DECEMBER 2015

MADRAC

Malaysian Adverse Drug Reactions Newsletter
National Pharmaceutical Control Bureau, Ministry of Health Malaysia

SAFETY ISSUES OF CURRENT INTEREST

SUCCINYLATED GELATIN INTRAVENOUS INFUSION PRODUCTS: SUMMARY OF SAFETY REVIEW IN 2015

by Noraisyah Mohd. Sani and Rema Panickar

Succinylated gelatin intravenous infusion (IVI) products are colloidal volume replacement fluid containing 4% modified fluid gelatin, characterised by a long polypeptide chain. Currently, there are four (4) IVI succinylated gelatin products registered in Malaysia, under the brand names Gelofusine®, Infusol SG® and Gelaspan®.

In February 2015, the NPCB initiated a review into the safety and quality of these products. This review was triggered by a sudden spike in the number of product complaints and ADR reports received, as well as concerns raised by some clinicians on the risk of anaphylactic reactions linked to a particular product.

Safety and Quality Review

The NPCB conducted a full review of all IVI succinylated gelatin products, looking at usage trends and ADR reports over the past few years. Quality investigations were carried out where possible on samples of the batches involved in the complaints and ADR reports of anaphylaxis.

The investigations revealed no quality issues, as all the batches passed the relevant tests, including sterility and bacterial endotoxin tests. The manufacturing records showed there were no deviations in the manufacturing process of these batches.

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CONTENT

To report an adverse drug reaction:

1. Visit portal.bpfk.gov.my
2. Click on the circle: 'ADR Reporting'.
3. Go to report as a healthcare professional online or via hardcopy.
4. Submit the form once completed.

Alternatively, please contact:

The Drug Safety Monitoring Centre,
National Pharmaceutical Control Bureau,
Ministry of Health
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To join the NPCB Safety Information Mailing List, please send an email to fv@bpfk.gov.my
This publication is also available on our website: portal.bpfk.gov.my

Local ADR Reports related to Succinylated Gelatin Infusion Products

Between years 2001 to July 2015, the National ADR Monitoring Centre, NPCB, received 133 reports (276 adverse events) suspected to be related to IVI succinylated. The most commonly reported reactions were rigor (57 adverse events) and chills (42), involving 58 reports (43.6%). About 22.8% (63 adverse events) involved mild skin reactions such as knee itchiness, urticaria, itching and rash.

There were 22 reports of anaphylaxis over the past 15 years, involving various brands of IVI succinylated gelatin. In general, an immunological response to products containing protein source such as gelatin is expected. Based on the ADR reports received, the **reactions were not brand-related**. Allergy testing carried out by a dermatology unit on four (4) patients who had suffered ADRs to one IVI succinylated gelatin product also revealed that the patients were allergic to a second brand.

It was noticed that the adverse events **'chills and rigors'** were more frequently reported in **dengue patients**, and many of these patients recovered once their fluid therapy was changed to normal saline infusion. Healthcare professionals are reminded to monitor these patients closely and follow the Clinical Practice Guidelines for Management of Dengue Infection in Adults (revised 2nd Edition).

Usage data revealed that the quantity of IVI succinylated gelatin used in government health facilities across Malaysia was almost the same for the first six months of 2014 compared to the same period in 2015. However, a spike in the **number of ADR reports** was observed in Jan-March 2015. Analysis of the 2015 reports revealed that there was no clustering in terms of the product batches involved.

As the thorough review revealed **no quality and safety issues** with the suspected products, one possible contributing factor to the spike in reports may be intensified monitoring of the products in clinical use.

International ADR Reports

On a global scale, the WHO international ADR database revealed that the main adverse events reported for IVI succinylated gelatin products were anaphylactic and allergic reactions (52%), followed by mild adverse skin reactions (35%) such as rash, pruritus and urticaria. This differed slightly from the pattern of ADRs reported in Malaysia, where the most commonly reported reactions were rigors (21%) and chills (15%), with anaphylactic reactions constituting 8% of the total adverse events.

Disclaimer: *Based on this review, no quality or safety issues were identified at this point in time with IVI succinylated gelatin products registered in Malaysia. The NPCB will continue to monitor the safety of these products closely, keep healthcare professionals informed of any new information that emerges, and take appropriate regulatory action if required*.

