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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

SAFETY ISSUE OF CURRENT INTEREST

CARBIMAZOLE VS. PROPYLTHIOURACIL: A COMPARISON OF DRUG SAFETY PROFILES BASED ON SPONTANEOUS ADVERSE DRUG REACTION REPORTS IN MALAYSIA

By Vidhya Hariraj & Rema Panickar

Overview

Carbimazole and propylthiouracil (PTU) are antithyroid medicines used to treat certain causes of hyperthyroidism (such as Graves' disease, thyroid nodules which may release thyroid hormones, and some forms of cancer), as well as thyrotoxicosis or thyroid storm.

Generally, carbimazole is the first choice treatment for hyperthyroidism. PTU is considered second-line therapy, to be used when a patient is unable to tolerate carbimazole, to treat hyperthyroidism in pregnancy or breast feeding, and when surgery or radioactive iodine therapy are not suitable[1,2].

This article aims to compare the drug safety profiles of these two medications based on local postmarketing adverse drug reaction (ADR) reports and recent studies, to identify if there are major differences which could lead to changes in clinical practice recommendations.

Product Information

Both medicines were first registered in Malaysia in 1986. Currently, there are **5 products containing carbimazole 5mg** and **3 products containing PTU 50mg** registered with the Drug Control Authority of Malaysia, as shown in *Table 1 (overleaf).* A brief comparison of both drugs is detailed in *Table 2*.

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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

Table 1: Registered products containing carbimazole and propylthiouracil in Malaysia

No.	Product Name	Registration No.	Product Holder
Carbimazole products:			
1	Thymazole Tablet	MAL19950155A	Duopharma (M) Sdn. Bhd.
2	Carbimazole Tablet 5mg	MAL20132307AE	Biosis Pharmaceuticals Sdn. Bhd.
3	Camazol Tablet 5mg	MAL19860195A	Xepa-Soul Pattinson (Malaysia) Sdn. Bhd.
4	Carbiroid Tablet 5mg	MAL19880341A	Hovid Berhad
5	NeoMercazole Tablet 5 mg	MAL12020025AC	A. Menarini Singapore Pte. Ltd.
Propylthiouracil products:			
1	Propyl Tablet 50mg	MAL19930398A	Imeks Pharma Sdn. Bhd.
2	Propylthiouracil Tablet 50mg	MAL20040762A	Actavis Sdn. Bhd.
3	Propylthiouracil 50mg BP Tablet	MAL19940154A	Ziwell Medical Sdn. Bhd.

Table 2: Drug profile comparison of carbimazole and propylthiouracil [2,3,4,5]

	Carbimazole	Propylthiouracil
Mechanism of action	Carbimazole is a derivative of methimazole. It inhibits the formation of thyroid hormones by preventing the incorporation of iodide into tyrosyl residues, and inhibiting the coupling of iodotyrosyl residues.	Propylthiouracil (PTU) blocks the production of thyroid hormones by inhibiting the enzyme thyroid peroxidase. PTU also causes a gradual reduction in the level of circulating thyroid stimulating immunoglobulins in Graves' disease.
	Both drugs do not inactivate or interfere with release of previously formed thyroid hormones	
Dosage recommendation in MOH Drug Formulary (*FUKKM*)	ADULT: Initially 10 - 60 mg daily in divided doses. Maintenance: 5 - 20 mg daily CHILD: No dosage recommendation in *FUKKM*	ADULT: Initial dose: 300 - 450 mg daily in divided doses every 8 hours. Maintenance: 100 - 150 mg daily in divided doses every 8 - 12 hours CHILD: Initial 5 - 7 mg/kg/day in divided doses every 8 hours. Maintenance: 1/3 to 2/3 of the initial dose in divided doses every 6 - 8 hours.
Pharmacokinetic properties:		
Absorption	Almost complete	50-75%
Half-life ($t_{1/2}$)	3-13 hours	1-2 hours
Distribution	80% protein bound	80% protein bound
Metabolism	Kidney, 85%	Liver, 90%
Excretion	In urine as metabolites (88-93%)	In urine as a glucuronide conjugate (66%)

