

The National Pharmacovigilance Centre Newsletter



MINISTRY OF HEALTH & QUALITY OF LIFE

E-newsletter – Issue 2

May 2018

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EDITORIAL NOTE

Dear Health-Professional,

In our second newsletter, we have chosen to tell you about two cases, which can potentially constitute signals for Mauritius.

The two cases are about (a) the wrong prescribing and wrong dispensing of methotrexate tablets and; (b) the number of Stevens Johnson cases reported with carbamazepine tablets.

We wish to draw your attention that the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) has recommended:

- (a) The suspension of the marketing authorization for Hydroxyethyl Starch (HES) solution for infusion across the European Union;
- (b) The strengthening of the restrictions on use of Sodium Valproate and the introduction of new measures to avoid its use during pregnancy;
- (c) That retinoids should not be used in pregnancy.

We encourage you to report Adverse Drug Reactions. You now can do so online by clicking on the link: <http://health.govmu.org/English/Departments-Hospitals/National-Pharmacovigilance-Committee/Pages/How-to-report.aspx> or use any other method found on the last page of this newsletter.

We wish you a pleasant read and welcome your comments and suggestions on pharmacovigilancemauritius@gmail.com

Yours sincerely,

Dr. Yee Kin Tet Hoy Youn

LIST OF ABBREVIATIONS

ADRs – Adverse Drug Reactions

ANSM – Agence Nationale de Sécurité du Médicament

DMARD – Disease Modifying Anti-Rheumatic Drug

EMA – European Medicines Agency

FDA or USFDA – Food and Drug Administration

HCP – Health Care Professionals

HES – Hydroxyethyl Starch

HSA – Health Sciences Authority (Singapore)

MedDRA – Medical Dictionary for Regulatory Activities

NSAID – Non-Steroidal Anti-inflammatory Drug

PRAC – Pharmacovigilance Risk Assessment Committee

SCARs – Severe Cutaneous Adverse Reactions

SJS – Stevens Johnson Syndrome

UMC – Uppsala Monitoring Centre

WHO – World Health Organisation

SIGNAL

A signal is defined by World Health Organisation (WHO) as reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information. A signal is a hypothesis together with data and arguments and it is important to note that a signal is not only uncertain but also preliminary in nature.

Methotrexate tablets – cases of incorrect prescribing and dispensing in Mauritius

Mrs. S. Boolell, Mr. V. Mooneeramsing, The National Pharmacovigilance Centre, Mauritius

1. Introduction

Methotrexate is an antimetabolite used in the treatment of certain neoplastic diseases, severe psoriasis, and adult rheumatoid arthritis. Methotrexate inhibits the enzyme dihydrofolate reductase. Only one strength of methotrexate tablet is available in Mauritius namely 2.5 mg. Low dose Methotrexate (7.5 – 25 mg) is indicated for rheumatoid arthritis, psoriasis and inflammatory bowel disease¹. The unusual weekly dosing of methotrexate as compared to practically most medications

that are taken daily, heightens the risk of incorrectly taking the drug. Used appropriately, methotrexate is considered safe and efficacious; however accidental daily dosing can be lethal. Higher or more frequent doses can result in gastrointestinal mucosal ulceration, hepatotoxicity, myelosuppression, sepsis and death². In Rheumatoid Arthritis, the first line of treatment is methotrexate tablet, classified as a DMARD (Disease Modifying Anti-rheumatic Drug).

2. Methotrexate tablets in Public Hospitals and Private Practice

According to present statistics, we have around 15,000 cases of rheumatoid arthritis patients following treatment in our public hospitals. All cases are diagnosed and monitored by specialists. There are several instances where methotrexate is stopped periodically or permanently during the course of treatment. However, it has been noted by treating doctors in public

hospitals that patients have had recourse to self-medication.

Patients who have been prescribed methotrexate tablets can purchase the drug from private pharmacies. The brand registered in Mauritius is the same as the one available in public hospitals and is of similar strength and packaging size.

3. Adverse Drug Reaction cases reported

Since the beginning of 2018, 3 cases have been reported on Adverse Reactions with the use of methotrexate tablets.

Case	Age/Sex	Reactions (MedDRA terms)	Dechallenge/Rechallenge	Comments
1	84/M	Skin erosion	Dechallenge positive	Recovered
2	52/M	Pancytopenia, Sepsis secondary	Dechallenge negative	Passed away
3	54/M	Pancytopenia, Urea serum increased	Dechallenge positive	Recovered

The National Pharmacovigilance Centre suspects that there are several other cases that have not been reported. The Adverse Drug Reaction resulting from methotrexate tablets can be classified as serious resulting in fatality.

