical pimecrolimus-exposed AD patients were also at an increased risk (HR = 1.86, 95%CI 0.71 – 4.87) although not statistically significant.[5] Likewise, a nested case-control study by Arana *et al* (n = 625,915) also reported an increased risk of T-cell lymphoma with the use of topical tacrolimus (adjusted odd ratio (OR) = 4.95, 95% CI 1.86 – 13.19), but not with topical pimecrolimus (adjusted OR = 0.85, 95% CI 0.25 – 2.90).[6] Another study reviewed was by Schneeweiss *et al* who performed a nested case-control analysis and observed a four- and three-fold increase in lymphoma risk in patients receiving high cumulative amount of topical pimecrolimus (>100g) and corticosteroids (>100g), respectively, compared with those receiving low cumulative amount of topical corticosteroids (≤60g); tacrolimus analysis results were not interpretable due to small sample size.[7]

It is noteworthy that, although all of the studies included a proportion of paediatric patients, little information specific to this population was provided because the analyses were not stratified by age. The causal role of TCIs in lymphoma remains difficult to ascertain given the study limitations, such as misclassification of cases, relatively short duration of follow-up, and potential study biases. The PAC concurred that the applicability of the findings specifically to the paediatric population and to the long-term safety profile of TCIs remains questionable and agreed that the current US product labelling adequately represents the risks and benefits of Protopic® and Elidel® for their respective indicated use. US FDA was advised to continue monitoring occurrences of cancer cases with the use of these products and to update the PAC again with an updated literature review and an analysis from the registry on cancer cases at 5 years.

Similarly in May 2012, the UK Medicines and Healthcare products Regulatory Agency (MHRA) issued a Direct Healthcare Professional Communication to update healthcare professionals on the results of the above-mentioned epidemiological studies, and to remind them of risk minimisation measures for Protopic®. Further studies have also been planned, in agreement with the European Medicines Agency (EMA), to investigate the risk of cutaneous T-cell lymphoma following TCI therapy.

Local situation and HSA's advisory

In 2005, HSA and its Pharmacovigilance Advisory Committee (PVAC) had reviewed the available safety information and the recommendations for safe use of TCIs were published in the December 2005 issue of the Adverse Drug Reaction News bulletin.[8] Since their initial approval, the local package insert (PI) for Protopic® and Elidel® have been updated several times to strengthen the safety labelling. To date, HSA has not received any local reports of lymphoma associated with the use of TCIs.

Healthcare professionals are reminded to adhere to the following precautions to minimise the risks of TCIs which are reflected in the local PI:

- Continuous long-term use of TCIs in any age group should be avoided, and application limited to areas of involvement with atopic dermatitis.
- TCIs are not indicated for use in children less than 2 years of age.
- Use of topical tacrolimus in children aged 2 to 16 years of age is restricted to the lower strength preparation (Protopic® 0.03% ointment).
- TCIs should not be applied to lesions that are considered to be potentially malignant or pre-malignant.
- Lymphadenopathy present at initiation of therapy should be investigated and kept under review. Patients who receive TCIs, and who develop lymphadenopathy should be monitored to ensure that the lymphadenopathy resolves. In case of persistent lymphadenopathy, the aetiology of the lymphadenopathy needs to be investigated. In the absence of a clear aetiology for the lymphadenopathy or in the presence of acute infectious mononucleosis, discontinuation of therapy should be considered.
- TCIs should not be used in patients with congenital or acquired immunodeficiencies or in patients on therapy that causes immunosuppression. Excessive exposure of the skin to ultraviolet light including light from a solarium, or therapy with PUVA (psoralen and ultraviolet A [UVA]), UVA or ultraviolet B (UVB) should be avoided during treatment with TCIs.

Healthcare professionals are encouraged to report any adverse reactions suspected to be related to the use of Protopic® or Elidel® to the Vigilance Branch of HSA.