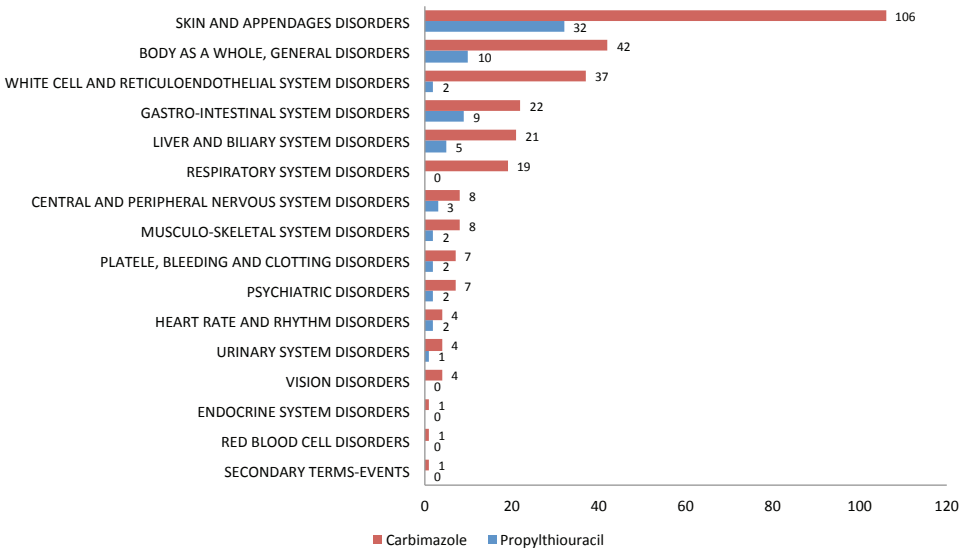
Spontaneous Adverse Drug Reaction (ADR) Reports In Malaysia

Since year 2000, the National Pharmaceutical Control Bureau (NPCB) has received 161 spontaneous ADR reports (292 adverse events) related to carbimazole, and 39 reports (70 events) related to PTU[6].

According to the Malaysian Statistics on Medicines (MSOM) 2008 report, carbimazole usage is about five (5) times higher than PTU in both public and private healthcare facilities. This may explain the difference in number of ADR reports received for these two drugs. Comparison of Malaysian adverse events based on system organ class (SOC) is detailed in *Graph 1*.

A search of the WHO adverse drug reaction database[7] revealed a total of 3,749 ADR reports related to carbimazole and 2,782 for PTU. The top three SOC involved were similar to Malaysia, namely 'Skin and appendages disorders', 'White cell and reticuloendothelial system disorders', and 'Body as a whole, general disorders'.

Graph 1: Comparison of adverse events according to system organ class for carbimazole and propylthiouracil (Jan 2000-June 2013)



(i) Skin and Appendages Disorders

This was the top system organ class (SOC) of ADRs reported for both drugs in Malaysia (36.4% for carbimazole and 45.7% for propylthiouracil- PTU). This was also the top SOC in the World Health Organisation (WHO) database (35% for carbimazole and 39% for PTU).

The reports received in Malaysia were mostly on various types of rash (55 events for carbimazole; 19 for PTU), pruritus (30; 11), and alopecia (5; 3). There were two (2) serious skin reaction reports on Stevens-Johnson syndrome (SJS), both associated with carbimazole.

More than 45% of the skin reactions for both drugs were just reported as rash, without stating the specific skin condition diagnosed. Healthcare professionals are advised to **specify the type of rash** in ADR reports, to help in causality assignment by allowing exclusion of alternative etiologies such as viral exanthems and bacterial infections. Skin reactions commonly associated with antithyroid medication are maculopapular rash, pruritus, urticaria and vasculitis[8].

(ii) Body as a Whole, General Disorders

Reports received for this SOC included fever, body ache, generalised weakness and headache. These commonly reported adverse events made up 14.4% of the reports for both carbimazole and PTU.