4. Discussion

Several literature reports worldwide have already notified serious morbidity and mortality associated with methotrexate medication errors³⁻⁷.

The source of medication errors are: (i) errors in prescribing, the weekly dose is

mistakenly written daily! ; (ii) the patient has wrongly understood his dosing regimen for the drug and takes a daily dose instead of weekly; (iii) the patient alters his dose by himself; (iv) auto medication by the patient even after doctor has temporarily or permanently stopped methotrexate.

5. Conclusion

Incorrect prescribing and dispensing methotrexate tablets can be fatal. All prescribers are reminded to pay particular attention while prescribing methotrexate. Pharmacists should be more vigilant while dispensing any prescription of methotrexate. The Pharmacist should do a thorough assessment of the patient requesting a prescription refill for that drug.

References

1. Tian H, Cronstein BN. Understanding the mechanisms of action of methotrexate. Bull NYU Hosp Jt Dis 2007; 65: 168-173.
2. Schmiegelow K. Advances in individual prediction of methotrexate toxicity: a review. Br J Haematol 2009; 146: 489-503.

3. Sinicina I, Mayr B, Mall G, Keil W. Deaths following methotrexate overdoses by medical staff. *J Rheumatol* 2011; 32: 2009-2011.
4. Blinova E, Volling J, Koczmara C, Greenall J. Oral methotrexate: preventing inadvertent daily administration. *Can J Hosp Pharm* 2008; 61: 275-277.
5. Bookstaver PB, Norris L, Rudisill C, et al. Multiple toxic effects of low-dose methotrexate in a patient treated for psoriasis. *Am J Heal Pharm* 2008; 65: 2117-2121.
6. Moisa A, Fritz P, Benz D, Wehner HD. Iatrogenically-related, fatal methotrexate intoxication: a series of four cases. *Forensic Sci Int* 2006; 156: 154-157
7. Singh YP, Aggarwal A, Misra R, Agarwal V. Low-dose methotrexate-induced pancytopenia. *Clin Rheumatol* 2007; 26: 84-87.

Carbamazepine - cases of Stevens Johnson Syndrome observed

Carbamazepine acts by the blockade of sodium channels, decreasing cell excitability, and suppressing neuronal firing. It is mainly indicated for epilepsy, trigeminal neuralgia and bipolar disorder. The most common side effects are ataxia, dermatitis and visual disturbances. Nine (9) cases of Stevens Johnson Syndrome (SJS) associated with carbamazepine have been reported between 2011 and 2014. Two (2) more cases have been reported in 2018. The US FDA has reported that the risk of carbamazepine induced SJS is estimated to be about 10 times higher in some Asian countries. Studies have established a strong correlation between the risk of developing SJS and the presence of HLA-B*1502, a variant of the HLA-B gene. A segment of the Mauritian population comprises of people from Chinese origin more precisely Han-Chinese. There is a potential risk of the presence of the HLA-B*1502 allele in the Mauritian population. This could be a subject of further research.

Mrs. S. Boolell, Mrs. K. Capery & Mr. A. Seeneevassen, The National Pharmacovigilance Centre, Mauritius

CHLORHEXIDINE – risk of allergic reactions



The Health Sciences Authority in Singapore has informed Healthcare Professionals about possible known risk of allergic reactions to patients whilst using chlorhexidine containing products. Chlorhexidine is a broad spectrum antiseptic widely used to reduce the risk of bacterial skin infections. Patients should be advised to discontinue use if any allergic reaction like rashes, wheezing or swelling of the face is experienced.

Reference: Product Safety Alerts, HSA, 29 September 2017 (<http://www.hsa.gov.sg/>)

Several mouth wash/rinse contain chlorhexidine and are on sale in supermarkets/pharmacies. HCPs should educate patients on the potential risks while using those products.

IBUPROFEN – risk of affecting hormonal levels in males

Ibuprofen is a Non-Steroidal Anti-Inflammatory Drug (NSAID) used primarily for pain and fever. L'Agence Nationale de Sécurité du Médicament from

France recommends using the lowest effective dose following results suggesting disruption in testicular physiology (precisely steroidogenesis) with large doses (1200 mg) of Ibuprofen for prolonged periods.