Advice to Healthcare Professionals:

- Please check the product package insert for information on the recommended method of administration, especially when administered by rapid infusion.
- Please adhere strictly to the recommended storage conditions to ensure the safety, quality and efficacy of the product.
- Healthcare professionals are advised to continue monitoring the use of these products, and report any suspected ADRs to the NPCB.

AMLODIPINE: POSSIBLE RISK OF BLURRED VISION
by Ng Chiew Seng

Blurred vision is defined as the loss of sharpness of vision and the inability to see fine details[1]. Blurred vision can be caused by a number of different things, from conditions that simply need correcting with glasses or lenses such as farsightedness and nearsightedness, to medical emergencies like acute glaucoma. Diabetic retinopathy, eye infection or inflammation, migraine and dehydration may also cause blurred vision.

Some drugs can cause blurred vision too. Examples include the following[2]:

- Antihistamines (particularly first generation antihistamines such as diphenhydramine, chlorpheniramine, promethazine and hydroxyzine, due to their anticholinergic effects)
- Corticosteroids (such as prednisolone, which can cause or worsen cataracts and glaucoma)
- Antipsychotics (due to their anticholinergic effects)
- Antineoplastics (such as cisplatin, oxaliplatin, cyclophosphamide, methotrexate, imatinib and tamoxifen)
- Ethambutol (due to optic neuritis)
- Hydroxychloroquine (due to disturbance of accommodation or corneal changes)

Local ADR Reports

Between year 2000 until April 2015, the NPCB has received a total of 487 spontaneous ADR reports related to blurred vision. Of these, amlodipine contributed the highest number of reports (34 reports; 7%), triggering a review by NPCB, as detailed below. Other drugs reported to cause blurred vision in Malaysia included perindopril (15 reports), metformin (13), lovastatin (11), diclofenac, prazosin, timolol (10 reports each), hydrochlorothiazide, simvastatin (9 reports each), and risperidone (8 reports).

Out of the 34 reports for amlodipine, majority (94.1%) were submitted by Ministry of Health (MOH) institutions whereas the rest were from product registration holders. Most of the patients were female (64.7%), and patient age ranged between 45-64 years (61.8%) with a mean age of 55 years. The time to onset of blurred vision post-amlodipine ingestion was mostly ≤1 hour (38.2%), and between 1 hour to 1 day (38.2%). About 16% of the cases reported an onset of >1 day, while the remaining two reports (6.5%) did not specify the time to onset. All the patients were reported to have recovered following drug removal[3].

Multiple brands of amlodipine were involved in the reports[3]. Visual impairment is documented as a less commonly observed side effect in marketing experience in local package insert of the originator Norvasc®[4]. Formulations of the various brands of amlodipine involved in the ADR reports are similar, and there is currently no evidence of association between excipients and vision disorders.

For all cases, the patients were not reported to have any underlying eye disorders. However, we cannot rule out other causes of blurred vision. For example, seven (7) patients had underlying diabetes mellitus, but the reports did not specify if the patients had diabetic retinopathy.

Blurred vision was the only adverse event mentioned in three (3) reports, whereas the other 31 reports contained other adverse events in addition to blurred vision. Some of these adverse events could be associated with blurred vision, such as headache (10 reports), oedema orbital (4 reports) and vomiting (3 reports)[3].

Globally, the WHO International ADR database contains 221 reports of blurred vision related to amlodipine.

Advice to Healthcare Professionals

- Blurred vision could be a symptom of visual impairment, which is documented as a less common adverse effect of amlodipine.
- Please advise patients, particularly those with underlying conditions such as diabetes mellitus and eye disorders like glaucoma or cataract, to seek medical advice if they suffer from blurred vision after taking amlodipine.

References:

1. Lusby FW (2014). Vision problems. Website: umm.edu/health/medical/ency/articles/vision-problems [Accessed: 24 August 2015].
2. Li J, Tripathi RC &Tripathi BJ (2008). Drug-induced ocular disorders.Drug *Saf* 31(2): 127-141.
3. The Malaysian Adverse Drug Reaction database, NPCB [Accessed: 30 April 2015].
4. Norvasc® Package Insert, Malaysia [version: August 2014].

