



# MADRAC *Newsletter*

For healthcare professionals only

Volume 20 | August 2016

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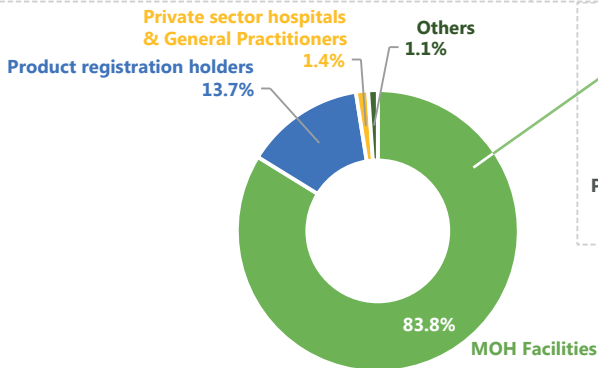
**13,675**

Total ADR Reports received

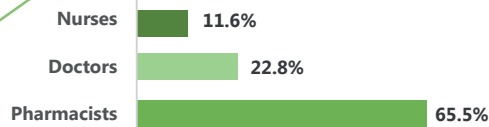


**12,603**

Viable New Reports



### MOH Facilities breakdown



### Top 3 System Organ Classes

- 1 Skin and Subcutaneous Tissue Disorders
- 2 General Disorders and Administration Site Conditions
- 3 Nervous System Disorders



### Completeness Score

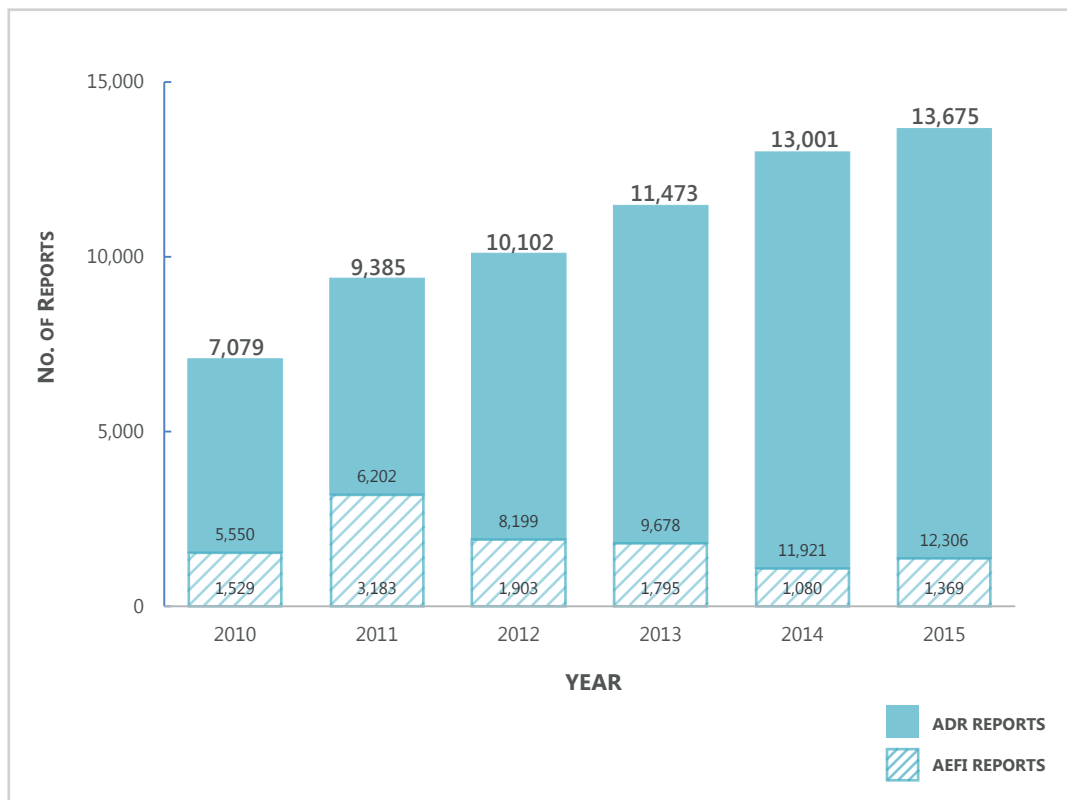
| Year | Score |
|------|-------|
| 2014 | 0.63  |
| 2015 | 0.72  |

## Annual Report for 2015

# Spontaneous Adverse Drug Reactions (ADRs) Reported in Malaysia (2015)

The NPRA received a total of 13,675 adverse drug reaction (ADR) reports in 2015, showing a 5.2% increase from the previous year (Figure 1). Once these reports were processed to exclude any duplicates, follow-up reports to cases sent in earlier, and rejected reports, a total of 12,603 viable new reports were entered into the Malaysian ADR database. These included 1,369 reports of Adverse Events Following Immunisation (AEFI) [please refer to page 5-6 for further details].

Figure 1: Total Number of ADR/ AEFI Reports Received in Malaysia (2010-2015)



## Quality of ADR Reports

While the quantity of ADR reports received in Malaysia has been increasing each year, the NPRA is also looking into the quality of reports to ensure that complete and accurate information is obtained for better quality assessment which will aid drug safety monitoring.

The World Health Organisation (WHO) Collaborating Centre for International Drug Monitoring, Uppsala, Sweden, measures report quality using the VigiGrade™ Completeness Score. This score ranges from 0.07 (poorly documented case) to 1 (well-documented) and is a measure of the amount of clinically relevant information provided in a report.

