MALAYSIAN ADVERSE DRUG REACTIONS NEWSLETTER

National Pharmaceutical Control Bureau, Ministry of Health Malaysia

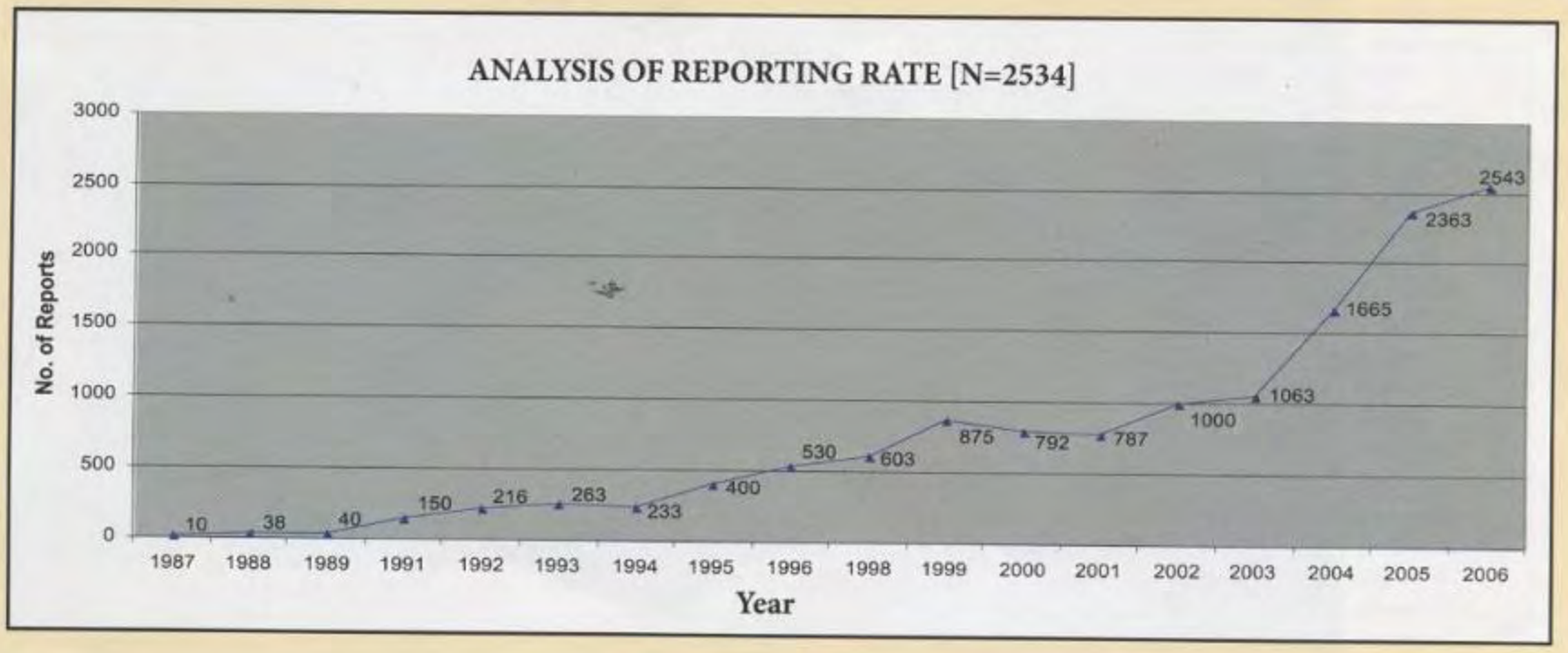
May 2007

www.bpfk.gov.my

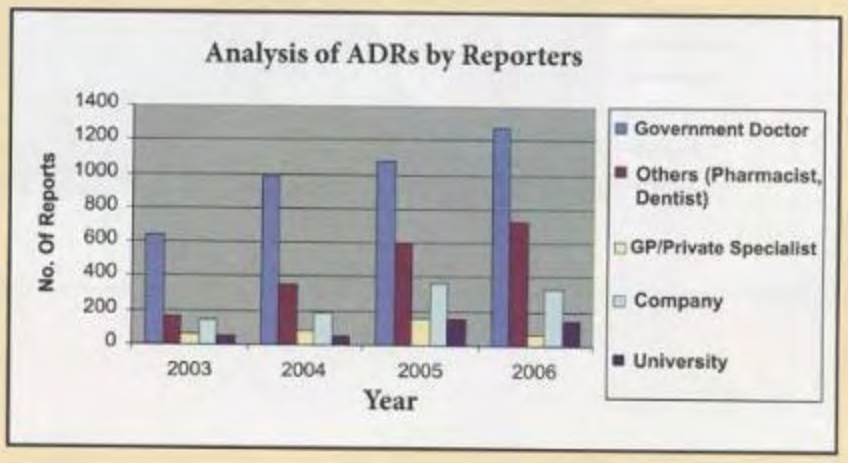
CONTENTS