References

1 *http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM208037.pdf*
2 *http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM261385.pdf*
3 *http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM255139.pdf*
4 *http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM255140.pdf*
5 *Ann Pharmacother. 2009;43:1956-63.*
6 *Pharmacoepidemiol Drug Safety 2010;19:S12 (Abstract).*
7 *Dermatology 2009;219:7-21.*
8 *HSA ADR News bulletin. December 2005, Vol. 7; No. 3.*

Alert on counterfeit LIGACLIP® EXTRA LIGATING CLIP CARTRIDGES

HSA would like to alert healthcare professionals to overseas reports of the distribution of counterfeit LIGACLIP® EXTRA LIGATING CLIP CARTRIDGES (Product Code LT300). The authentic LIGACLIP® product is manufactured by Ethicon Endo-Surgery (EES). Although HSA and the local authorised distributor, Johnson & Johnson Pte Ltd, have not received any reports of counterfeit clips being distributed locally, HSA would like to alert healthcare professionals to the possibility that they may have obtained counterfeit clips if these were purchased from unauthorised sources. As the performance, mechanical properties, biocompatibility and sterility of the counterfeit clips are unknown, HSA strongly discourages the purchase of these products from unauthorised sources. Please refer to the pictures below for instructions on how to identify the counterfeit clips.

LIGACLIP® EXTRA LIGATING CLIP CARTRIDGES are registered in Singapore for use on tubular structures or vessels wherever metal ligating clips are indicated.

Background

The counterfeit product was discovered as a result of an investigation by EES. It was purchased in the United States from an unauthorised distributor. EES is working closely with the US Food and Drug Administration (FDA) to investigate this matter and help to prevent further distribution of the counterfeit device.

HSA's actions and advisory

HSA had requested the authorised local distributor to disseminate a letter of notice on the counterfeit device to its customers. In addition, HSA advises healthcare professionals who may have obtained the clips from sources other than the authorised local distributor on the following:

1. Carefully examine all LIGACLIP® products before use and also inform the relevant staff in the operating room to do likewise. (Refer to pictures below for identification of counterfeits)
2. Quarantine any product suspected to be a counterfeit to halt further distribution.
3. Contact the authorised local distributor, Johnson & Johnson Pte Ltd to confirm if the suspected product is a counterfeit. If the product is a counterfeit, please report it to HSA via Email: *hsa_medical_device@hsa.gov.sg* or Tel: *6866 3560*.
4. Verify the origin of the LIGACLIP® product by contacting the source if it was not purchased from EES directly or from Johnson & Johnson Pte Ltd
5. Avoid the purchase of products from unauthorised sources (eg, internet sources).

Healthcare professionals are encouraged to report any adverse events suspected to be related to counterfeit LIGACLIP® products to the Vigilance Branch of HSA. More information about the counterfeit products is also available on EES website at *www.ees.com/counterfeit*.

How to identify counterfeit LIGACLIP® EXTRA LIGATING CLIP CARTRIDGES

Please note that the counterfeit looks very similar to the genuine LIGACLIP® EXTRA LIGATING CLIP CARTRIDGES. Clear differences to identify a counterfeit are marked with an arrow and are described below:

*Features of the **Counterfeit** Product*

1 An unusual font on the sales unit box distorts the company name.

2 Individual clip package misspells "STERILE" as "STEMIKE."

*Features of the **Authentic** LIGACLIP® EXTRA LIGATING CLIP CARTRIDGES*

1 EES product clearly indicates the company name on the sales unit box.

2 EES individual clip package is correctly labelled.

Enhancements to the medical device regulatory framework

On 20 April 2012, HSA announced that it has enhanced the regulatory framework for the lower risk Class A and B medical devices. This is to facilitate expedited access and lower regulatory fees for these products. Class A and B devices account for about 70% of all medical device applications received by HSA. Further enhancements are also being planned for the higher risk Class C and D devices. These initiatives seek to better address the concerns of the medical device industry and healthcare professionals while ensuring public safety.

Background

HSA adopts a risk-stratified approach, in-line with international best practices to ensure that consumers have access to safe, good quality and effective devices, and to facilitate prompt recalls when defects are detected. The regulations were implemented in phases since 2007 to allow stakeholders adequate time to transit to a full regulatory framework.

In the run up to the full implementation of medical device registration on 1 January 2012, HSA had intensified its dialogues with its stakeholders. Based on the feedback received and experiences gained with the initial implementation of the regulations, HSA further enhanced its framework to facilitate access to the low risk medical devices. To ensure that patient safety is not compromised while customising different levels of controls, the enhancements were based on the broad principles that include judicious referencing of key independent overseas agencies[1], consideration of a history of safe use, and a shift of focus from pre-market evaluation to greater post market surveillance, audit and enforcement. Highlights of the enhancements relevant to healthcare professionals are outlined in Table 1.