Through continuous efforts to educate reporters on the importance and techniques of quality reporting, the NPRA has seen an increase in our average Completeness Score

from **0.45** in 2010-2013, to **0.63** in 2014, and **0.72** in 2015.

## Who were the Top ADR Reporters?

Following the same trend as previous years, Ministry of Health (MOH) staff submitted majority of the reports (83.8%), as shown in Figure 2. MOH pharmacists were the highest reporters, followed by MOH doctors, and the product registration holders. There was a decrease in the number of reports received from private sector doctors, which is a cause for concern as unreported ADRs will delay or prevent the detection of drug safety issues.

Figure 2: ADR/ AEFI Reports by Reporter Category (2010-2015)

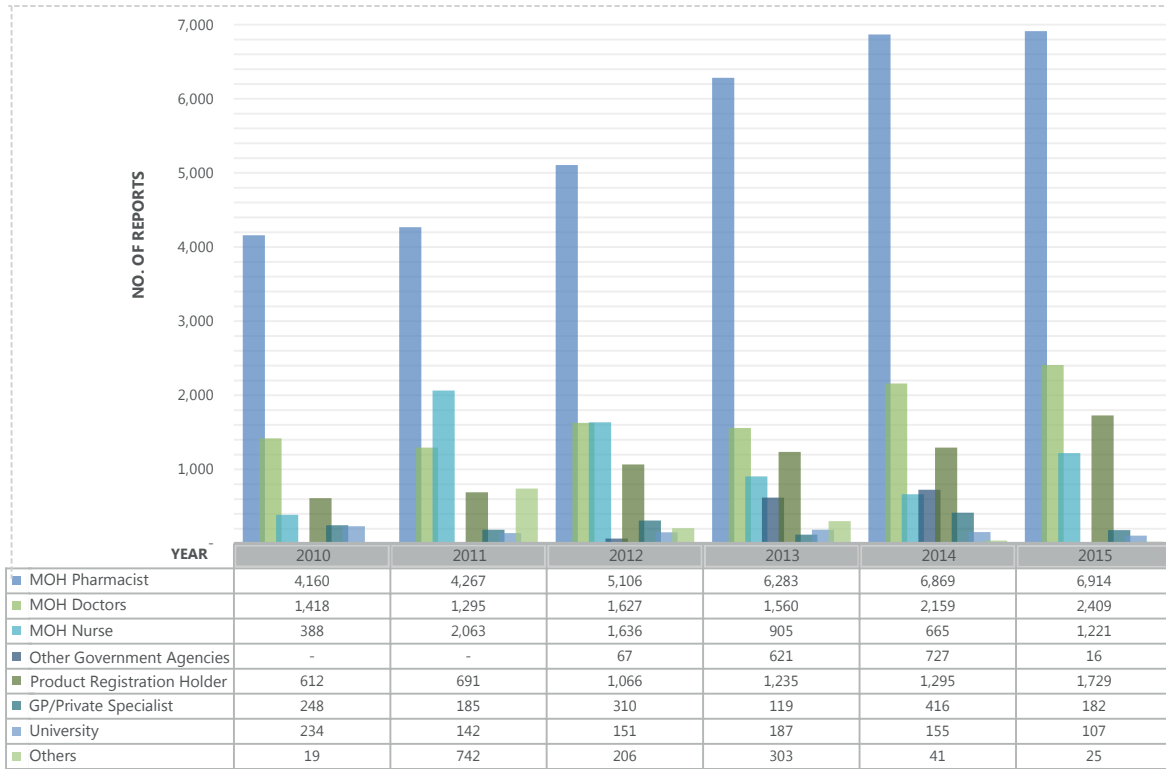
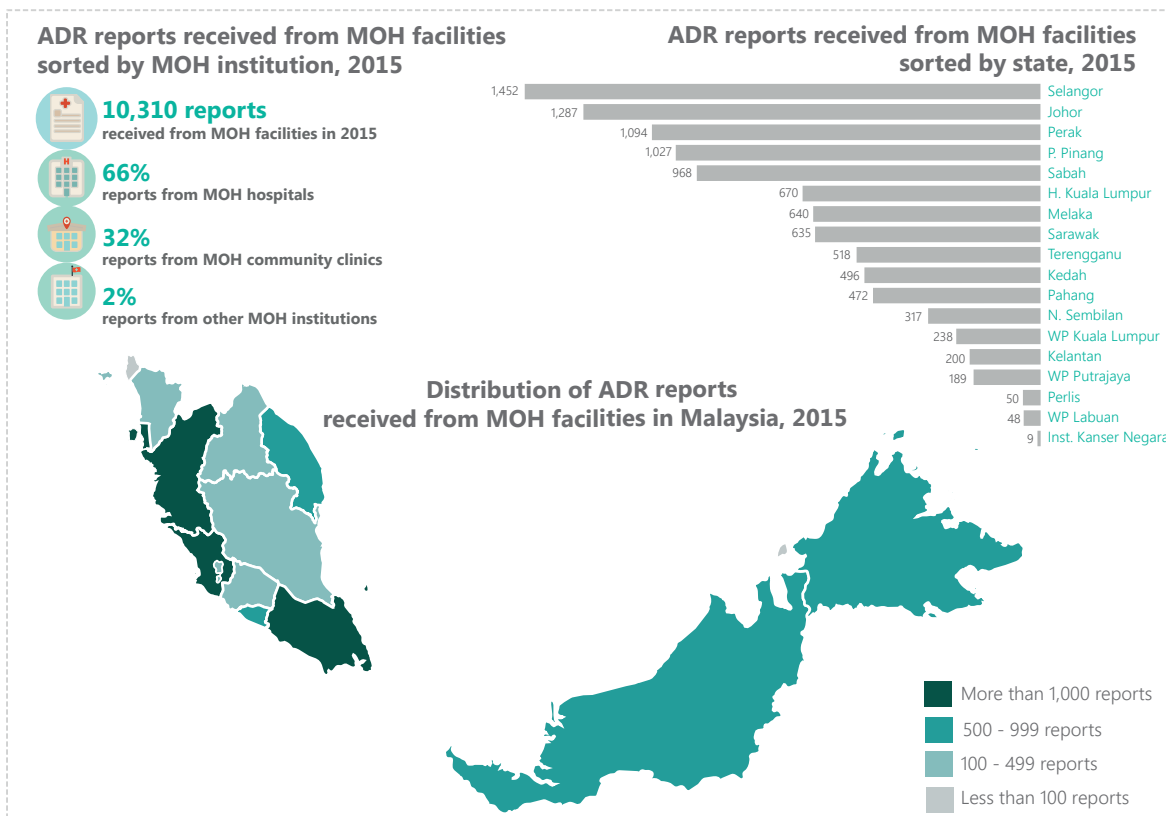


