AUGUST 2014

MADRAC

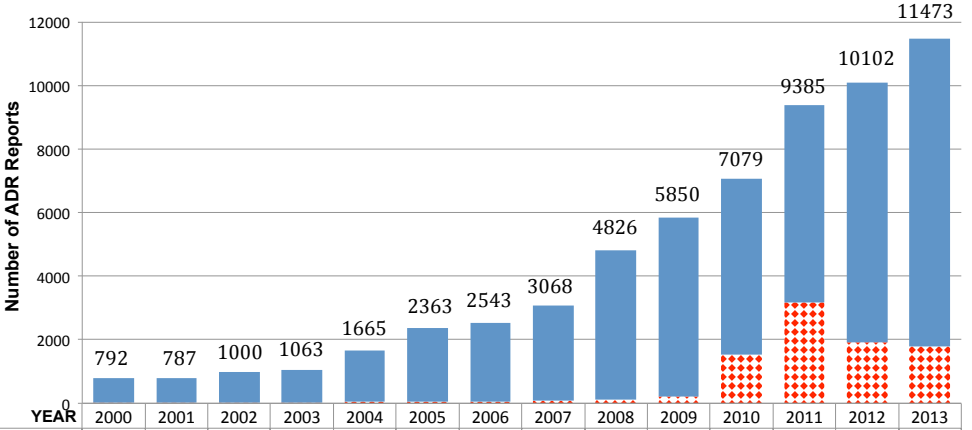
Malaysian Adverse Drug Reactions Newsletter
National Pharmaceutical Control Bureau, Ministry of Health Malaysia
This newsletter is also available on our website: http://www.bpfk.gov.my

ANNUAL REPORT FOR 2013

SPONTANEOUS ADVERSE DRUG REACTIONS REPORTED IN MALAYSIA (2013)

Efforts to encourage reporting of adverse drug reactions (ADRs) continued to show results in 2013. The total ADR reports received increased by 13.5% to 11,473 reports as compared to 10,102 reports in 2012 (***Graph 1***).

Graph 1: Total ADR Reports Received in Malaysia Annually (Year 2000-2013)



YEAR	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
ADR REPORTS (WITHOUT AEFI)	778	777	974	1050	1613	2295	2504	2993	4694	5636	5550	6202	8199	9678
AEFI REPORTS	14	10	26	13	52	68	39	75	132	214	1529	3183	1903	1795

Continued on page 2

CONTENT

To report an adverse drug reaction:
1. Visit http://www.bpfk.gov.my
2. Click on the red box, 'Reporting Medicinal Problems'.
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,
PO Box 319, Jalan Sultan,
46730 Petaling Jaya, Selangor.

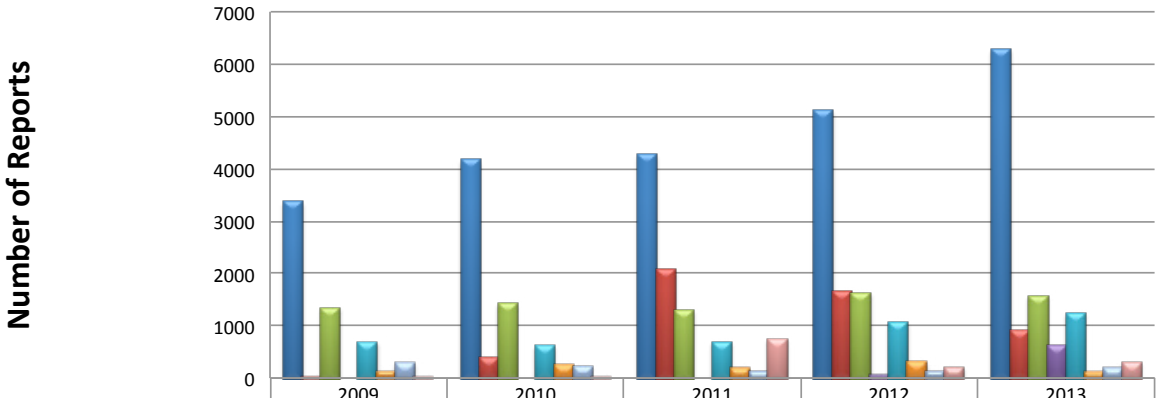
Tel : +603-7883 5400
Fax : +603-7956 7151