CARDIOVASCULAR ADVERSE EVENTS RELATED TO DICLOFENAC
by Wo Wee Kee and Rema Panickar

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) used to relieve pain and inflammation. It is indicated for the treatment of rheumatism, acute attacks of gout, dysmenorrhea, and painful post-traumatic or post-operative inflammation. It acts by inhibiting the cyclooxygenase-1 (COX-1) and COX-2 enzymes. This stops synthesis of prostaglandin, which is an important mediator of pain and inflammation. The innovator products containing diclofenac sodium and diclofenac potassium were registered in Malaysia in 1986 and 1996 respectively.

The Malaysian Statistics on Medicines (MSOM) data for 2004-2010 revealed that diclofenac was the most commonly utilised NSAID every year, except in 2008. This survey recorded usage in 2010 of 3.3066 DDD/100 population/day[1].

Cardiovascular Risk of Diclofenac

In October 2012, the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) began a review on the cardiovascular (CV) safety of diclofenac.

In late 2013, EMA concluded that the **CV effects of long-term, high dose** (≥150mg daily) systemic diclofenac are similar to those of COX-2 inhibitors[2]. The benefits of diclofenac still outweigh the risks, however it is recommended that the precautions on the risks of arterial thromboembolic events with COX-2 inhibitors be applied to diclofenac as well.

These **risk minimisation steps** include[3]:

(i) contraindication in patients with serious underlying heart or circulatory conditions, such as heart failure, heart disease, circulatory problems or a previous MI or stroke.
(ii) patients with significant risk factors for CV events (hypertension, hypercholesterolemia, diabetes mellitus or smoking) should be treated with diclofenac only after careful consideration.

In Malaysia, the NPCB completed a full review on the safety of diclofenac in October 2015, resulting in a directive issued by the Drug Control Authority (DCA) for all products containing diclofenac (systemic formulation) to update their package inserts with information regarding the cardiovascular risk.

Similar safety information updates have been implemented by other international regulatory agencies, including Health Canada and the Therapeutic Goods Administration, Australia.

Overview of ADR reports on Diclofenac

From year 2000 until June 2015, the National Centre for Adverse Drug Reactions Monitoring received **2,106 adverse drug reaction (ADR) reports** related to diclofenac, comprising 4,188 adverse events[4]. The three most commonly reported System Organ Classes (SOC) were body as a whole - general disorders (1,500 events; 35.8%), skin and appendages disorders (1,478; 35.3%), and respiratory system disorders (467; 11.2%) **[Table 1]**.

The most commonly reported adverse events were periorbital oedema (588; 14%), itching (505; 12%), shortness of breath (297; 7.1%), orbital oedema (263; 6.3%) and rash (236; 5.6%).

Analysis of the **WHO International ADR database** showed a total of more than 73,000 reports suspected to be related to diclofenac. Skin and appendages disorders were also the highest reported SOC and Cardiovascular disorders ranked 8th with 4,300 reports, as listed in **Table 1** above. The most frequently reported cardiovascular adverse events worldwide were hypotension (1,216 reports; 28%), tachycardia and palpitations (1,105; 25%), hypertension (717; 16%), and circulatory failure (510; 12%).

Table 1: Comparison of Top 10 SOC and the top adverse events for diclofenac reported in Malaysia and worldwide

MALAYSIA	WHO ADR DATABASE
Body As A Whole- General Disorders (35.8%) - periorbital oedema, orbital oedema	**Skin And Appendages Disorders (30%)**
Skin And Appendages Disorders (35.3%) - itching, urticaria, rash	**Gastro-Intestinal System Disorders (25%)**
Respiratory System Disorders (11.2%) - shortness of breath	**Body As A Whole - General Disorders (18%)**
Vision Disorders (4.5%) - eye pruritus, teary eyes	**Immune System Disorders (16%)**
Gastro-Intestinal System Disorders (4.5%) - vomiting, nausea	**Neurological System Disorders (9%)**
Central & Peripheral Nervous System Disorders (3.1%) - dizziness, headache	**Respiratory System Disorders (8%)**
Cardiovascular-related Disorders (2.5%) - hypotension, palpitations	**Secondary terms (6%)**
Urinary System Disorders (1.1%) - acute renal failure	**Cardiovascular-related Disorders (6%)**
Application Site Disorders (0.4%) - injection site pain/ swelling	**Urinary System Disorders (5%)**
Musculo-skeletal System Disorders (0.3%) - muscle cramp, muscle ache	**Psychiatric Disorders (5%)**

Diclofenac-related Cardiovascular Adverse Events Reported in Malaysia

Among the ADR reports received for diclofenac, the cardiovascular-related SOC as a whole **ranked 8th place** with **52 reports** (2.5%). However, majority of these reports (46; 88.5%) involved cardiovascular adverse events such as hypotension, palpitations and tachycardia associated with reported **anaphylactic/allergic reactions**.