(iii) White Cell and Reticuloendothelial System Disorders

There were 37 adverse events (13%) under this SOC associated with carbimazole which were reported as agranulocytosis (17), neutropenia (14), granulocytopenia (2), leucopenia (2), and febrile neutropenia (2). For PTU, two adverse events (2.9%) for this SOC (leucopenia and neutropenic sepsis) have been received in Malaysia from two separate ADR reports. The WHO database contained 1,080 reports (29%) for carbimazole and 636 (23%) for PTU related to this SOC.

Three (3) deaths were reported in Malaysia due to neutropenic sepsis, all related to patients who were taking carbimazole. All three cases were assigned causality C3 (possibly-related) by MADRAC as the patients were taking other concomitant medications and some had underlying illnesses.

(iv) Gastrointestinal System Disorders

Commonly reported adverse events under this SOC for both drugs were nausea, vomiting, diarrhoea, oral ulceration and constipation.

(v) Liver and Biliary System Disorders

The main adverse events reported in this SOC were hepatic enzymes increased, jaundice and hyperbilirubinemia. Reflecting the same trend as the other SOCs, there were more reports for carbimazole than PTU. Although the overall reporting incidence involving this SOC for both drugs was 7%, which is lower than the WHO data (12-14%), patients should be monitored closely for signs and symptoms of liver injury to prevent severe hepatotoxicity.

Updates in Prescribing Practice

Management of adverse drug reactions

There is about 50% **cross-sensitivity** between carbimazole and propylthiouracil, therefore close monitoring is required if switching between these two drugs due to adverse effects[8]. For mild skin reactions, the drug may be continued with antihistamine treatment. However, severe reactions (e.g. SJS, agranulocytosis, or liver failure) require antithyroid drugs to be stopped immediately and radioiodine therapy may be considered.

As PTU may cause hypoprothrombinemia and bleeding, prothrombin time should be monitored during therapy especially before surgery[3].

Efficacy and safety of high-dose carbimazole therapy

There have been suggestions that high-dose carbimazole treatment (≥60mg per day) may improve long-term remission rates in Graves' disease, however studies have failed to confirm this effect. Conversely, trials showed that this high-dose treatment led to more frequent minor and major side effects, especially skin reactions[8,11].

Management of hyperthyroidism in pregnancy and breastfeeding[1,9,10]

(i) Hyperthyroidism must be well controlled in pregnancy, avoiding even mild hypothyroidism or thyrotoxicity which increase the risk of abnormal brain development, miscarriages, prematurity, etc.

(ii) The **minimum effective dose** of antithyroid medication should be used. Both drugs cross the placenta, and in high doses may cause fetal goitre and hypothyroidism.

(iii) Breastfeeding[10]**:**

- Mothers should be counselled to take the medication in divided doses immediately following each breastfeeding session.

In 2011 and 2013 respectively, the American Thyroid Association and the National Institute for Health and Care Excellence (NICE), United Kingdom published updated guidelines on the management of hyperthyroidism during pregnancy and postpartum. The NPCB is reviewing this issue and current practice in Malaysia with the aim of updating the prescribing information of these antithyroid medications.

Advice for Healthcare Professionals Regarding Carbimazole and PTU:

- Patients should be provided with written information on the side effects of these medicines[9].
- Patients and caregivers should be educated to stop taking the medication and seek treatment immediately at the first sign of rash, fever, sore throat, mouth ulcers, or bruising.
- Patients should be given pre-pregnancy counselling, and monitored closely throughout the pre-pregnancy, ante-, and postnatal periods.
- Both drugs carry a potential risk of serious hepatotoxicity, including liver failure and death. Patients should be monitored closely for signs and symptoms of liver injury. Discontinue treatment promptly if liver injury is suspected.
- A diagnosis of the specific type of skin rash should be obtained and reported. Please attach the Cutaneous ADR Classification Form to report the type of rash (available on www.bpfk.gov.my).
- Any suspected adverse reaction related to carbimazole or PTU should be reported to the National Pharmaceutical Control Bureau, especially involving use in pregnancy, breastfeeding or effects on newborn children.