Editorial Staff

ADR Reporters

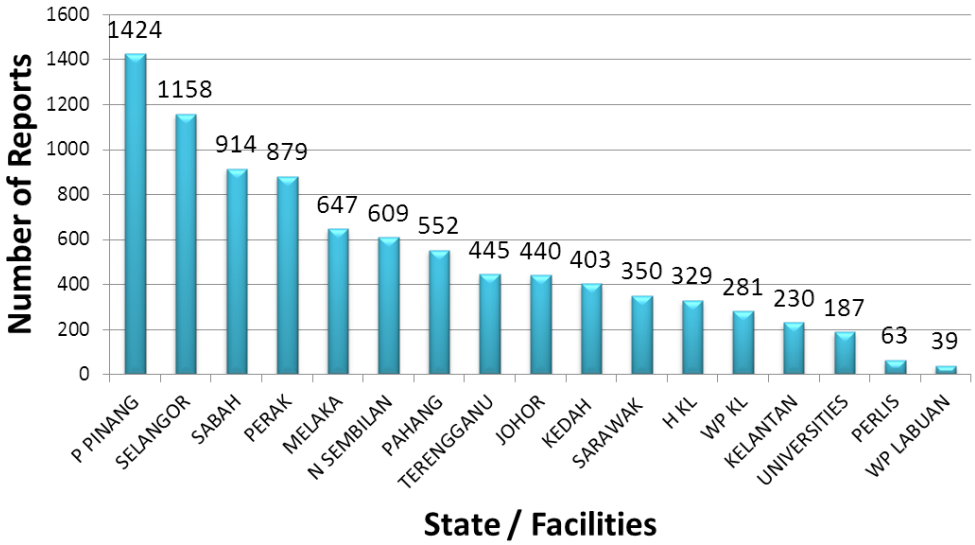
Ministry of Health (MOH) pharmacists continued to contribute the majority of reports (54.7%; 6283 reports), followed by MOH doctors (13.6%; 1560) and product registration holders (10.8%; 1235). The number of ADR reports submitted by MOH nurses and private sector doctors dropped sharply as compared to 2012 (***Graph 2***). A breakdown of reports received from MOH facilities according to state is shown in ***Graph 3***.

Graph 2: ADR Reports According to Reporter Category (Year 2009-2013)



	2009	2010	2011	2012	2013
MOH Pharmacists	3358	4160	4267	5106	6283
MOH Nurses	25	388	2063	1636	905
MOH Doctors	1340	1418	1295	1627	1560
Other Govt Agencies	0	0	0	67	621
Product Registration Holders	686	612	691	1066	1235
GPs / Private Specialists	144	248	185	310	119
Universities	281	234	142	151	187
Others	16	19	742	206	303