OVERVIEW OF ADVERSE DRUG REACTIONS (ADR) REPORTING IN MALAYSIA FOR THE YEAR 2006

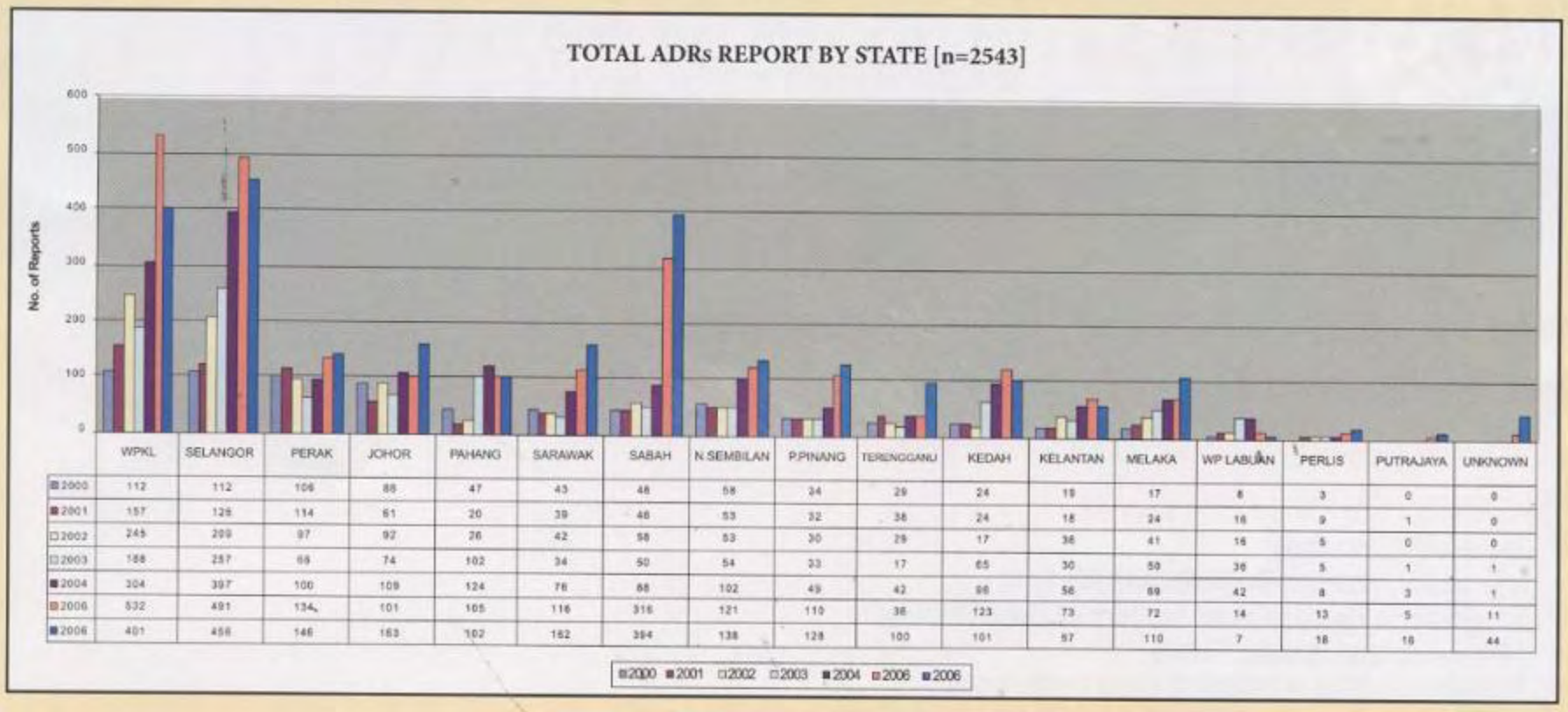
In 2006, there was an increase in the number of ADR reports received by NPCB. A total of 2543 reports were received compared to 2363 reports in 2005. (Figure 1)