Of the remaining six (6) reports suspected to be related to cardiovascular adverse events, the ADRs reported were hypotension (2), myocardial infarction- MI (2), palpitation, and increased blood pressure. One of the cases reporting MI was submitted by the product registration holder and contained very limited details, therefore was assigned causality C5 (insufficient information). The second case involved a 50 year old male who was reported to have suffered an MI five (5) years after starting to take the suspected drugs. He was taking multiple self-prescribed painkillers including diclofenac 50mg when required, to treat chronic migraine. The patient subsequently recovered and this case was given the causality C3 (possibly-related to the suspected drugs).

MADRAC agreed that although the number of cardiovascular ADR reports related to diclofenac in Malaysia is small, underreporting cannot be ruled out. **Increased vigilance and monitoring** of cardiac adverse events in patients taking high-dose (≥150mg daily), long-term diclofenac treatment and patients with underlying cardiovascular disease is necessary.

The DCA issued a directive on 21 October 2015 for all diclofenac-containing products (systemic formulation) to update their package inserts with safety information related to the cardiovascular risk *[Ref: (30)dlm.BPFK/PPP/07/25]*. The updates include a new contraindication as mentioned below, strengthening of warnings, and additional adverse effects. Kindly refer to the directive (available on the NPCB website) and updated package inserts for detailed information.

Advice to Healthcare Professionals

- Diclofenac is now **contraindicated** in severe cardiac failure.
- Use the **lowest effective dose for the shortest duration** necessary to control symptoms.
- Generally **not recommended** for use in patients with established cardiovascular disease or uncontrolled hypertension. If needed, patients with significant cardiovascular risk factors should only be treated with diclofenac after careful consideration and at doses of ≤100mg daily if used for more than four weeks.
- **Please report** any adverse events suspected to be related to the use of diclofenac to the NPCB, to ensure comprehensive data analysis for drug safety profiling.

References:
1. Malaysian Statistics On Medicines (MSOM) 2010, Ministry of Health Malaysia.
2. EMA. New safety advice for diclofenac: New measures aim to minimise cardiovascular risks. [25 September 2013]
3. HSA. New contraindication on the use of high dose diclofenac for more than four weeks in selected groups of patients. http://www.hsa.gov.sg [27 February 2014]
4. National Centre for Adverse Drug Reaction database. [Accessed: April 2014]

REGULATORY MATTERS

DIRECT HEALTHCARE PROFESSIONAL COMMUNICATIONS (DHPCs) REVIEWED AND APPROVED BY NPCB IN 2015

Direct Healthcare Professional Communications (DHPCs) are issued by product registration holders with approval from NPCB, to increase awareness on particularly important safety issues or changes in prescribing information involving a product. The following table lists all the DHPCs approved by the NPCB in 2015.

NO.	DATE	PRODUCT NAME (ACTIVE INGREDIENT)	DRUG SAFETY ISSUE
1	12 Feb	Artrodar® (diacerein)	New restrictions of use to limit the risk of severe diarrhoea and effects on the liver
2	23 Mac	Xgeva® 120mg Solution for Injection (denosumab)	Updated recommendations to minimise the risk of severe symptomatic hypocalcaemia (SSH) and osteonecrosis of the jaw (ONJ)
3	4 Aug	Motilium® (domperidone)	New recommendations to minimise cardiac risk
4	13 Aug	Forxiga® (dapagliflozin)	Risk of diabetic ketoacidosis during treatment with sodium glucose co-transporter 2 (SGLT2) inhibitor - dapagliflozin
5	14 Dec	Cellcept® (mycophenolate mofetil)	Teratogenic risk – important new pregnancy prevention advice for women and men

MONTELUKAST: RISK OF THROMBOCYTOPENIA

Montelukast is a selective leukotriene receptor antagonist that inhibits the effects of cysteinyl leukotrienes in the airways. It has been associated with the risk of thrombocytopenia, resulting in a directive being issued by the Malaysian Drug Control Authority (DCA) on 28 September 2015 to update the local package inserts (PIs) with information on this side effect.