Contact information

HSA views healthcare professionals as important partners in the successful implementation of the medical device regulatory framework. Feedback or enquiries on the enhancements to the regulatory framework may be made through email *(HSA_MD_Info@hsa.gov.sg)*.

Healthcare professionals also play an important role to help safeguard public health by reporting adverse events suspected to be related to medical devices to HSA's Vigilance Branch via the weblink: *www.hsa.gov.sg/ae_online*.

We look forward to our continued partnership in ensuring that safe, effective and good quality medical devices are used in Singapore.

Table 1: Overview of key initiatives announced on 20 April 2012
(Details are available on the HSA website at www.hsa.gov.sg)

Initiative	Potential benefit(s) to HSA's stakeholders
Enhancement of the regulatory framework for lower risk (Class A and B) medical devices ***Class A medical devices*** From 1 May 2012 ■ All Class A medical devices, except sterile devices, will be exempted from registration. ■ Turnaround time for registration of Class A (sterile) medical devices will be reduced from 60 working days to 30 working days. ***Class B medical devices*** From 1 Sep 2012 HSA will be implementing the following new registration routes: ■ Immediate Registration Route for Class B medical devices that have already been approved by two independent regulatory reference agencies[1] and marketed without any safety concerns for at least three years in these jurisdictions. ■ Expedited Registration Route for i. Class B devices which have already been approved by at least one independent regulatory agency[1] and marketed in this jurisdiction or in Singapore without any safety concerns for at least three years; or ii. Class B devices which have already been approved by two independent regulatory reference agencies[1]. ■ Regulatory fees for the 2 new routes will be reduced to $1,400. ■ Turnaround time for the expedited registration route will be 60 working days, excluding stop-clock.	The enhancements will result in immediate access to non-sterile Class A medical devices and faster and expedited access for Class A and B medical devices. Applicants will also benefit from lower regulatory fees.
Enhancement of Special Authorisation Routes (SAR) ■ Fees for special authorisation routes (SAR) will be temporarily offset and absorbed by HSA if all the medical devices listed in the SAR application are the subject of pending product registration or change notification applications that have been submitted by 31 December 2012. ■ The validity period of all approved SAR applications will be extended to 12 months (instead of the previous 3-6 months). ■ Qualified medical practitioners can import unregistered medical devices for the treatment of unmet medical needs in their patients via GN-26 (Guidance on the import of an unregistered medical device for supply on Named-Patient Basis) and/or GN-27 (Guidance on the import of unregistered devices for supply to clinical laboratories, medical clinics or private hospitals licensed under the PHMC Act). ■ The process for the GN-27 has been enhanced to allow consolidation of a list of unregistered medical devices for different healthcare facilities into a single application. ■ Fees for SAR have also been lowered. More details on the fees are available on the HSA website at *www.hsa.gov.sg*	Applicants will benefit from reduced regulatory cost associated with applications to import and supply unregistered medical devices via the special authorisation route.
Importation of medical devices on the Transition List (T-List)[2] ■ Medical devices on the T-List can continue to be imported and supplied while product registration applications are being evaluated.	Healthcare professionals and users of medical devices will not face any disruptions in the access and supply of essential medical devices.

1 *US Food and Drug Administration (FDA), EU Notified Bodies, Australian Therapeutic Goods Administration (TGA), Health Canada and Japan Ministry of Health, Labour and Welfare*

2 *The Transition List (T-List) was one of the measures implemented in November 2009 during the rolling out of the regulatory framework to facilitate continued access to medical devices while their applications were reviewed.*

Updates on Prescription-Only Medicines (POMs) with exemptions for limited sale and supply without prescription

In order to facilitate consumers' access to medicines, HSA has embarked on a biannual review to identify Prescription Only Medicines (POM) which may be supplied without prescription by pharmacists under exemptions where they are deemed sufficiently safe for use with reduced medical supervision. Three new POMs have been assessed to meet the criteria to be granted exemptions for limited sale and supply without prescription as of 1 July 2012. The current exemptions for ibuprofen and domperidone solid and liquid oral preparations have also been amended.