As in previous years, doctors based in Government Hospitals were the most active, submitting 50% of the total number of reports received. It is noteworthy that reporting by other health professionals, such as pharmacists and dentists, increased 19.8% from 2005. (Figure 2)

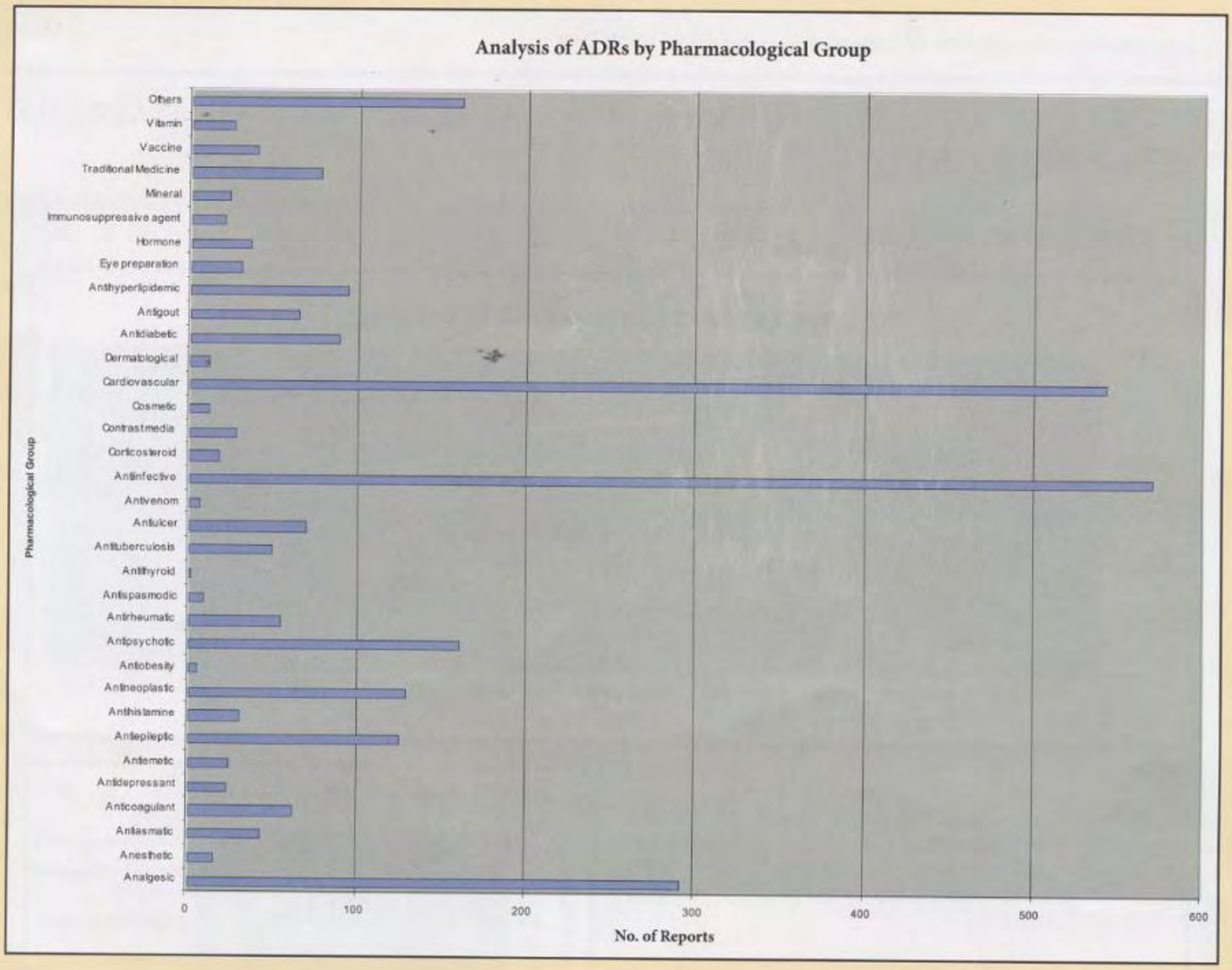


The reporting rate from various states is shown in Figure 3. Selangor submitted the highest number of reports, followed by WP KL and Sabah