Thrombocytopenia is characterised as a platelet count of 150 x 10^3 per µL or less, that may increase the risk of bleeding such as epistaxis, bruising, petechiae, and gingival bleeding. Drug-induced thrombocytopenia is relatively common; it often occurs within 5 - 7 days of initiating therapy and the condition usually resolves within 7 - 14 days upon drug discontinuation.

Background of the Safety Issue

Following three (3) reports of thrombocytopenia linked with montelukast use in Japan since 2012, the Pharmaceuticals and Medical Devices Agency (PMDA) Japan conducted an investigation on the safety of montelukast sodium based on the opinions of expert advisors and available evidence. This resulted in product PI updates to include 'thrombocytopenia' under the section 'Clinically significant adverse reactions'.

Investigations by the product registration holder revealed a total of **109 post-marketing reports associated with thrombocytopenia** across the globe since Singulair® was first marketed in 1998 until 28 October 2014. It was found that this adverse event affected patients of all ages (range 1 - 93 years), and the median onset of reaction was 16 days after starting treatment. Out of the 109 reports, 24 reports (22%) reported positive dechallenge and three (3) positive rechallenge, while 22 reports (20%) had confounding factors such as concurrent medication and/or underlying diseases such as viral disease that may have contributed to the adverse event.

Local Scenario

There are currently 35 registered montelukast products in Malaysia, which are available as tablets, chewable tablets and oral granules. It is approved for the prophylaxis and chronic treatment of asthma in adults and paediatric patients aged 12 months and above, and for the relief of daytime and night-time symptoms of seasonal allergic rhinitis in patients aged 2 years and older.

ADR Reports

Since year 2000, the NPCB has received **94 montelukast-related ADR reports** with a sum of **160 adverse events**. As of now, **no reports of thrombocytopenia** have been received locally.

Most of the adverse events were made up of skin and appendages disorders (34 cases, 21%) such as rash and pruritus; gastro-intestinal system disorders (31 cases, 19%) such as diarrhoea and vomiting; and psychiatric disorders (31 cases, 19%) such as insomnia, aggressive behaviour and hallucination. Majority of the cases (78%) were caused as C3 (possibly-related to the drug) as there were concurrent medications which may have contributed to the ADRs.

The prescribing information of Singulair® has been updated with this side effect, and all other products containing montelukast are required to update their PIs as mentioned in the DCA directive [Ref: *(31)dlm.BPFK/PPP/07/25]* which may be downloaded from the NPCB website.

Advice to Healthcare Professionals

- Montelukast should be used with caution in patients on anti-platelet therapy such as aspirin.
- Counselling points: Advise patients or their caretakers to be on the lookout for signs of bleeding such as nose bleeds, bleeding gums when brushing teeth, slow healing of wounds, and bruising.
- Screen patients on montelukast for signs of bleeding or slow healing during follow-up appointments.
- Monitor platelet levels when necessary, e.g. when a patient presents with bloody stool.
- Please report to the NPCB all adverse events suspected to be related to the use of montelukast.

DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITORS: RISK OF SEVERE JOINT PAIN

Overview

Dipeptidyl Peptidase-4 (DPP-4) inhibitors, or the 'gliptins', belong to a class of oral antidiabetic drugs that are used with diet and exercise. Inhibition of the enzyme DPP-4 temporarily stops the degradation of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic hormone (GIP) at the gastrointestinal tract, thereby prolonging the effects of GLP-1 and GIP. Both GLP-1 and GIP cause a glucose-dependent increase in insulin secretion, and GLP-1 also contributes to glucose homeostasis by exerting effect on insulin biosynthesis and inhibiting glucagon release. This, in turn, leads to a net antihyperglycaemic effect.