Exemptions for limited sale and supply of POM without prescription with effect from 1 July 2012

1. Azelaic acid topical preparations containing 20% w/w for treatment of mild to moderate acne vulgaris
2. Triamcinolone intranasal spray containing not more than 55mcg/actuation for prevention and treatment of allergic rhinitis
3. Levocetirizine oral solid and liquid preparations containing not more than 5mg and 5mg/ml respectively for symptomatic treatment of allergic rhinitis and chronic idiopathic urticaria

Amendment to exemptions for limited sale and supply without prescription with effect from 1 July 2012

1. Amendment of maximum daily dose of ibuprofen oral solid and liquid preparations from age-based to a weight-based dosing.

   This is to align the recommendation to the current prescribing practice whereby weight-based maximum daily dose of ibuprofen of 30mg/kg would be more appropriate for children.This is also aligned to current dispensing practice.
2. Amendments to the maximum daily dose, maximum supply and minimum age of domperidone oral solid and liquid preparations.

   These restrictions are implemented in view of the potential increased risk of cardiac disorders such as serious ventricular arrhythmia and sudden cardiac death associated with chronic use of domperidone above 30mg daily.

Record keeping and patient confidentiality

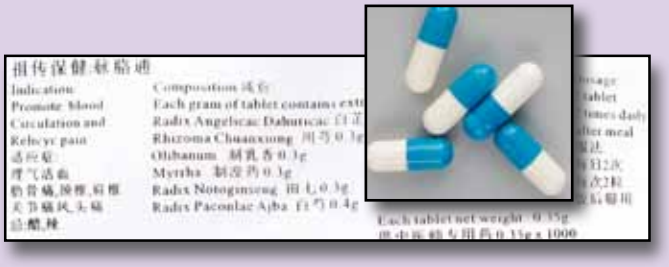
The requirement for mandatory record keeping of supply of Pharmacy Only (P) medicines and POM with exemption for limited sale and supply without prescription has been fully implemented as of 1 Feb 2012. This requirement is intended to better safeguard consumers who buy P medicines. Pharmacists would be able to follow up with their customers/patients, should there be any issues concerning the use and quality of these medicines. These records

would also assist the pharmacist in the identification of potential interactions between medicines or inappropriate use by patients thereby contributing further to quality patient care and patient safety. All pharmacists are reminded to keep all records relating to patients and their medications strictly confidential in accordance to the Code of Ethics (available from the Singapore Pharmacy Council website at *www.spc.gov.sg*).

All healthcare professionals are encouraged to report adverse reactions related to these medicines to the Vigilance Branch of HSA. For more information on reclassified medicines and POMs with exemptions for limited sale and supply without prescription, including downloadable patient information leaflets, frequently asked questions and mandatory recording requirements, please visit our website at: *http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/western_medicines/reclassified_medicines.html.*

Reports on illegal capsules adulterated with dexamethasone

HSA would like to alert healthcare professionals to recent cases of illegal capsules found to be adulterated with dexamethasone.[1] These capsules were sold as herbal or traditional medicines to treat arthritic and joint pain, and promote blood circulation. They were either green-white or blue-white in colour and packaged in transparent bottles with a printed slip of herbal ingredients.



Description of reported cases

The three reported cases involved patients between 40 to 80 years of age. They had obtained these capsules from peddlars or friends. One patient in his 80's developed Cushing's syndrome after consuming the adulterated capsules for about one year for the relief of chronic back pain, and had to be warded in the intensive care unit. The second patient, in his 40's, had sustained a fracture requiring surgical intervention following long-term consumption of the capsules for pain relief of gout. The third patient, in her 50's, had consumed a few of the illegal capsules for pain relief of her stiff neck before her family member stopped her use of the capsules and reported the case to HSA. The family member had suspected adulteration of the capsules as it provided her rapid pain relief.

HSA's advisory

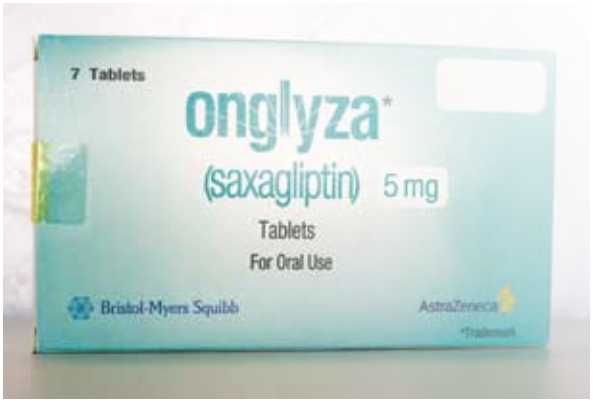
HSA has issued a Press Release on 12 July 2012 to warn members of the public of these adulterated capsules and advised those who have taken the capsules to seek medical attention as soon as possible, before discontinuing the capsules to avoid steroid withdrawal symptoms.