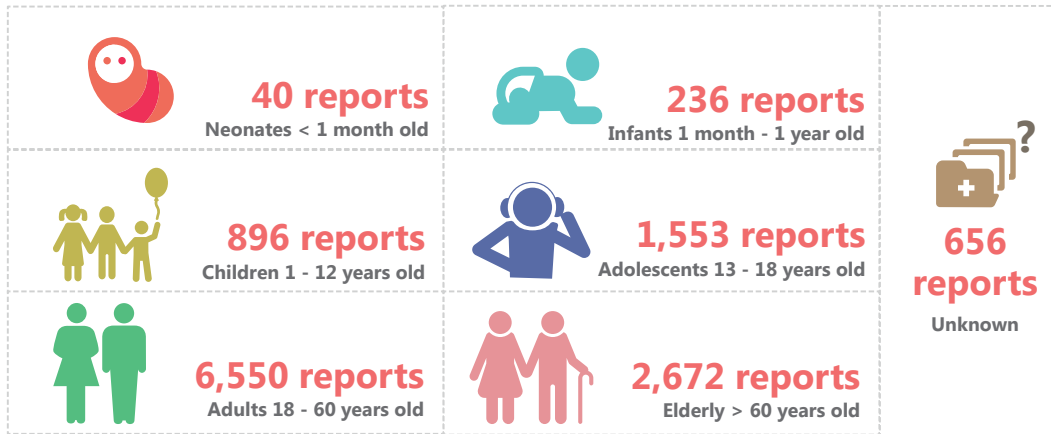
Figure 3: ADR/ AEFI Reports Received from MOH Facilities According to State (2015)



## What do we know about the Patients Affected?

Among the ADR reports received for 2015, 57% involved female patients, 41% male patients, while the remaining 2% of the reports did not specify the patient's gender. When analysed by patient age group, it was found that 52% of the reports involved adults aged between 18 to 60 years, 21.2% involved the elderly aged above 60 years, and about 9.3% involved children aged 12 years and below.

Figure 4: ADR Reports by Patient Age Group



## What Were the Main Types of Reactions Reported?

The ADR reports for 2015 involved a total of 20,665 adverse events, with 'Skin and subcutaneous tissue disorders' making up 30% of the adverse events reported. The top ten System Organ Classes (SOC) of adverse events based on Medical Dictionary for Regulatory Activities (MedDRA) reported are shown in Figure 5.



Figure 5: Top Ten System Organ Classes of Adverse Events Reported

## A Focus on Adverse Events Following Immunisation (AEFI)

The World Health Organisation (WHO) defines an Adverse Events Following Immunisation (AEFI) as:

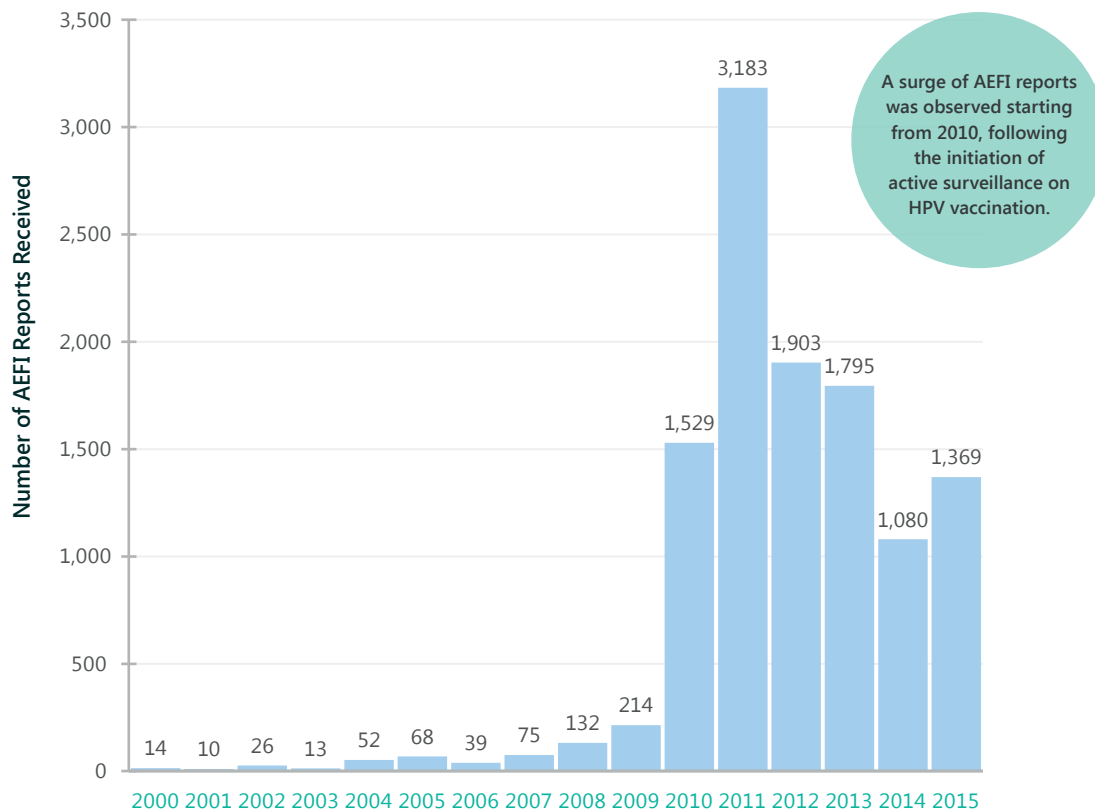
*Any untoward medical occurrence which follows immunisation and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.*

### Statistics on AEFIs

Between years 2000 to 2015, the National ADR Monitoring Centre, NPRA has received a total of 11,502 AEFI reports. As seen in Figure 6, a surge of AEFI reports was observed starting from 2010, following the initiation of active surveillance on Human Papilloma Virus (HPV) vaccination when the vaccine was introduced into the National Immunisation Program in September 2010.

In 2015, a total of 1,369 AEFI reports were received, with 2,597 adverse events. This was an increase of 26.8% as compared to 1,080 reports in 2014. Majority of the AEFI reports received in 2015 involved the HPV vaccines (1,094 reports, 79.9%), while the remaining 275 AEFI reports (20.1%) involved other vaccines registered in Malaysia.