References:

1. Malaysian Endocrine and Metabolic Society (2000). *Practice Guidelines for Thyroid Disorders: The Malaysian Consensus*. Ministry of Health Malaysia.
2. Micromedex Healthcare Information version 2.0. [Accessed: 2 August 2013]
3. Propyl Tablet approved Malaysian package insert (version Aug 2011).
4. Camazol Tablet approved Malaysian package insert (version Jan 2008).
5. Ministry of Health Malaysia Drug Formulary (FUKKM). [Accessed: 2 August 2013]
6. The Malaysian Adverse Drug Reaction Database. [Accessed: 2 August 2013]
7. WHO Global ICSR Database [Accessed: 2 August 2013].
8. Scanlon M. & Rees A. (Eds.) (2008). *Specialist Training in Endocrinology*. Elsevier Limited, UK, pp:67-68.
9. Clinical Knowledge Summaries (2013). *Hyperthyroidism: Prescribing Information.* National Institute for Health and Care Excellence (NICE), UK. [Accessed:3 August 2013]
10. Stagnaro-Green A, Abalovich M, Alexander E, et al. (2011). *Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum*. Thyroid 21(10):1094-1096.
11. Grebe SKG, Feek CM, Ford HC, et al. (1998). *A randomized trial of short-term treatment of Graves' disease with high-dose carbimazole plus thyroxine versus low-dose carbimazole*. Clin. Endocrinol. 48:585-592.

LOCAL ADR CASE REPORTS

PROMETHAZINE - USE IN CHILDREN AGED LESS THAN TWO YEARS

By Lee Sing Chet

Case 1:

A one-and-a-half-month old Malay boy had apnoea, cyanosis and decreased oxygen saturation after being given syrup promethazine. The medication was prescribed for the indication of cough from a private clinic. He was also given syrup paracetamol and syrup amoxicillin/clavulanate.

Two (2) days later, he had an apnoeic episode at home and his lips became cyanosed before he was admitted to the hospital. The noted oxygen saturation was 88%, hence oxygen therapy was given. The child then recovered and was discharged. The causality given was C3 (possibly-related).

Case 2:

A second recent case involved a Malay boy aged one and a half months. He was given syrup promethazine for worsening cough by a private hospital. However his cough did not resolve and the child was admitted 2 days later due to rapid breathing. Nebulisation and antibiotics were given in the hospital. He was later discharged with polaramine, salbutamol and ampicillin/sulbactam.

A day later, the child had another cyanotic episode, with the absence of apnoea. His upper and lower limbs were jerking. No drooling of saliva, uprolling of eyeballs or post-ictal drowsiness were observed. The child's mother treated him with nebuliser and performed Cardiopulmonary resuscitation (CPR) at home, following which he recovered. The report was given causality C3 (possibly-related).

Note from the Drug Safety Monitoring Centre:

The Drug Safety Monitoring Centre, NPCB would like to remind all healthcare professionals that products containing promethazine are **contraindicated** for use in paediatric patients less than 2 years of age due to the risk of fatal respiratory depression. In paediatric patients aged 2 to 6 years, promethazine should to be used with **caution**. Several risk minimisation steps have been taken by the NPCB, such as communication of this safety concern via the MADRAC Newsletter[1] and issuing reminder letters to healthcare professionals[2,3]. Please report all adverse events suspected to be associated with the use of promethazine, particularly when it involves paediatric use.