Healthcare professionals are encouraged to ask their patients about the use of complementary health products while taking their medical history. Healthcare professionals are also reminded to consider the possibility of the consumption of adulterated complementary health products if they encounter similar cases and to report these to the Vigilance Branch of HSA.

References

1 *http://www.hsa.gov.sg/publish/hsaportal/en/news_events/press_releases/2012/hsa_alerts_public.html*

Acute pancreatitis and serious hypersensitivity reactions reported with saxagliptin



HSA would like to highlight recent overseas post-market cases of acute pancreatitis and serious hypersensitivity reactions reported in patients treated with saxagliptin (Onglyza®, Kombiglyze®, Bristol-Myers Squibb) from July 2009 to September 2011.

Saxagliptin belongs to the class of antidiabetic drugs known as dipeptidyl peptidase-4 (DPP-4) inhibitors. DPP-4 inhibitors work by inhibiting the enzyme DPP-4, which slows down the inactivation of incretin hormones such as glucose-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). This results in prolongation of the actions of these hormones in glucose homeostasis. These hormones cause insulin release from the pancreatic beta cells in a glucose-dependent manner but are inactivated by DPP-4 enzymes within minutes.

Locally, saxagliptin has been licensed since November 2010, under the brand name Onglyza®. It was recently approved in February 2012 for use as a combination product with metformin under the brand name Kombiglyze®.

Overseas post-marketing reports of acute pancreatitis and serious hypersensitivity reactions

Fifty-six cases of overseas post-marketing reports of acute pancreatitis associated with saxagliptin have been received between July 2009 and September 2011 while 70 cases of angioedema and 11 cases of anaphylactic responses have been received from July 2009 to January 2011 and February 2011 respectively.

In the cases where pancreatitis was reported, more than half of these had resolved or were resolving at the time of reporting. There were, however, two fatal reports – one patient with a history of cholelithiasis and who was subsequently diagnosed with pancreatic carcinoma; and the other with a history of hypercholesterolemia where the cause of death was recorded as sepsis, acute pancreatitis and acute cholescystitis.

With regard to hypersensitivity reactions, the adverse reactions reported included anaphylaxis, angioedema, and exfoliative skin conditions. The onset of these reactions occurred within the first three months after initiating saxagliptin, with some reports occurring after the first dose. Some of these cases also had confounding factors which included pre-existing medical conditions or concomitant medications. There was one report of a fatal anaphylactic reaction, in which hypersensitivity to saxagliptin could not be ruled out.

Local situation and HSA's advisory

To date, HSA has not received any local reports of acute pancreatitis and serious hypersensitivity reactions associated with saxagliptin use.

A Dear Healthcare Professional Letter was issued on 5 March 2012 to inform healthcare professionals on the risk of acute pancreatitis and serious hypersensitivity reactions reported in patients treated with saxagliptin.[1] The local package inserts for Onglyza® and Kombiglyze® have also been updated to include these warnings.

HSA would like to remind healthcare professionals that the safety concern of acute pancreatitis is not restricted to saxagliptin. There have been overseas post-marketing reports of pancreatitis observed with the use of other DPP-4 inhibitors like sitagliptin and vildagliptin, indicating the possibility that pancreatitis could be a class effect of DPP-4 inhibitors.[2-4]

Physicians are reminded to monitor their patients carefully for acute pancreatitis and hypersensitivity reactions. Onset of the hypersensitivity reactions were reported to occur within first three months of initiating saxagliptin therapy in some of the overseas reports. Some signs and symptoms of acute pancreatitis include persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting. Serious hypersensitivity reactions include anaphylaxis, angioedema or exfoliative skin conditions.

Healthcare professionals are also encouraged to report adverse drug reactions suspected to be associated with the use of DPP-4 inhibitors to the Vigilance Branch of HSA.

References

1 *HSA website. Dear Healthcare Professional Letters (DHCPL)*
2 *http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm183764.htm*
3 *HSA ADR News Bulletin. April 2010, Vol 12; No. 1.*
4 *Endocr Pract 2011; 17(3):334-6.*

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All website references were last accessed on 2 Aug 2012.