Reference: Point d'information, ANSM, 10 January 2018, France (www.ansm.sante.fr)

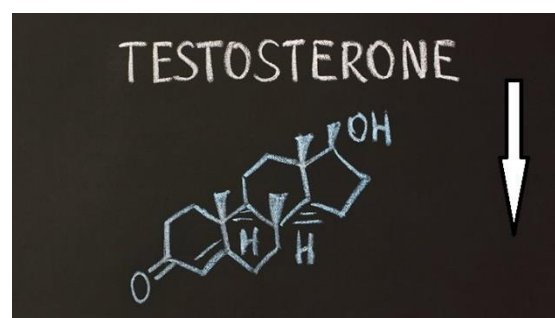
Local facts on Ibuprofen

Ibuprofen is prescribed extensively in Public Hospitals as well as in Private Practice.

Quantity procured in Public Hospitals:

Ibuprofen 200 mg: 3.4 M

Ibuprofen 400 mg: 3.0 M



GLIBENCLAMIDE – South Asian Population to be cautious

Out of one hundred Adverse Drug Reaction (ADR) reports analysed by Uppsala Monitoring Centre (UMC) on cases of palpitations with the use of glibenclamide tablets, 59 came from **South Asian countries**. The genotype of those people seem to make them highly predisposed to the ADR. UMC has classified this as a signal and is being closely monitored. Glibenclamide is no more in the Essential Drug List of Public Hospitals. The drug is still registered and marketed in the Private Sector. Prescribers are requested to be vigilant and report any ADR with the use of glibenclamide.

Reference: Comoglio, R. H. SIGNAL Newsletter, Risk Group Signals: Glibenclamide, April 2018



BLOOD GLUCOSE RANGES

The National Institute for Clinical Excellence (NICE) recommended target blood glucose (sugar) levels are stated below for adults and children with type 1 diabetes and type 2 diabetes.

	Type 1 diabetes	Type 2 diabetes	Children w/ type 1
Before meals Pre prandial	4 to 7 mmol/L 72-126 mg/dl	4 to 7 mmol/L 72-126 mg/dl	4 to 8 mmol/L 72-144 mg/dl
After meals Post prandial 2hrs after meal	Under 9 mmol/L 162 mg/dl	Under 8.5 mmol/L 153 mg/dl	Under 10 mmol/L 180 mg/dl

The ranges are guidelines provided by the National Institute for Clinical Excellence (NICE) but each individual's target range should be agreed by their doctor or diabetic consultant.

Join over 45,000 people on the Diabetes Forum at: www.diabetes.co.uk/forum

 /Diabetes.co.uk 

CEFTRIAXONE INJ – hepatitis in geriatrics

ADR reports analysed by UMC suggests a strong causal relationship between ceftriaxone and hepatitis in patients 75 years and older. Ceftriaxone is a third generation cephalosporin antibiotic indicated for a large number of infections. Ceftriaxone is widely prescribed in hospital settings in Mauritius and prescribers should be cautious while concomitantly prescribing other drugs that are potentially hepatotoxic.

Reference: Boyd, I. SIGNAL Newsletter, Risk Group Signals: Ceftriaxone, April 2018



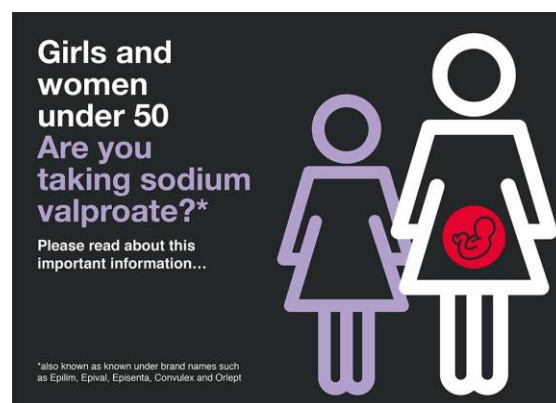
“Let us make sure that the smile stays on! Let us be vigilant with the use of ceftriaxone with the elderly population.”