References:

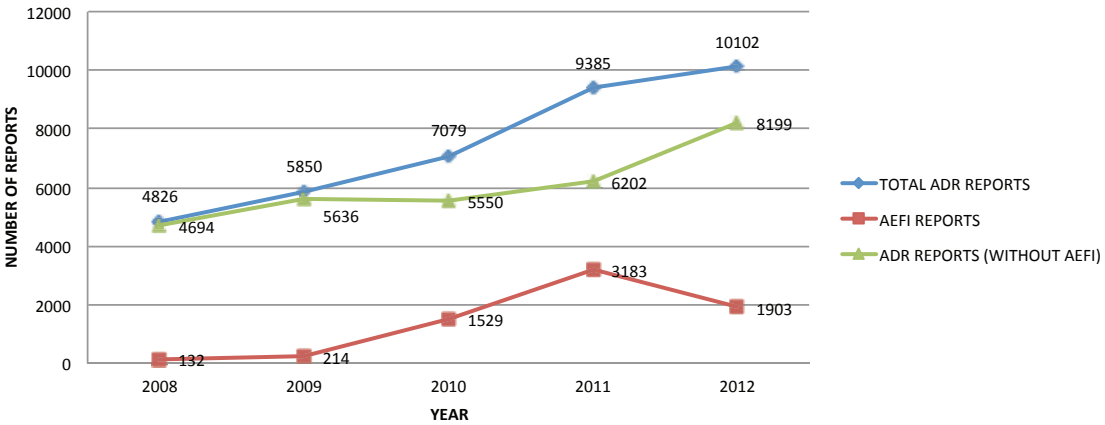
1. MADRAC Bulletin edition December 2007 and edition August 2010.
2. BPFK. *Amaran Dari U.S. Food & Drug Administration (US FDA) Berkaitan Penggunaan Ubat Untuk Rawatan. Ruj. (54)* dlm BPKF/17/FV/2.8 [21 February 2008]
3. *BPFK. Promethazine: Kontraindikasi Dalam Kanak-Kanak Berumur Kurang Daripada 2 Tahun.* Ruj. (50) dlm. BPFK/PASCA/FV/2.15 (18 April 2013)

ANNUAL REPORT FOR 2012: LOCAL ADR REPORTS

SUSPECTED ADVERSE DRUG REACTIONS REPORTED IN 2012: AN OVERVIEW

The increasing number of ADR reports received has reached a total of **10102** reports in the year 2012, indicating a 7.6% increase from the previous year. However, there was a 40% decrease in the number of Adverse Event Following Immunisation (AEFI) reports received (*please refer to Graph 2*).

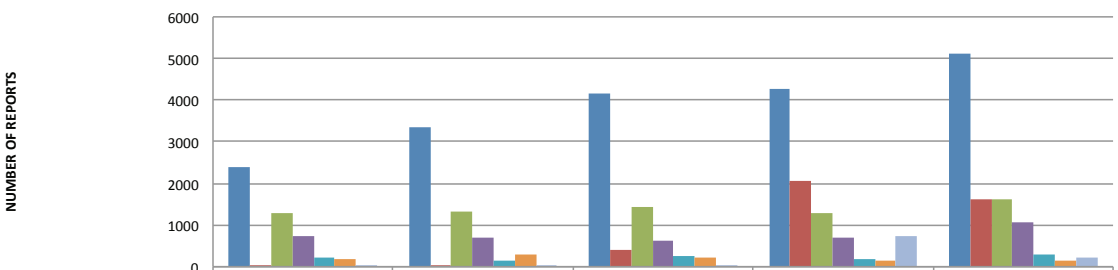
Graph 2: Suspected Adverse Drug Reaction Reports Received in Malaysia (Year 2008-2012)



ADR Reporters – Similar to previous years, the majority of reporters (82.8%) comprised of Ministry of Health (MOH) professionals, with 5107 reports (50.5%) being submitted by MOH pharmacists, followed by 1636 (16.2%) by MOH nurses and 1624 (16.1%) by MOH doctors (Graph 3).

This year saw the submission of reports from two new categories, namely two reports from the Armed Forces Hospital in Taiping, Perak, and 65 reports from the National Population and Family Development Board (LPPKN) which conducts the HPV Vaccination Program for 18 year-old Malaysian women.