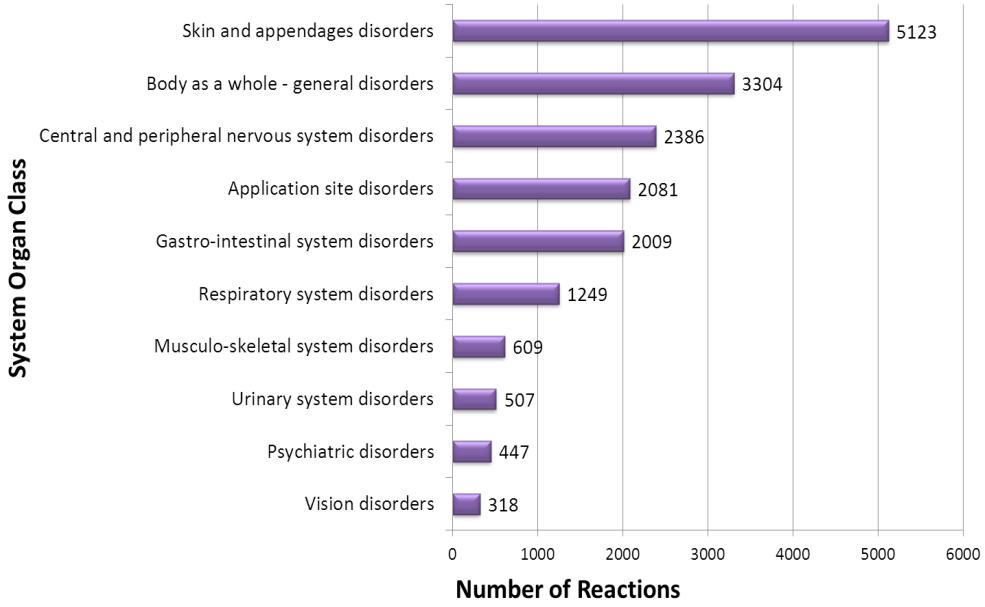
Graph 3: ADR Reports Received From MOH Facilities According to State



System Organ Class

Overall, there were 19,846 adverse events reported in 2013. The top ten WHO System Organ Classes (SOCs) involved are shown in ***Graph 4***, with 'Skin and appendages disorders' and 'Body as a whole- general disorders' topping the list for the second year in a row.

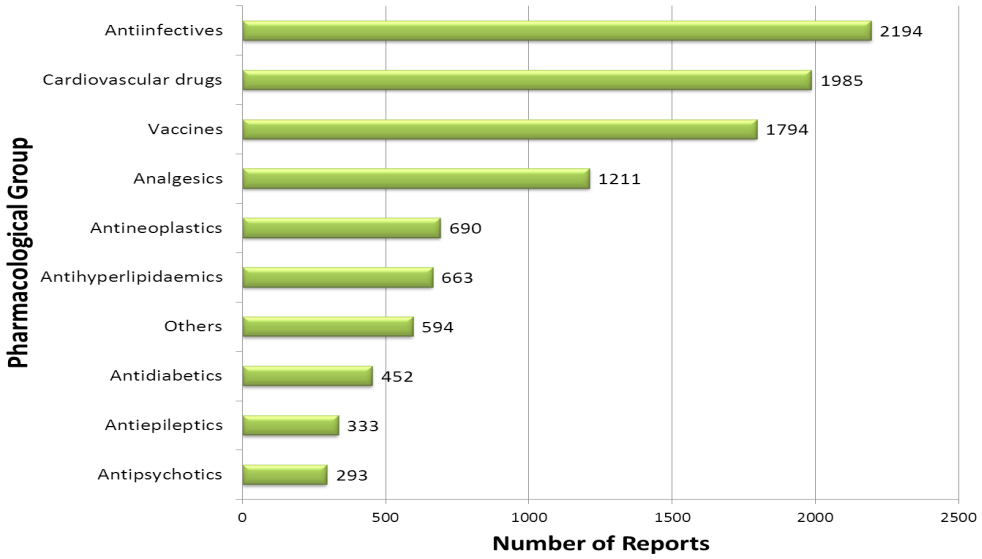
Graph 4: Top Ten System Organ Classes of Suspected Adverse Drug Reactions Reported (2013)



Pharmacological Group

The highest number of reports for 2013 came from anti-infective drugs (17.8%), followed by cardiovascular agents (16.1%) and vaccines (14.5%). The top ten pharmacological groups reported to cause ADRs are shown in ***Graph 5***.

Graph 5: Top Ten Pharmacological Groups of Suspected Adverse Drug Reactions Reported (2013)



Patient Age Group

The majority of reports (3,213; 28.7%) involved patients aged between 41-60 years, followed by the age group 19-40 years (2,893; 25.8%), and the elderly (>60 years of age) which amounted to 2,234 reports (19.9%). There is a high possibility of under-reporting of ADRs involving children, as only 7.8% or 880 reports involved children aged 12 years and below.