**Figure 6: Total Number of AEFI Reports Received in Malaysia (2000-2015)**

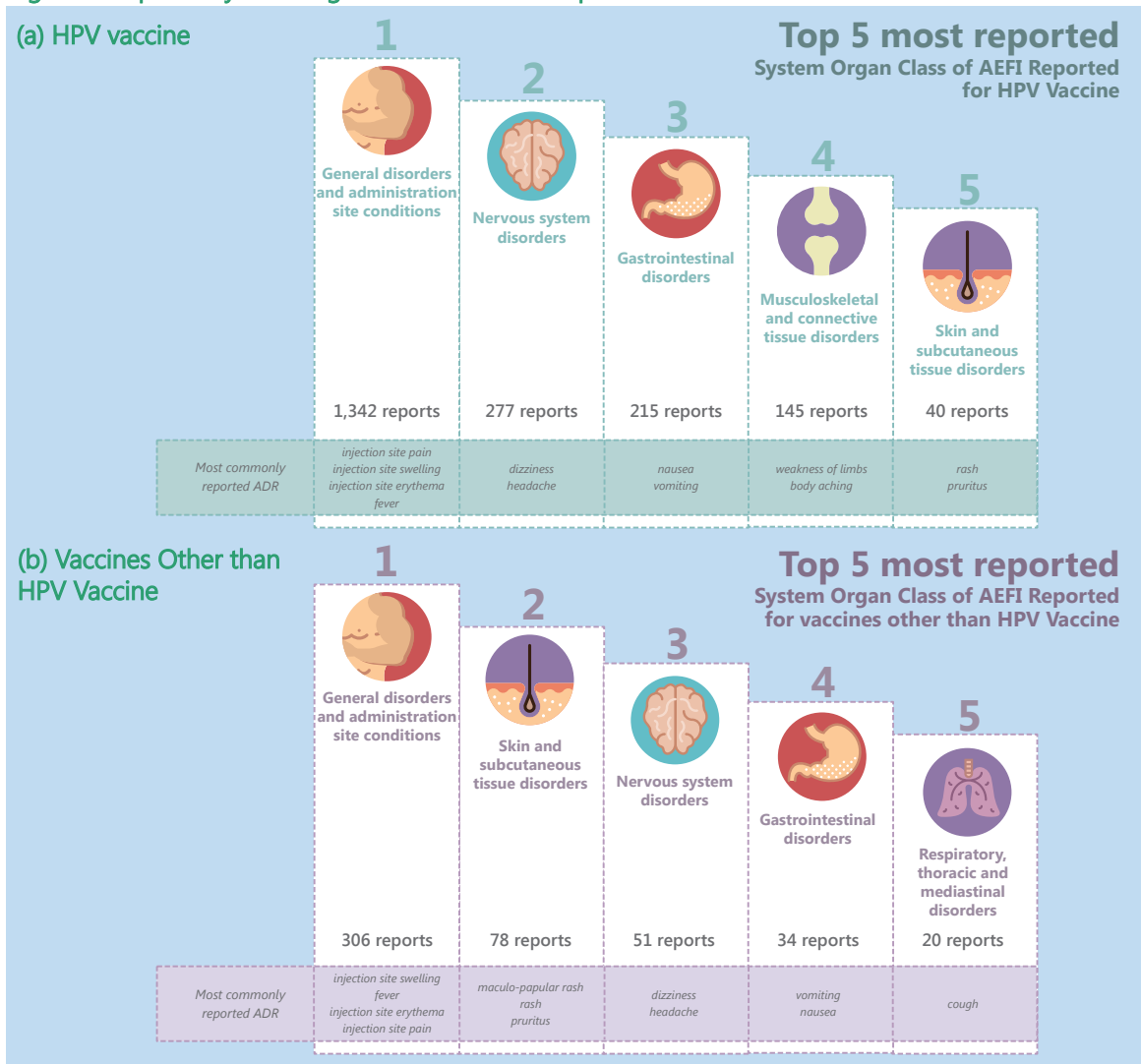


### Type of Reactions

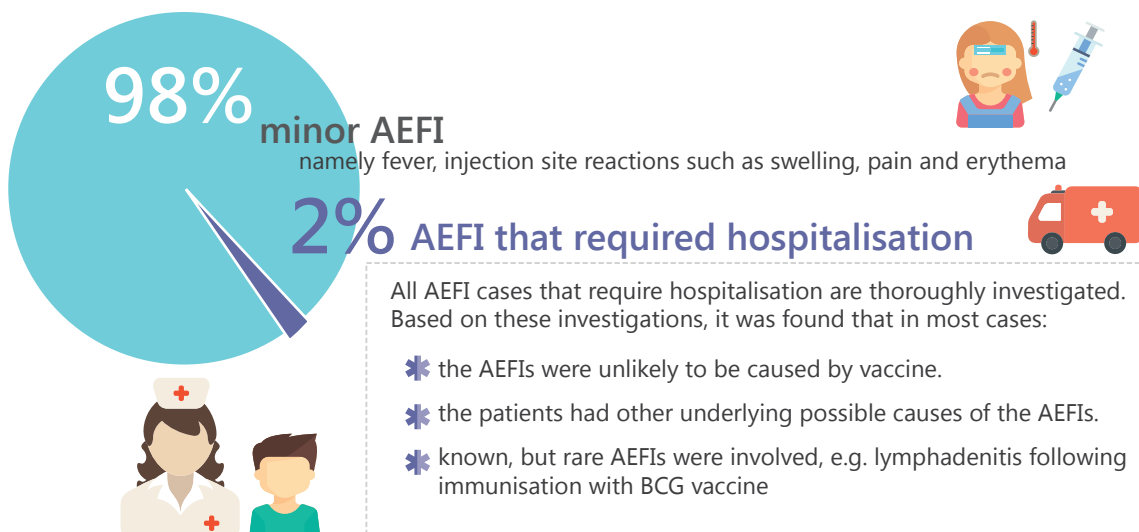
For HPV vaccines, a total of 2,032 adverse events were reported in 2015. As seen in Figure 7, the MedDRA System Organ Class (SOC) 'General Disorders and Administration Site Conditions' such as injection site pain, injection site swelling, injection site erythema and fever contributed the most reports (66.0%). Other commonly reported SOCs and their adverse events are also described in Figure 7(a).

For vaccines other than HPV, a total of 565 adverse events were reported in 2015. 'General Disorders and Administration Site Conditions' contributed the most reports (54.2%), followed by 'Skin and Subcutaneous Tissue Disorders' (13.8%) and 'Nervous System Disorders' (9.0%) with the commonly reported AEFIs are described as in Figure 7(b).

Figure 7: Top Five System Organ Classes of AEFI Reported for:



## 2015 Summary of AEFI Reporting



In addition, the incidence rate of AEFI reported in Malaysia is lower than the incidence rate reported by the World Health Organisation (WHO).

For example, the incidence rate of BCG lymphadenitis reported by WHO is 1 per 1,000 - 10,000 doses, and the incidence rate of BCG lymphadenitis reported in Malaysia is 0.14 per 10,000 doses.

## Regulatory Matters

# Bisphosphonates: Risk of osteonecrosis of the external auditory canal

Bisphosphonates are a group of medicines used in the treatment of osteoporosis and Paget's disease, as well as in cancer regimens for metastatic bone cancer and multiple myeloma. Examples of bisphosphonates include alendronate, clodronate, ibandronic acid, amidronate, risedronate and zoledronic acid. Recently, bisphosphonates have been reported to be associated with the adverse event osteonecrosis of the external auditory canal (EAC).

Osteonecrosis of the EAC is a rare condition characterised by the ulceration of the floor of the bony external auditory canal with an underlying bony necrosis. The pathophysiology is still unknown, but the mechanism was suggested to be similar to that of osteonecrosis of the jaw which is known to be associated with bisphosphonate use.

NPRA has reviewed this safety issue and a directive [*Bil. (38) dlm. BPFK/PPP/07/25*] was issued for all local package inserts (PIs) for bisphosphonate-containing products to be updated with information on the risk of osteonecrosis of the EAC.

## Background of the safety issue

In September 2015, the European Medicines Agency (EMA) completed a review on the risk of osteonecrosis of the EAC with the use of bisphosphonates<sup>1</sup>. Having considered the evidence from clinical trials, published literature and spontaneous reporting, it was concluded that although the risk is very rare,

recommended measures should be taken to further minimise this risk, including an update to the PIs to highlight the new safety information.