Graph 3: Suspected Adverse Drug Reaction Reports According To Reporter (Year 2000-2012)

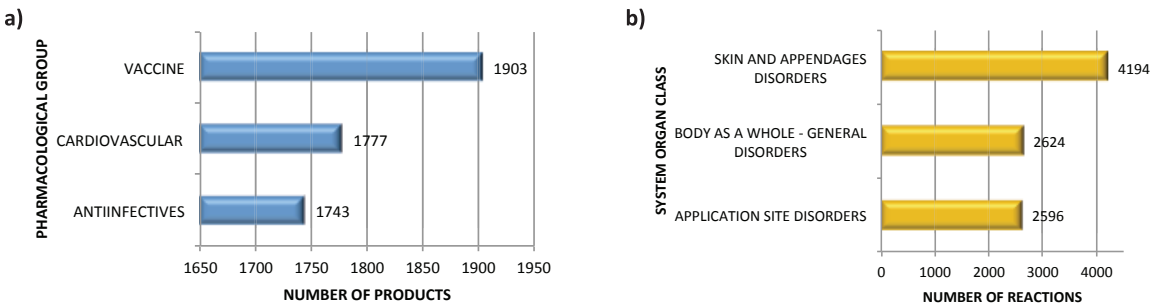


YEAR	2008	2009	2010	2011	2012
MOH Pharmacists	2401	3358	4160	4267	5107
MOH nurses	3	25	388	2063	1636
MOH doctors	1272	1340	1418	1295	1624
Product Registration Holders	751	686	612	691	1067
Private Specialists / GPs	214	144	248	185	311
Universities	173	281	234	142	151
Others	12	16	19	742	206

ADR Reports by Pharmacological Groups - Following the same trend as 2011, the highest number of ADR reports by pharmacological group was from vaccines (1903 reports; 18.8%), followed by cardiovascular drugs with 1777 suspected products (17.6%), and anti-infectives with 1743 suspected products (17.3%) (**Graph 4a**). The high number of reports involving vaccines is due to the active surveillance program conducted on the Human Papilloma Virus (HPV) vaccine through the Ministry of Health HPV Vaccination Programme.

ADR Reports by System Organ Class (SOC) - Most of the ADRs reported involved the WHO System Organ Class (SOC) 'Skin and Appendages Disorders' (23%), followed by 'Body as a Whole- General Disorders' (14%), and 'Application Site Disorders' (14%) (**Graph 4b**).

Graph 4: a) Top Three Pharmacological Groups of Suspected Adverse Drug Reactions Reported (2012)
b) Top Three System Organ Classes of Suspected Adverse Drug Reactions Reported (2012)



REGULATORY MATTERS

VOTRIENT® (PAZOPANIB) - CHANGE IN FREQUENCY OF SERUM LIVER TEST MONITORING FOR HEPATOTOXICITY

Votrient® (pazopanib hydrochloride) is an inhibitor of certain specific enzymes known as protein kinases, which are involved in the growth and spread of cancer cells. In Malaysia, Votrient® is registered with the Drug Control Authority (DCA) since 2010 in two strengths, i.e. 200mg and 400mg. It is indicated for the treatment of patients with advanced and/or metastatic renal cell carcinoma (RCC) and for the treatment of patients with advanced Soft Tissue Sarcoma (STS), who have received prior chemotherapy. The efficacy of Votrient® for the treatment of patients with adipocytic STS or gastrointestinal stromal tumours has not been demonstrated.

Since 2010, the Drug Safety Monitoring Centre has received **two (2) ADR reports** associated with pazopanib hydrochloride. These contained **seven (7) adverse events**, namely asthenia, dizziness, chest discomfort, appetite decreased, feeling of warmth, palmar plantar erythrodysasthesia and headache.