Background of the Safety Issue

In August 2015, the NPCB received a safety alert from the United States Food and Drug Administration (US FDA) about the risk of DPP-4 inhibitors causing joint pain that can be severe and disabling. The FDA review of their Adverse Event Reporting System database identified 33 cases of severe arthralgia suspected to be related to the use of DPP-4 inhibitors reported between October 2006 (when the first DPP-4 inhibitor was approved) to December 2013. Analysis of the reports revealed that patients may start to have symptoms of joint pain anywhere from **one day to years** after they started taking the drugs, 10 of the cases reported patients requiring hospitalisation, and with discontinuation of the medicine, symptoms resolved in less than a month. When restarted on the same drug or a different DPP-4 inhibitor, some patients experienced a recurrence of symptoms.

Local Scenario

There are currently 25 products containing DPP-4 inihibitors (namely sitagliptin, vildagliptin, saxagliptin and linagliptin) registered in Malaysia. These are available as single-ingredient products or in combination with metformin.

Since the drug was first registered in 2007, the NPCB has received a total of **291 reports** with 461 adverse events suspected to be related to DPP-4 inhibitors. The adverse events reported were mostly mild, such as rash (30), nausea (20), itching (18), diarrhoea (17), and headache (16).

There were **three (3) reports related to joint pain** involving sitagliptin. The first case was reported by a physician concerning a 45-year old male who was started on sitagliptin for the treatment of type-2 diabetes mellitus. One week after starting the drug, the patient experienced lethargy, joint pain and fever-like feeling with chills, which were considered to be disabling as he could not last working throughout the day. After discontinuing the drug, the patient recovered. The physician felt that the adverse events were related to therapy with the drug.

The other two reports on joint pain involved women aged 70 and 72 years respectively. Both were started on sitagliptin 100 mg daily and were reported to experience joint pain as well as body ache. Sitagliptin therapy was continued in spite of the adverse events. Both reports were submitted by the product registration holder, and no further information was provided.

All three cases were given causality C3 (possibly-related to drug) due to presence of concurrent medications that could have led to the development of the adverse events, and no rechallenge information to support the certainty of the drug causing the adverse event.

Advice to Healthcare Professionals

- Advise patients to seek immediate medical attention if they experience severe and persistent joint pain.
- DPP-4 inhibitors should be considered as a possible cause for severe persistent joint pain, and the drug should be discontinued if appropriate.
- Please report any adverse drug reactions involving DPP-4 inhibitors to the NPCB.

FUSAFUNGINE: RISK OF SERIOUS ALLERGIC REACTIONS

Fusafungine is an antibacterial agent with anti-inflammatory properties that displays its bacteriostatic activity against microorganisms responsible for both infections and super-infections of the respiratory tract. It has been developed as a topical oral and/or nasal spray. Recently, its use has been associated with the **risk of serious allergic reactions, including anaphylaxis.**

Background of Safety Issue

On 11 September 2015, NPCB received an alert that the European Medicines Agency (EMA) had started a risk and benefit reassessment on the usage of products containing fusafungine. This was upon the request of the Italian Medicines Agency (AIFA) which had highlighted an increased number of reports related to serious allergic reactions with the drug. The majority of the adverse events reported involved bronchospastic reactions (excessive and prolonged contractions of the airways' muscles leading to breathing difficulty). In addition to this, the AIFA had also probed the efficacy of fusafungine therapy and the risk of antibiotic resistance.

Local Scenario

In Malaysia, there is one registered product containing fusafungine, which is Locabiotal® Solution. It is currently approved for local antibacterial adjuvant treatment of diseases of the upper respiratory tract (in adults and adolescents aged 12 years and above). Since it was first registered in 1997, NPCB has received **three (3) ADR reports** related to its use, with adverse events such as **chest tightness, shortness of breath, breathing difficulty and oesopharyngeal irritation.**

The NPCB has communicated with the product registration holder of Locabiotal® Solution and the package insert has been updated with information on the risk of serious allergic reactions. Further review of post-marketing data by the product registration holder found that the majority of allergic events involved paediatric patients below the age of 12 years. It was also shown that serious allergic reactions are more frequently reported in patients with an existing allergic background.

The NPCB will continue to monitor this safety issue to ensure a positive risk-benefit balance for fusafungine.

Summary of updated prescribing information for Locabiotal® Solution:

New Contraindications

- Children under 12 years
- Patients with allergic tendencies and bronchospasm

Warnings and Precautions

In case of allergic reaction, Locabiotal® should be stopped and not be re-administered. Due to the risk of anaphylactic shock, in case of respiratory, laryngeal or cutaneous (pruritus, generalised erythema) signs, an urgent intramuscular injection of adrenaline (epinephrine) may be necessary. The usual dose of adrenaline is 0.01 mg/kg by intramuscular route. The dose may be repeated after 15 – 20 minutes if needed.