On a global scale, a total of **29 reports** of osteonecrosis of the EAC were associated with bisphosphonate use. The reports were either from clinical literature (11), identified by the product registration holders (10), or from the European regulatory agencies database (8). It was found that most cases of osteonecrosis of the EAC were linked to long-term use of bisphosphonates (two years or longer). Other risk factors included steroid use, chemotherapy and/or local trauma or infection.

## Local Scenario

In Malaysia, there are currently **30 products** containing bisphosphonates registered with the Drug Control Authority (DCA). These products are available in tablet or injection formulations, either as single agents or combination products.

Since year 2000, the NPRA has received **350 ADR reports** with **628 adverse events** suspected to be related to bisphosphonates<sup>3</sup>. With regards to this current safety issue, there were eight (8) reports of osteonecrosis (6) and osteonecrosis of jaw (2). There was also one (1) report of decreased hearing associated with alendronate use, which improved upon stopping the medication.

## References

1. EMA (2015). Recommendations for update of product information Bisphosphonates – Osteonecrosis of the external auditory canal (EMA/PRAC/590240/2015)
2. National ADR Database, NPRA [Accessed February 2016].

## Advice to Healthcare Professionals

- Suspect the possibility of osteonecrosis of the external auditory canal in patients receiving bisphosphonates if patient presents with ear symptoms, including ear pain, otorrhea and chronic ear infections.
- **Counselling:** Advise patient to report any ear pain, discharge from the ear, or any ear discomfort during bisphosphonate treatment.
- Report any adverse events associated with bisphosphonate use to the NPRA.

## Regulatory Matters

# Cajeput Oil (*Melaleuca leucodendran*): Risk of glottal spasm and bronchospasm

Cajeput oil is an essential oil derived from a local plant called *Kayu Putih* (*Melaleuca leucodendran*)<sup>1</sup>. It is popularly known as *minyak telon* or *minyak kayu putih*, and is traditionally used to provide relief of muscle pain, muscle cramps, muscle strains and abdominal discomfort. It is very commonly used in infants and small children during post-natal care to provide relief of bloating or abdominal distension, as well as to give warmth after a bath.

of body aches, abdominal discomfort and to provide warmth in infants after a bath. Five (5) of these products are indicated for use in infants and children.

From year 2001 to August 2015, the National ADR Monitoring Centre, NPRA has received **four (4) ADR reports** associated with the use of cajeput oil-containing products, all of which involves children aged between 8 days to 14 months.

Three (3) of the reports documented three (3) skin adverse drug reactions, namely contact dermatitis, papular rash, and skin hyperpigmentation. One (1) report involved accidental ingestion, in which the patient experienced vomiting.

NPRA has reviewed this safety issue and a directive [*Bil. (44) dlm. BPFK/PPP/07/25*] was issued for all local package inserts (PIs) for cajeput oil containing products to be updated with information on the risk of glottal spasm and bronchospasm.

## Background of the safety issue

Preparations containing the oil should not be applied to the faces of infants or small children, as glottal spasm might occur<sup>2</sup>. A literature review has shown that there are warnings of adverse reactions such as glottal spasm, bronchospasm or even asthma-like attacks in paediatric patients when cajeput oil is applied on the face<sup>3</sup>. This could result in breathing difficulties in infants and small children.

## Local Scenario

In Malaysia, there are a total of **20 products** containing cajeput oil for topical use registered under the Drug Control Authority (DCA) since year 2001. In general, products that contain cajeput oil are formulated in combination with other mineral oils, and are indicated for the relief

## References

1. Global Information Hub on Integrated Medicine (Globinmed).
2. Physician's Desk Reference (PDR) for Herbal Medicines 2nd Edition (2000) *p136*.
3. Cajeput Oil in: Natural Medicines. Sommerville (MA): Therapeutic Research Center; 2015 [cited 09 Jun 2016]. Available from: <https://naturalmedicines.therapeuticresearch.com>.
4. National ADR Database, NPRA [Accessed June 2016].

## Advice to Healthcare Professionals

- Consider cajeput oil as a triggering factor in paediatric patients presenting with asthma or other respiratory problems, as it has been reported that cajeput oil preparations may cause breathing problems that mimic asthma-like symptoms.
- Advise parents and caretakers NOT to apply cajeput oil containing products (*minyak telon*) on or around the face of the child.
- Educate parents and caretakers to be alert on the risk of breathing difficulty with the use of cajeput oil products, and to seek immediate medical attention if the child experiences any breathing problems.
- Please report to NPRA any adverse event related to cajeput oil or any other essential oil-containing products.



## Regulatory Matters

# Glivec® (imatinib) and Tasigna® (nilotinib): Risk of Hepatitis B Reactivation

Tyrosine kinase inhibitors (TKIs) are an important new class that interferes with specific cell signalling pathways and thus allows targeted therapy for specific malignancies<sup>1,2</sup>.

## Background of the safety issue

The NPRA received a safety alert from the European Medicines Agency (EMA) on the risk of Hepatitis B Virus (HBV) reactivation in patients treated with BCR-ABL TKIs, namely imatinib and nilotinib.

HBV reactivation is characterised by an abrupt rise of HBV DNA during or closely after chemotherapy in patients with previously inactive or resolved HBV infection.