DRUG SAFETY ISSUES DISCUSSED IN 2013

In 2013, a total of 26 drug safety issues were identified, reviewed and presented at MADRAC meetings to discuss regulatory actions required. Risk minimisation measures taken included updating of the product **package inserts**, distribution of Direct Healthcare Professional Communications (**DHPC**s) to alert practitioners on the issues, or **publication** of the safety issues in the MADRAC bulletin or Reaksi Drug Safety newsletter. ***Table 1*** lists safety issues discussed by MADRAC in 2013 and resulting actions.

Table 1: Drug Safety Issues Discussed by MADRAC in 2013 and Resulting Risk Minimisation Actions

MADRAC Meeting Date	Safety Issue Discussed	MADRAC Recommendation/ Resulting Actions			
		PI Update	DHPC	Publication of article	Further review
21/2/2013	Pradaxa® (dabigatran etexilate mesylate): New Contraindication For Pradaxa In Patients With Prosthetic Valves	√		√	
	Mabthera® (rituximab): Association with Toxic Epidermal Necrolysis (TEN) and Stevens-Johnson Syndrome (SJS)	√		√	
18/4/2013	Prolia® and Xgeva® (denosumab): Association With Risk of Anaphylactic Reactions and Atypical Femoral Fracture	√		√	
	Trimetazidine-containing Products: New Recommendations On The Restriction Of Use	√			
	Miacalcic® (calcitonin salmon): European Medicines Agency (EMA) Suspends The Intranasal Formulations And Recommends New Restrictions For All Injectable Formulations				√
	Non-Steroidal Anti-Inflammatory Drugs (NSAIDS): Association With Cardiovascular Risks				√
13/6/2013	Avastin® (bevacizumab): Association With Necrotising Fasciitis	√			
	Champix® (varenicline): Association With Risks of Cardiovascular Adverse Events: A Review Update				√
	Diane 35® (cyproterone Acetate, ethinylestradiol): Suspension of Marketing Authorisation in France	√		√	
	Codeine-containing products: Adverse Drug Reactions Associated with Children (21 months-9 years) Undergoing Adenotonsillectomy and/or Tonsillectomy			√	
22/8/2013	Trobalt® (retigabine): Restriction Of Indication Resulting From Observed Pigment Changes (Discolouration) of Ocular Tissue (Including Retina), Nails, Lips, and/or Skin	√	√		
	Votrient® (pazopanib): Important Change in Frequency for Serum Liver Enzymes Monitoring	√	√		
	Mabthera® (rituximab): New Risk Management of Hepatitis B Reactivation in Patients Prior to Initiation of Therapy	√	√	√	
	Paracetamol-containing products: Association with Serious Skin Adverse Drug Reactions				√
	Lovastatin-containing products: New Restrictions To Reduce Muscle Injury				√

MADRAC Meeting Date	Safety Issue Discussed	MADRAC Recommendation/ Resulting Actions			
		PI Update	DHPC	Publication of article	Further review
22/8/2013 & 24/10/2013	Hydroxyethyl Starch (HES)-containing products: Suspension of Marketing Authorisation by European Medicines Agency (EMA) Due To Increased Mortality And Risk Of Kidney Injury Requiring Dialysis	√		√	
24/10/2013	Erythropoetin Stimulating Agents: Adverse Drug Reaction Reports Associated with Pure Red Cell Aplasia (PRCA) Received by National Pharmaceutical Control Bureau				√
	Lariam® (mefloquine): Association with Visual Disturbance Including Optic Neuropathy	√		√	
	Oral Ketoconazole-containing products: Suspension of Marketing Authorisation by European Medicines Agency (EMA) Due To Association with the Risk of Hepatotoxicity	√	√	√	
12/12/2013	Protaxos® (strontium ranelate): Association With Increased Risk Of Serious Heart Problems	√	√	√	
	Tygacil® (tygecycline): Association With Increased Risk of Death			√	
	Erythropoetin Stimulating Agents -Associated Pure Red Cell Aplasia (PRCA) Adverse Drug Reaction Reports in Malaysia: An Update Following Contraindication of the Subcutaneous Route for Eprex in Singapore				√
	Xeloda® (capecitabine): Association with Toxic Epidermal Necrolysis (TEN) and Stevens-Johnson Syndrome (SJS)	√	√		
	Jevtana® (cabazitaxel): Potential For Medication Error During Preparation	√	√		
	Frisium® (clobazam): Association with Toxic Epidermal Necrolysis (TEN) and Stevens-Johnson Syndrome (SJS)	√	√		