GUIDE FOR ADR REPORTERS

NEW AND IMPROVED ADR REPORTING FORM ('BLUE FORM')

The NPCB has updated the ADR reporting 'blue form' for healthcare professionals as part of our continual efforts to increase the quality of ADR reports received in Malaysia.

In 2010, a study conducted on ADR forms from ten (10) different countries (including the United Kingdom, the United States of America, Canada and Australia) found that the **Malaysian ADR form scored the highest** on the point system used in the study, with **16 out of 18 points**[1].

This form has recently been updated as the NPCB aims to:

(i) improve completeness of information collected;
(ii) improve clarity of the form;
(iii) provide guidance to reporters.

What's new?

New features of the updated form include:

- New columns: seriousness of reaction, type of report (initial/ follow-up);
- More specific column headings;
- A reminder to state patient pregnancy status, allergies, hepatic/renal dysfunction, where relevant.
- Full contact details for NPCB;
- Marked mandatory fields to be completed;
- An **ADR Reporting Guide**, as detailed overleaf.

Please tell us what you think

Efforts have been taken to make our ADR forms user-friendly, easy to understand, and accessible. We would greatly appreciate any **feedback or suggestions** for further improvement.

ADRs should be reported to the NPCB using one of the following forms, which can be downloaded from our website (portal.bpfk.gov.my), filled, and then submitted to the NPCB via post, fax or email.

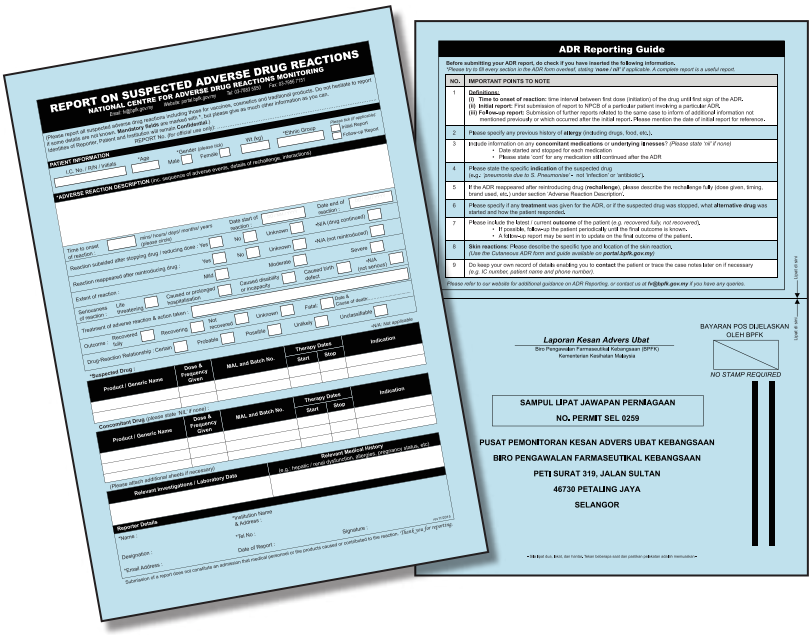
REPORTER	ADR FORM OF CHOICE
Healthcare Professionals	• **ADR 'blue form'**
Pharmaceutical Industry	• **Suspect Adverse Reaction Report Form (CIOMS* Form I)**
Consumer/Public	• **AEFI* form** (specifically for minor reactions after immunisation) • **Consumer Complaints Relating to Medicines** (for any complaints related to quality, safety and efficacy of medications, including prescription medicines, traditional products, or to report unregistered products.