SODIUM VALPROATE – Risk of malformations and neurodevelopmental delay

The Pharmacovigilance Risk Assessment Committee (PRAC) of European Medicines Agency (EMA) has recommended strengthening the restrictions on use of Sodium Valproate and introducing new measures to avoid its use during pregnancy. The licensed use of Sodium Valproate are epilepsy, bipolar disorder and in some countries for the prevention of migraine. HCPs are reminded that Sodium Valproate should not be used during pregnancy and in women of childbearing potential **unless it is the only appropriate treatment and might be lifesaving**. The attention of Pharmacists is drawn to the following: The recommended measures aimed at (i) better counselling women about the risks of Valproate treatment; explaining the need for effective (ii) contraception throughout the treatment; (iii) carrying out pregnancy tests before starting and during the treatment as needed.

Reference: EMA/145600/2018

http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Valproate_2017_31/Recommendation_provided_by_Pharmacovigilance_Risk_Assessment_Committee/WC500243552.pdf



HYDROXYETHYL STARCH IV solution – recommendation to suspend marketing licenses

PRAC has recommended the suspension of the marketing authorization for Hydroxyethyl Starch (HES) solution for infusion across the European Union. HES products are synthetic colloid solutions used for plasma volume expansion in a range of clinical settings. In view of serious risks that certain patient populations are exposed to, PRAC has recommended the suspension of the marketing authorization for HES solutions.

Reference: EMA/35795/2018

http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Hydroxyethyl_starch_107i/Recommendation_provided_by_Pharmacovigilance_Risk_Assessment_Committee/WC500241325.pdf

EPOETINS – Risk of Severe Cutaneous Adverse Reactions (SCARs)

PRAC of EMA recently completed a detailed analysis of SCARs associated with epoetin containing medicines. PRAC concluded that SCARs namely Stevens Johnson Syndrome and Toxic Epidermal Necrolysis are considered a class effect for all epoetins.

Reference: WHO Pharmaceutical Newsletter, Regulatory matters: Epoetins, 2018 No 1
<https://www.hpra.ie/docs/default-source/publications-forms/newsletters/hpra-drug-safety-newsletter-edition-83.pdf?sfvrsn=5>



A patient with Stevens Johnson Syndrome

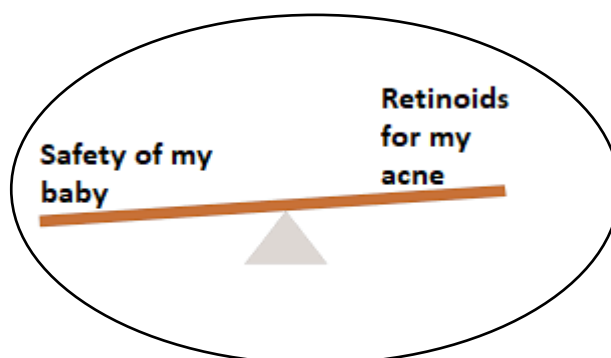
RETINOIDS – can harm the unborn child



Retinoids are derivatives of Vitamin A used to treat a number of skin conditions including acne and psoriasis. Both acitretin and isotretinoin are teratogenic and embryogenic. Women who are or intend to become pregnant must not use either oral or topical retinoids. A possible risk of neuropsychiatric disorder has also been observed with oral retinoids.

Reference: EMA/165360/2018

http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2018/03/WC500246349.pdf



BENZOCAINE CONTAINING PRODUCTS – Risk of serious and potentially fatal blood disorder

The U.S. Food and Drug Administration (FDA) is warning that over-the-counter (OTC) oral drug products containing benzocaine should not be used to treat infants and children younger than 2 years. These products carry serious risks and provide little to no benefits for treating oral pain, including sore gums in infants due to teething. Benzocaine, a local anaesthetic, can cause a condition in which the amount of oxygen carried through the blood is greatly reduced. This condition, called methemoglobinemia, can be life threatening and result in death.



Definitely not with a benzocaine teething gel!!!

Pharmacist's advice: Tips to parents & caregivers

- Gently rub or massage the child's gums
- Use a firm rubber teething ring

REPORTING ANY ADR OR SUSPECTED QUALITY OF MEDICINES

How to report?

Manually

- Get hold of the Pharmacovigilance Reporting forms (see copy below) from the Pharmacist in your health institution.
- Fill the form and submit to the POC* (Point of Contact).