SAFETY ISSUES OF CURRENT INTEREST

STATINS: IMPORTANT SAFETY LABELLING CHANGES

by Lee Sing Chet

HMG-CoA reductase inhibitors, or more commonly known as statins, are widely used to treat dyslipidaemia as well as for the primary and secondary prevention of cardiovascular disease. The Malaysian Clinical Practice Guidelines on Management of Dyslipidemia (2011) recommends statins as the drug of choice for reducing low-density lipoprotein cholesterol (LDL-C)[1]. However, this group of drugs has been associated with several safety issues over the past years, such as muscular adverse effects related to drug interactions, an increase in blood glucose, and cognitive impairment. This article summarises a review by NPCB on the safety profile of statins.

Muscular adverse effects – Interactions with other medications

Like other lipid-lowering agents, statins can cause myopathy and, rarely, life-threatening rhabdomyolysis. **Simvastatin, lovastatin** and **atorvastatin** are metabolised by the isoenzyme cytochrome P450 3A4 (CYP3A4). CYP3A4 inhibitors (as listed in ***Table 2***) can interact with these statins and increase their plasma concentration, thus increasing the risk of muscular adverse effects. On the other hand, **fluvastatin, rosuvastatin** and **pravastatin** are relatively insensitive to CYP3A4 inhibitors and therefore clinically significant interactions are less likely. However, caution is recommended when a known CYP3A4 inhibitor is used together with any statin. Please refer to the individual product package inserts for specific recommendations on contraindications or statin dose adjustments.

Table 2: Examples of CYP3A4 inhibitors that interact with statins

Strong CYP3A4 Inhibitors	Moderate CYP3A4 Inhibitors
• HIV protease inhibitors (e.g. ritonavir, boceprevir, telaprevir) • Azole antifungals (e.g. itraconazole, ketoconazole, posaconazole, voriconazole) • Macrolide antibiotics (e.g. erythromycin, clarithromycin) • Gemfibrozil • Cyclosporine • Danazol	• Amiodarone • Amlodipine • Verapamil • Diltiazem • Niacin (≥1g/day)

In general, all statins should be used with caution in combination therapy with **other lipid-lowering agents** such as gemfibrozil, fenofibrate and lipid-lowering doses of niacin (≥1g/day), as either agent can cause myopathy when given alone. The recommendations for use differ amongst different statins based on individual pharmacokinetic properties.

The NPCB is currently working with product registration holders of all statin-containing products to include new contraindications and dose limitations into local package inserts. Directives and circulars related to this issue can be found on the NPCB website (www.bpfk.gov.my --> News & Publications --> Circulars/ Directives).

Increased HbA1c and fasting blood glucose (FBG)

In recent years, multiple trials including meta-analysis have shown that statins can raise blood glucose and might be associated with new-onset diabetes[2-4]. However, the trials also concluded that the diabetes risk is low compared with the benefit of statin therapy in reducing coronary events[3-4]. Sattar *et al.* determined

that treating 255 patients with statins for 4 years would result in one (1) extra case of diabetes, but would prevent 5.4 major coronary events (coronary heart disease death and nonfatal myocardial infarction) for each reduction of 1.0 mmol/L in LDL-C[4]. Furthermore, post-hoc analysis of the JUPITER trial reported that in patients with at least one major risk factor for diabetes treated with rosuvastatin, a total of 134 vascular events or deaths were avoided for every 54 new cases of diabetes diagnosed. Whereas for those with no major diabetes risk factors, a total of 86 vascular events or deaths were avoided with no new cases of diabetes diagnosed[5].