A cumulative review of data from clinical trials and post-marketing experience conducted by the Pharmacovigilance Risk Assessment Committee (PRAC) EMA, has shown that HBV reactivation has occurred in chronic HBV carriers after receiving treatment with BCR-ABL TKI. Some of these cases included acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome<sup>3</sup>.

In February 2016, EMA concluded that HBV reactivation is considered as a class effect of BCR-ABL TKI in the European Union, although the mechanism and the frequency of HBV reactivation during exposure is not known at this time. Following this, the product information of BCR-ABL TKI containing products were updated and a direct healthcare professional communication (DHPC) letter was issued to disseminate the new safety information.

## Local Scenario

In Malaysia, there are a total of **6 registered products** in the class of BCR-ABL TKIs with active ingredient imatinib (**Glivec®**) and nilotinib (**Tasigna®**). Both imatinib and nilotinib are generally indicated for the treatment of chronic myeloid leukemia (CML), while imatinib is also indicated for other malignancies.

Based on the ADR Monitoring Centre, NPRA database, there were a total of **927 ADR reports** received for imatinib since year 2002 and **107 ADR reports** received for nilotinib since year 2008. For imatinib, there were 18 reports involving the System Organ Class (SOC) 'liver and biliary disorders' (1.9%), including one (1) case each for hepatitis B and hepatitis B antibody positive. There were 2 reports for nilotinib with SOC liver and biliary disorder (1.9%) but none of the reports were related to hepatitis B and hepatitis B antibody positive.

On 11 March 2016, NPRA has reviewed this safety issue and has approved the DHPC letter and package insert update to reflect this new safety information.

## References

1. Arora and Scholar (2005). Role of Tyrosine Kinase Inhibitor. *The Journal of Pharmacology and Experimental Therapeutics* 315:971.
2. Gotink & Verheul (2010). *Angiogenesis* (2010) 13:1-14. Anti-angiogenic tyrosine kinase inhibitors: What is their mechanism of action.
3. EMA (2016). PRAC recommendations on signals: Adopted at the PRAC meeting of 8-11 February 2016. Recommendations for update of product information Bcr-abl tyrosine kinase inhibitors–Hepatitis B virus (HBV) reactivation. (EMA/PRAC/87046/2016).

## Advice to Healthcare Professionals

- Patients should be tested for hepatitis B infection before initiating treatment with imatinib or nilotinib.
- Patients currently on imatinib or nilotinib should have baseline testing for hepatitis B infection in order to identify chronic carriers of the virus.
- Carriers of hepatitis B virus who require treatment with imatinib or nilotinib should be closely monitored for signs and symptoms of active hepatitis B infection throughout therapy and for several months following termination of therapy.
- Please report to the NPRA any ADRs suspected to be related to imatinib or nilotinib.

## Regulatory Matters

# Adempas® (Riociguat): New Contraindication for Patients with Pulmonary Hypertension Associated with Idiopathic Interstitial Pneumonia (PH-IIP)

Riociguat is the first member of a new class of compounds, known as the soluble guanylate cyclase (sGC) stimulators. Riociguat independently stimulates sGC as well as sensitises it to the body's free nitric oxide, thereby decreasing endothelial dysfunction and reducing pulmonary artery blood pressure. Adempas® is approved for use in patients with chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension (PAH) [please refer to the package insert for full prescribing details].

An evaluation of the interim results concluded that the **benefit-risk balance of riociguat in patients with PH-IIP is negative**, and recommended that this information to be included in the product information of Adempas® as a new contraindication.

## Local Scenario

Adempas® has been registered in Malaysia since year 2014, and at the time of this publication, the NPRA has not received any ADR reports related to this product.

## Background of the safety issue

The RISE-IIP study was a randomized, double-blind, placebo-controlled, multicentre phase II clinical trial to investigate the efficacy and safety of Adempas® patients with symptomatic PH associated with idiopathic interstitial pneumonias (PH-IIP)<sup>2</sup>. This study was terminated early when preliminary results revealed **an increased mortality** in patients receiving Adempas® (17 deaths) compared to those receiving placebo (4 deaths). **Serious adverse events, mostly respiratory disease or lung infections**, were also reported more frequently in the patient group receiving Adempas® compared to placebo group.

In agreement with NPRA, the product registration holder of Adempas® has issued a Direct Healthcare Professional Communication (DHPC) letter on this matter. The local package insert of Adempas® will be updated with the new contraindication related to this safety issue.

## Reference

1. Ghofrani, HA et al. (2010). Riociguat for pulmonary hypertension. *Future Cardiol.* 6: 155-166.

## Advice to Healthcare Professionals

- Riociguat is contraindicated in patients with PH-IIP.
- If any patients with PH-IIP are currently being treated with riociguat, the treatment should be discontinued and their clinical status must be carefully monitored.
- The benefit-risk profile of Adempas® remains positive in both of its approved indications, as mentioned above.
- All healthcare professionals are encouraged to report suspected adverse drug reactions related to riociguat to the NPRA.

## What's New?

# The Consumer Side Effect Reporting Form

## The importance of reporting ADRs



Adverse drug reactions (ADRs) or side effects may vary for each individual. Although many are identified during drug development, only a restricted number of patients are treated during this phase. Once a medicine is available on the market and more people use it, previously unknown or rare ADRs are likely to emerge. Analysis of ADR reports will help make medicine use safer for everyone, and may even help identify new side effects of a medicine.