For more details, please contact:
The Drug Safety Monitoring Centre,
NPCB Pharmacovigilance Section.
Tel.: 03-7801 8464 Fax:03-79567151
Email: fv@bpfk.gov.my
Website: **portal.bpfk.gov.my → Public**

**CIOMS: Council for International Organisations of Medical Sciences*
AEFI: Adverse Event Following Immunisation

ADR Reporting Guide Provided on Updated Form

NO.	IMPORTANT POINTS TO NOTE
1	**Definitions:** **(i) Time to onset of reaction:** time interval between first dose (initiation) of the drug until first sign of the ADR. **(ii) Initial report:** First submission of report to NPCB of a particular patient involving a particular ADR. **(iii) Follow-up report:** Submission of further reports related to the same case to inform of additional information not mentioned previously or which occurred after the initial report. Please mention the date of initial report for reference.
2	Please specify any previous history of **allergy** (including drugs, food, etc.).
3	Include information on any **concomitant medications** or **underlying illnesses?** *(Please state 'nil' if none)* • Date started and stopped for each medication • Please state 'cont' for any medication still continued after the ADR occurred
4	Please state the specific **indication** of the suspected drug (e.g.: *'pneumonia due to S. Pneumoniae'* - not 'infection' or 'antibiotic').
5	If the ADR reappeared after reintroducing drug (**rechallenge**), please describe the rechallenge fully (dose given, timing, brand used, etc.) under section 'Adverse Reaction Description'.
6	Please specify if any **treatment** was given for the ADR, or if the suspected drug was stopped, what **alternative drug** was started and how the patient responded.
7	Please include the latest / current **outcome** of the patient *(e.g. recovered fully, not recovered)*. • If possible, follow-up the patient periodically until the final outcome is known. • A follow-up report may be sent in to update on the final outcome of the patient.
8	**Skin reactions:** Please describe the specific type and location of the skin reaction. *(Use the Cutaneous ADR form and guide available on **portal.bpfk.gov.my**)*
9	Do keep your own record of details enabling you to **contact** the patient or trace the case notes later on if necessary *(e.g. IC number, patient name and phone number)*.



Reference:
1. Bandekar MS, et al. (2010). Quality check of spontaneous adverse drug reaction reporting forms of different countries.*Pharmacoepidemiol Drug Saf.*19(11):1181-5.

GUIDE FOR ADR REPORTERS

ADR REPORTS INVOLVING ANTITUBERCULOSIS DRUGS

First and foremost, the Drug Safety Monitoring Centre would like to thank all reporters for the continuous effort in reporting adverse drug reactions. Although the number of reports received has increased tremendously every year, many of the reports submitted contain insufficient details required to carry out the necessary safety analysis and causality evaluation.

In this issue of the MADRAC Bulletin, we focus on the reporting for anti-tuberculosis (anti-TB) drugs. In 2014 alone, the NPCB received **118 ADR reports** involving the four anti-TB drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol), of which almost 80% reported the use of combination products containing all four drugs in one tablet. However, **only 10 reports** detailed the stepwise rechallenge of anti-TB drugs which was performed after the ADR occurred. Information on **rechallenge and final outcome** of the patient is **vital** to compare the safety profiles between brands, combination products and single active ingredient products.

Besides making sure that the report is completely filled in, here are several **points to ponder** when reporting adverse events for anti-TB drugs:

Reports involving serious ADRs requiring urgent attention	**An initial report may be submitted first, then a follow-up report sent in after a final outcome is known.** Follow-up report should include details on dechallenge/ rechallenge, final outcome and the final antituberculosis therapy given (Note: Please include date of initial report or attach a copy of initial report for reference purposes).
Reports involving mild to moderate ADRs	**If it does not involve a serious ADR, please follow-up the patient until the final outcome is attained before submitting the report.** Do include details of the final antituberculosis therapy given.
If stepwise rechallenge or desensitisation is performed, please report the following:	**Time of rechallenge/desensitisation.** Dose of the drug(s) used in rechallenge/desensitisation. **Reactions observed.** Treatment of adverse reaction and action taken. **Outcome of the rechallenge/desensitisation.**
Adverse Reaction Description	**Describe the adverse events in sequence with a notable time frame.** If it involves skin adverse reactions, please use the Cutaneous ADR Classification Form. **If it involves hepatic enzyme anomalies, please include the liver function test results.**
Drug details	**Specify the product brand name and registration number (MAL no).** **Include the dosage, frequency and duration.**
Other important details	**Additional sheets may be attached if necessary to describe further details.** Reporter details and contact number should be included in case further information is required.

The NPCB thanks you for reporting suspected ADRs. These reports are an essential part of ensuring the safe use of medicines as well as the safety of patients in Malaysia. If you have any questions, please contact us at 03-7801 8462 / 7801 8470 or send an email to fv@bpfk.gov.my.