Since year 2000, the NPCB Drug Safety Monitoring Centre has received a total of 21 adverse drug reaction (ADR) reports on worsening glycemic control associated with statins. The reported events included polyuria/ nocturia (18), dysuria (2), hyperglycemia (2), abnormal glucose tolerance (1), micturition urgency (1) and polydypsia (1).

While evidence indicates that statins as a class may increase glucose levels, the benefits in reducing cardiovascular events outweigh the hyperglycemic risk. Healthcare professionals are advised to **monitor patients** both clinically and biochemically, especially those at risk of diabetes. Risk factors include impaired glucose tolerance, impaired fasting glucose, BMI >23kg/m^2, hypertension and raised triglycerides[6].

Cognitive impairment

Additionally, statins have also been associated with cognitive impairment (e.g. memory loss, forgetfulness, amnesia, memory impairment, confusion) which have been reported, albeit rarely, in the worldwide post-marketing setting. The reports are generally non-serious and reversible upon statin discontinuation, with variable times to symptom onset (ranging from 1 day to years) and symptom resolution (median 3 weeks)[7]. This information is being updated into local package inserts.

Locally, a total of four (4) ADR reports associated with cognitive impairment were received with the adverse events including memory loss (2) and amnesia (2). The patients' age ranged from 44 to 47 years old. In all four cases, the statins were discontinued following the ADRs. Outcomes were reported in three cases, where two recovered and one had not yet recovered at the time of reporting[8].

Advice for Healthcare Professionals:

- Use with caution when co-prescribed with CYP3A4 inhibitors. Refer to individual package inserts for the recommendations, including contraindications or statin dose adjustments.
- Monitor patients for hyperglycemic symptoms especially those at risk of diabetes.
- Monitor patients for symptoms of cognitive impairment.
- Please report all adverse events suspected to be associated with statins.

References:

1. Malaysian Clinical Practice Guideline on The Management of Dyslipidemia (2011).
2. Ridker PM *et al*. (2008). *Rosuvastatin to prevent vascular events in men and women with elevated C-Reactive Protein (JUPITER trial)*. N Engl J Med 359(21):2195-207.
3. Rajpathak SN *et al*. (2009). *Statin Therapy and Risk of Developing Type 2 Diabetes: A Meta-Analysis.* Diabetes Care 32:1924-1929.
4. Sattar N *et al*. (2010). *Statins and risk of incident diabetes: a collaborative meta-analysis of randomized statin trials.* Lancet 375(9716): 735-742.
5. Ridker PM *et al*. (2012). *Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial*. Lancet 380(9841): 565-571.
6. Malaysian Clinical Practice Guideline on Management of Type 2 Diabetes Mellitus (4th edition). (2009).
7. US FDA (2012). *Important safety label changes to cholesterol-lowering statin drugs.* Drug Safety Communication.
8. The Malaysian Adverse Drug Reaction Database, NPCB. [Accessed: 21 July 2014]

LOCAL ADR CASE REPORTS

TINNITUS FOLLOWING USE OF METFORMIN

A 45-year-old woman developed ringing in both ears after taking metformin for the first time. She was diagnosed with diabetes mellitus in November 2013 and started on metformin 500 mg twice daily. Her concomitant medications were simvastatin and perindopril, which she had been taking since May 2013.

Within two to three hours of taking the first dose of metformin, she complained of tinnitus. Upon stopping the medication, the adverse reaction resolved. Her concomitant medications were continued. This report was given the causality C2 (probably-related).

Local Data

The Malaysian Adverse Drug Reaction (ADR) database contains **six (6) other reports** of tinnitus suspected to be related to metformin-use, making up 0.5% of the total local reports for this active ingredient. The affected patients were aged between 51 to 68 years. The reports involved several different brands and one combination product, with reported **time to onset** of tinnitus generally ranging from one hour to one day. Three (3) cases reported the tinnitus resolving when the dose of metformin was decreased. In two cases, the patients were taking concomitant medication such as sulfonylureas, simvastatin, amlodipine and perindopril. All the reports were assigned causality **C2 or C3** (possibly-related) by MADRAC.