## What we have now

Currently, the NPRA provides ADR reporting forms for healthcare professionals (widely known as the 'blue form'), and a reporting form for medicines complaints by consumers. The existing consumer complaints form may be used for all types of medicinal product complaints, such as side effects, efficacy issues, or reporting unregistered products. However, in the effort to simplify the form for the convenience of consumers, the information collected tends to lack many important details required for a useful ADR

## What's new?

As we continue to expand pharmacovigilance in Malaysia, we have introduced an ADR reporting form specifically for consumers; the Consumer Side Effect Reporting Form (ConSERF).

Currently, more than 50 other countries worldwide have their own consumer ADR direct reporting forms, for example the United Kingdom, Australia, the United States of America, and Canada.

**ConSERF**  
BORANG PELAPORAN KESAN SAMPINGAN UBAT UNTUK PENGGUNA  
PUSAT PEMONITORAN KESAN ADVERSA UBAT KEBANGSAAN  
NATIONAL CENTRE FOR ADVERSE DRUG REACTIONS MONITORING

**ConSERF**  
CONSUMER SIDE EFFECT REPORTING FORM  
NATIONAL CENTRE FOR ADVERSE DRUG REACTIONS MONITORING

**Information about the person who had the side effect**

Name: \_\_\_\_\_ Nationality:  Malaysian  Other: \_\_\_\_\_  
 \*Gender:  Male  Female \*Ethnicity:  Malay  Chinese  Indian  Other: \_\_\_\_\_  
 \*Age: \_\_\_\_\_ \*Tel. Number: \_\_\_\_\_  
 \*Any health problems / allergies / pregnancy? (please specify): \_\_\_\_\_  
 (e.g. Diabetes, high blood pressure, asthma, allergy to penicillin, or all weeks pregnant)

**Reporter details**

Date of report: \_\_\_\_\_  
 Reporter's name: \_\_\_\_\_  
 \*Tel. Number: \_\_\_\_\_  
 Email address: \_\_\_\_\_

**Information about the medication(s) suspected to cause the side effect, and other medications**

\*Suspected Medicines(s): (please attach additional sheets if necessary)

| Suspected medicine name (include A&N, number of boxes) | Dosage (e.g. 50mg three times daily) | Started | Stopped | Reason for use |
|--|--------------------------------------|---------|---------|----------------|
|  |                                      | DDMMYY  | DDMMYY  |                |

\*Were any other medicines taken at the same time?:  Yes (please give the details below)  No

| Other medicine(s) name (include A&N, number of boxes) | Dosage (e.g. 50mg three times daily) | Started | Stopped | Reason for use |
|---|--------------------------------------|---------|---------|----------------|
|   |                                      | DDMMYY  | DDMMYY  |                |

**Information on the side effect(s)**

1. \* Date of side effect(s): a) Reaction started on [ ] [ ] [ ] [ ] [ ] [ ] b) Reaction subsided on [ ] [ ] [ ] [ ] [ ] [ ]

2. \* Please describe the side effect(s) experienced:

3. \* How long was the medication(s) taken before the side effect appeared? [ ] minutes/hours/days/months/years (choose)

4. \* Did the side effect subside when the medication(s) was stopped?  Yes  No  Did not stop taking the medicine

5. \* Did the side effect reappear when the medication(s) was taken again?  Yes  No  Did not take again

6. \* How serious was the side effect? (select all that apply below)

Mild or slightly uncomfortable  Had to seek medical advice  Admitted to the hospital

Uncomfortable but could carry out daily activities  Bad, interferes with daily activities  Other: \_\_\_\_\_

7. \* Was any treatment given/medication taken to overcome the side effect?  Yes (please specify)  No

8. \* What is the current outcome of the side effect?

Fully recovered  Getting better  Side effects continuing  Caused death

Thank you for reporting.

**Now available – an ADR form just for the public!**

## Why have a new form?

Many studies have shown the benefits of running a direct consumer reporting system alongside healthcare professional reporting of ADRs, for example:

- Consumer reports tend to provide better understanding of the patients' experience and how ADRs affect the quality of life.
- Consumers tend to report different types of ADRs compared to healthcare professionals.
- ADRs for different classes of products are captured, such as traditional products and health supplements.

With the implementation of this system, we hope to build up a more comprehensive ADR database, capturing previously missed information.

## How do consumers report?

ConSERF is available online at <http://npra.moh.gov.my>.



The first version is available in two languages: Bahasa Melayu and English. A brief guide for reporters has been provided on the reverse side of the form. Consumers are also encouraged to speak to their pharmacists for assistance in completing and submitting the forms. Once completed, the form should be posted back to NPRA.

### For Healthcare Professionals

## How to report adverse drug reactions?


NPRA encourages the reporting of all suspected adverse drug reactions to medicines, including vaccines, over-the-counter medicines, as well as traditional health supplements.





To report adverse drug reaction:

1. Visit [npra.moh.gov.my](http://npra.moh.gov.my)
2. Click on **ADR Reporting**
3. Go to report as a healthcare professional online or via hardcopy.
4. Submit the form once completed.

Completed hard copy forms may be submitted via post or fax at:

 The Pharmacovigilance Section,  
National Pharmaceutical Regulatory Agency (NPRA),  
Ministry of Health, Malaysia.  
Lot 36, Jalan Universiti,  
46200 Petaling Jaya,  
Selangor.

 +603 7883 5550

 +603 7956 7151

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