Electronically

1. By sending an email to: pharmacovigilancemauritius@gmail.com
2. For adverse drug reactions at: <https://form.myjotform.com/80387732894571>
3. For quality issues at: <https://form.myjotform.com/80393242855561>

The different POCs:

1. SSRN Hospital: Mr. A. Seeneevassen, Pharmacist/Sr Pharmacist
2. Dr. A. G. Jeetoo Hospital: Mrs. K. Capery, Pharmacist/Sr Pharmacist
3. Victoria Hospital: Mrs. B. Nuckchady-Hurry, Pharmacist/Sr Pharmacist
4. Flacq Hospital: Ms. N. Eathally, Pharmacist/Sr Pharmacist
5. J. Nehru Hospital: Mrs. S. Hurbissoon, Pharmacist/Sr Pharmacist
6. S. Bharati Eye Hospital: Ms. S. Lalloo, Pharmacist/Sr Pharmacist
7. Brown Sequard Mental Health: Mrs. H. B. Uteene, Pharmacist/Sr Pharmacist
8. Central Supplies Division: Mr. V. Mooneeramsing, Pharmacist/Sr Pharmacist

The reports will be dealt with full confidentiality.

ADR reports are posted on the Vigibase® database managed by WHO Monitoring Centre, Uppsala, Sweden.

REPORT OF SUSPECTED ADVERSE DRUG REACTIONS

Send to: National Pharmacovigilance Committee

10th Floor, Emmanuel Anquetil Building

Port-Louis

Email: Pharmacovigilancemauritius@gmail.com

PATIENT DETAILS

Patient's Initials:.....

Sex: Male/Female

Age:

SUSPECTED DRUG(S) / VACCINE

Trade Name	Dosage	Route	Started on	Stopped on	Indication

SUSPECTED REACTIONS

Date of onset

Duration of reaction

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OTHER MEDICATIONS

Drug	Dose	Route	Started on	Stopped on	Indication

ADDITIONAL INFORMATION (Medical History, other medications, known allergies, suspected drug interactions)

.....

.....

REPORTER DETAILS

Name and Professional Address:

.....

.....

.....

Phone:.....

Email:

Signature:

<p style="text-align: center;">NATIONAL PHARMACOVIGILANCE COMMITTEE USE ONLY</p> <p>Date of receiving report:</p> <p>Local Report No:</p>
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In Confidence

REPORT OF SUSPECTED QUALITY ISSUES

Send to: National Pharmacovigilance Committee
10th Floor, Emmanuel Anquetil Building,
Port-Louis.

Email: Pharmacovigilancemauritius@gmail.com

Date:

Name of Drug:

Dosage Form:

Batch No:

Name of Manufacturer:

Country of Manufacture:

Name of Active Ingredient:

Date of Purchase:

Expiry Date:

Name of Supplier:

Storage Conditions:

Please indicate which quality requirement is substandard (Please tick all that apply):

Discoloration

Disintegration

Unpalatable

Cracking

Presence of Particles/Lichen

Defective Packaging

Other Quality Issues:

.....
.....
.....

Name and Professional Address:

.....
.....
.....

Phone:

Email:

Signature:

NATIONAL PHARMACOVIGILANCE COMMITTEE USE ONLY

Date of receiving report:

Local Report No:

PHARMACOVIGILANCE TRAINING SESSIONS - with Nurses

The month of April was rich in pharmacovigilance training sessions organised with Nursing Officers via Continuous Nurses Education. Hospitals involved were (i) SSRN Hospital, (ii) Dr. A. G. Jeetoo Hospital, (iii) Victoria Hospital and (iv) J. Nehru Hospital. Warm thanks goes to the Regional Nursing Administrators (RNAs) of the different regions who organised the venue and informed the participants. The responsive crowd and pertinent questions that we got at the end of the sessions showed the keen interest of nursing officers in pharmacovigilance.

We welcome them on board our national program and look forward to get reports from them.



WHOLESALE PHARMACIES – Their involvement in Pharmacovigilance

The personnel of Wholesale Pharmacies were also given training on the basics of pharmacovigilance and how it relates to their activities. Companies involved were: (i) A. E Patel & Co Ltd, (ii) Ducray Lenoir (iii) FTM Limited, (iv) Healthactiv, (v) PNL, (vi) Unicorn Trading. It was an opportunity to elaborate more on the reporting system established in Mauritius and also recent changes in the guidelines for reporting ADRs. Manufacturers and Marketing Authorisation Holders worldwide hold a keen interest on the safety profile of their medicines and it is very encouraging to see the deep concern of wholesale pharmacies in Pharmacovigilance.

We urge you to feel free to contact us on pharmacovigilancemauritius@gmail.com for any assistance.



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