International Data

A search of the WHO ADR database* revealed **51 reports** of tinnitus linked to metformin since the year 1997 (excluding Malaysian reports). Most of the cases (43%) involved patients aged between 45 to 64 years, affecting both genders equally.

The Drug Safety Monitoring Centre, NPCB would like to highlight this adverse event to all healthcare professionals. This is to encourage active surveillance of all patients taking metformin and allow appropriate clinical intervention to be made if the ADR is identified. Please report any adverse events suspected to be associated with the use of metformin, in particular any complaints of tinnitus.

**DISCLAIMER: This information comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases. This information does not represent the opinion of WHO.*

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IMPLANON NXT® (ETONOGESTREL): DRUG INTERACTION WITH RIFAMPICIN

The NPCB received an ADR report on **inefficacy** of the contraceptive implant Implanon NXT® (etonogestrel). The contraceptive failure is suspected to be due to an interaction with antituberculosis drugs that the patient was taking.

The implant was inserted in May 2013, but in Feb 2014, a physician reported that the patient was pregnant. The patient had been started on rifampicin and isoniazid in December 2013 at a respiratory clinic, however the healthcare professionals involved were not made aware that the patient was on Implanon NXT®.

It is documented that concurrent use of rifampicin and contraceptives may decrease the plasma concentration of estrogens and thus decrease contraceptive effectiveness. This is due to the cytochrome P450 enzyme-inducing effect of rifampicin. There is no documented interaction between isoniazid and contraceptive drugs.

Other drugs which may interact with hormonal contraceptives resulting in reduced contraceptive efficacy include **antivirals** such as efavirenz, nevirapine and ritonavir, certain **antiepileptics**, for example carbamazepine or phenytoin, cephalosporins, and penicillins.

Since the year 2000, NPCB has received 48 ADR reports related to Implanon NXT®, with seven (7) of these possibly indicating inefficacy (reported ADR terms: medicine ineffective, pregnancy, pregnancy unintended). Six of these reports were given the causality C3 (possibly-related to the drug) while the remaining one report was assigned causality C5 (insufficient information to analyse report). Other frequently reported ADRs related to Implanon NXT® were menstrual disorders (20), implant site reactions (14), and skin reactions (11) such as rash, cellulitis or pruritus.

Advice to Healthcare Professionals:

- If rifampicin is co-administered with a combination or progestin-only contraceptive, the patient should be advised to use an **alternate non-hormonal contraceptive** method of birth control.
- The patient should be monitored closely for signs of breakthrough bleeding and/or pregnancy.
- Patients who are started on Implanon NXT® should be **counselled to inform** their healthcare professionals of the implant use before taking any other medication.
- During drug history taking, patients should be **specifically asked** about any concomitant use of contraceptive medication, including implants.
- Please report any ADRs suspected to be due to Implanon NXT® to the Drug Safety Monitoring Centre, NPCB.

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REGULATORY MATTERS

UPDATE ON PROTAXOS® (STRONTIUM RANELATE): BLACK BOX WARNING TO MINIMISE CARDIOVASCULAR RISK

On 4 August 2014, a circular was issued by NPCB listing risk minimisation steps that must be implemented for products containing strontium ranelate following its association with serious cardiac disorders. This safety issue was previously featured in the MADRAC Bulletin December 2013 edition.

The Drug Control Authority agreed to several package insert (PI) updates, including:-

(i) Addition of a **black box warning** at the beginning of the PI:

> This product should only be used for whom treatment with other medicinal products approved for the treatment of osteoporosis is not possible due to, for example, contraindications or intolerance.
>
> This product is contraindicated in patients with:
> - established, current or past history of ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease;
> - uncontrolled hypertension;
> - current or previous venous thromboembolic events (VTE);
> - temporary or permanent immobilisation

(ii) Tightening of the **indication** to:

- treatment of severe/ established osteoporosis in postmenopausal women at high risk of fracture to reduce the risk of vertebral and hip fractures;
- treatment of severe/ established osteoporosis in men at increased risk of fracture

Currently, Protaxos® is the only product containing strontium ranelate registered in Malaysia. A Direct Healthcare Professional Communication (DHPC), together with a Prescriber Checklist, has been approved by NPCB on 13 August 2014 for distribution by the product registration holder. NPCB will continue to monitor the safety profile of this product.