NPCB would like to inform healthcare professionals that the local package insert (PI) for Votrient® will be updated with new safety recommendations regarding serum liver test monitoring for hepatotoxicity, as follows:

- ***Serum liver function tests should be carried out before starting treatment with pazopanib, and now at weeks 3, 5, 7, and 9.***
- ***Subsequent tests should be made at months 3 and 4, and periodically thereafter as indicated.***
- ***If elevated liver enzyme values are found, they should be managed by increased monitoring or temporary or permanent interruption of treatment, as described in section 4.4 of the current product insert (PI).***

MABTHERA® (RITUXIMAB) - NEW RISK MANAGEMENT OF HEPATITIS B REACTIVATION IN PATIENTS PRIOR TO INITIATION OF THERAPY

MabThera® (rituximab) is a monoclonal antibody that works by eradicating CD20+ cells in lymphoma patients by several distinct mechanisms, including complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC) and apoptosis. Mabthera® has been registered in Malaysia since 1999 and is indicated for Non-Hodgkin's Lymphoma, chronic lymphocytic leukaemia (CLL), and rheumatoid arthritis (*please refer to the approved package insert for the details).*Since year 2004, the Drug Safety Monitoring Centre has received **39 reports** on rituximab. However, none were related to Hepatitis B reactivation.

NPCB would like to inform healthcare professionals that the existing information on Hepatitis B reactivation of the Local Package Insert for MabThera® is being updated to reflect the new management recommendations, as follows:

- ***Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with MabThera® as per local guidelines.***
- ***Patients with active hepatitis B disease should not be treated with MabThera®.***
- ***Patients with positive hepatitis B serology should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.***

AVASTIN® (BEVACIZUMAB) - ASSOCIATION WITH NECROTISING FASCIITIS

Avastin® (bevacizumab) is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human Vascular Endothelial Growth Factor (VEGF) in *in vitro* and *in vivo* assay systems. In Malaysia, there are 3 products containing bevacizumab registered with the DCA since 2005. Avastin® is indicated for metastatic colorectal cancer; metastatic breast cancer; advanced, metastatic or recurrent Non-Small Cell Lung Cancer; advanced and/or metastatic Renal Cell Cancer; glioblastoma; and epithelial ovarian, fallopian tube and primary peritoneal cancer (*please refer to the approved package insert for the details).*

Recently, NPCB was notified on global **cases of necrotising fasciitis, including fatal cases** which have been reported in patients receiving Avastin® in both clinical trials and post-marketing setting. The local package insert (PI) for Avastin® will be updated with this new safety information.

Since year 2005, the Drug Safety Monitoring Centre has received **17 spontaneous reports** on bevacizumab. However, none related to necrotizing fasciitis. The reports received consisted of 21 events, as follows: gastrointestinal bleeding (3), hypertension (2), abdominal discomfort, conjunctival haemorrhage, eye infection, febrile neutropenia, intracranial haemorrhage, headache, hepatic failure, hypertension pulmonary, lip sensitivity, muscle stiffness, nosebleed, proteinuria, rectal bleeding, slurred speech, stroke, and weight increase (1 each). All reports have been given a causality of **C3 (possibly-related).**

NPCB would like to remind all healthcare professionals that ***Avastin® therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated.***

GUIDE FOR ADR REPORTERS: IMPROVING THE QUALITY OF REPORTS

Important Note: *Please fill every section in the ADR form, stating* ***'none/-/nil'*** *if applicable.*

Is your report complete? A Checklist for ADR reporters

Frequently missing information	√
Any history of allergy (including drugs, food, etc.)?	
Any concomitant medications? (*Please state 'nil' if none*) • Date started and stopped for each medication • Please state 'cont' for any medication still continued after the ADR	
Any underlying illnesses?	
The specific indication of the suspected drug (e.g.: 'pneumonia due to S. Pneumoniae'- not 'infection' or 'antibiotic').	
If the ADR reappeared after reintroducing drug, please describe the rechallenge fully (dose given, timing, etc.).	
Was any treatment given for the ADR? (*Please describe*)	
What is the latest/ current outcome for the patient? (e.g. recovered)	
Description of the specific type and location of skin reaction? (*Use the Cutaneous ADR form available on* www.bpfk.gov.my)	
Do keep your own record of details enabling you to contact the patient/ trace the case notes later on if necessary (e.g. IC number, patient name and phone number).	

DISCLAIMER: The list above is not exhaustive and additional information requested may vary depending on safety issues that arise.