Advice to Healthcare Professionals:

- Strontium ranelate should only be used for patients who cannot be treated with other osteoporosis medication
- Each patient should be evaluated with respect to cardiovascular risk **before** starting treatment, and regularly (generally every 6 to 12 months) **during** treatment.
- Treatment should be discontinued if the patient develops:
  - (i) ischaemic heart disease, peripheral arterial disease, cerebrovascular disease or uncontrolled hypertension
  - (ii) an illness or condition leading to immobilisation
  - (iii) signs or symptoms of serious skin reactions such as SJS, TEN or DRESS* (the drug should not be restarted at any time)
- Healthcare professionals are reminded to report any adverse drug reactions involving strontium ranelate.

**SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis; DRESS: drug reaction with eosinophilia and systemic symptoms*

GUIDE FOR ADR REPORTERS: A FOCUS ON QUALITY

WHAT IS THE WHO COMPLETENESS SCORE?

The National ADR Monitoring Centre has been successful in promoting awareness on the importance of reporting ADRs, leading to an exponential increase in the number of ADR reports received in Malaysia over the last 25 years.

The WHO recommendations for an optimal National Pharmacovigilance Centre include submission of 200 or more ADR reports per million population annually. Malaysia has consistently surpassed this target since 2009, and in the past two years, emerged among the top 20 countries worldwide in terms of number of Individual Case Safety Reports (ICSRs) submitted per year and population.

Now the focus is shifting towards increasing the **quality** of ADR reports. This is to ensure that data collected is useful and contributes towards signal detection of drug safety issues.

The WHO Uppsala Monitoring Centre measures ICSR quality using the Documentation Grading - Completeness Score system. This is a score between 0 (poorly documented case) to 1 (well documented), measuring the amount of information provided in an ICSR[1]. It is calculated from eight (8) fields of information deemed important for medical assessment, including time to onset, outcome, age at onset, and primary source.

Over the past five years, Malaysia has consistently obtained an average completeness score of around 0.45. There were no ICSRs from Malaysia scoring 0.75 or above, with about 4% of the reports scoring 0.25 or less. Measures are being taken to improve on this score, for example by educating reporters on essential fields to be completed, conducting courses nationwide, and providing checklists for ADR reporting (*see previous issues of MADRAC Bulletin – Aug & Dec 2013*).

The main fields in Malaysian ADR reports with incomplete or missing information based on the WHO report are shown in ***Table 3***, along with methods of improvement. The indication of the suspected drug needs to be as specific as possible, for example 'essential hypertension' or 'hypertension secondary to endocrine disorders'. NPCB officers currently enter disease codes for each suspected drug based on the WHO International Statistical Classification of Disease and Related Health Problems 10th Revision (ICD-10)[2].

Table 3: Common fields of missing or incomplete information in Malaysian ADR Reports

Field(s) of information	Requirements for higher Completeness Score
Indication of suspected drug	Should be very specific based on the WHO ICD-10 classification[2]
Drug start date & Date of ADR onset	Include full date (day - month - year) where known
ADR description	Should be as detailed as possible
Outcome of patient	The outcome should be reported (reporter to follow-up on whether the patient eventually recovered from the ADR, or condition worsened, etc.)

References:

1. Lundin T and Fors SL (2014). *Vigibase: Quality in focus*. WHO Uppsala Report 65:6-7.
2. WHO (2014). *International Statistical Classification of Diseases and Related Health Problems 10th Revision.* http://apps.who.int/classifications/icd10/browse/2015/en. [Accessed 3 August 2014].