	WPKL	SELANGOR	PERAK	JOHOR	PAHANG	SARAWAK	SABAH	N.SEMBILAN	P.PINANG	TERENGGANU	KEDAH	KELANTAN	MELAKA	WP LABUAN	PERLIS	PUTRAJAYA	UNKNOWN
2000	112	112	106	88	47	43	48	58	34	29	24	19	17	8	3	0	0
2001	157	126	114	61	20	39	48	53	32	36	24	18	24	16	9	1	0
2002	245	209	97	92	26	42	58	53	30	29	17	36	41	16	5	0	0
2003	188	257	66	74	102	34	50	54	33	17	65	30	50	36	5	1	1
2004	304	397	100	109	124	76	88	102	49	42	86	56	69	42	8	3	1
2006	532	491	134	101	105	116	316	121	110	36	123	73	72	14	13	5	11
2006	401	456	146	163	102	162	394	138	128	100	101	97	110	7	18	18	44

Analysis of the reports received by pharmacological group is shown below.



SUMMARY OF REGULATORY ACTIONS TAKEN IN 2006

During the course of the year, the following recommendations were proposed by MADRAC and accepted by the Drug Control Authority (DCA):

PRODUCTS	REGULATORY ACTIONS IMPLEMENTED	DCA MEETING
IRESSA	AstraZeneca forwarded an appeal to the DCA to support the use of IRESSA as a monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of both platinum-based and docetaxel chemotherapies and to support the lifting of the current restriction on promotion of IRESSA in Malaysia. The appeal was based on efficacy and safety aspects. Efficacy aspect: i. *In the ISEL study, IRESSA has demonstrated a statistically significant and clinically relevent survival advantage to best supportive care in a pre-planned subgroup of patients of Asian racial origin in a second/third line treatment setting* ii. *The IRESSA Expanded Access Programme in Malaysia has shown that IRESSA benefits patients across races in Malaysia* Safety aspect : i. *As of January 2006, of the 827 patients who were treated with IRESSA, only 2 cases of ILD were reported in Malaysia. (reporting rate 0.24%. Reporting rate in the rest of the world :other South East Asian countries excluding Japan : 0.23%)* Based on this review, the DCA lifted the restriction on promotion of IRESSA in Malaysia.	**181 (May 2006)**
Promethazine In Children	Based US FDA review reports of Promethazine safety profile, the DCA decided that the following warning statement should be included in the package inserts of all products containing promethazine hydrochloride: ***"It (brand or generic names) should not be used in pediatric patients less than 2 years of age because of the potential for fatal respiratory depression".***	**DCA 181 (May 2006)**
Gatifloxacin	Following the serious cases of both hypoglycaemia and hyperglycaemia reported with gatifloxacin during post marketing surveillance, the US/FDA directed the labeling of all products containing gatifloxacin to be reviewed. The updates include labeling changes to strengthen the existing WARNING on hypoglycaemia and hyperglycaemia and to add a CONTRAINDICATION for use in diabetic patients. Due to these safety concerns, the DCA cancelled the registration of all products containing gatifloxacin.	**DCA 181 (May 2006)**
Black Cohosh	Case reports of hepatotoxicty in patients using *Cimicifugae Racemosae* (Black Cohosh) lead to safety warnings on products in the UK. In Malaysia, Black Cohosh is classified as a traditional medicine which can be bought without prescription and is easily accessible. Therefore, the DCA agreed with MADRAC's proposal that all black cohosh products should carry the following precautionary statement: • ***Stop taking this product if signs and symptoms suggestive of liver injury develop such as tiredness, loss of appetite, yellowing of the skin and eyes or severe upper stomach pain with nausea and vomiting or dark urine and consult your doctor immediately.*** • ***Patients using herbal medicinal products should tell their doctor about it.***	**DCA 183 (July 2006)**
Arginine	The Journal of the American Medical Association (JAMA) has published the results of a study on L-Arginine Therapy in Acute Myocardial Infarction (AMI). The study was investigating the possible benefits of L-Arginine on cardiovascular parameters following AMI but was stopped as a result of six deaths. In view of the finding that L-Arginine did not improve cardiovascular circulation after the first heart attack but could increase the risk of death if used after a heart attack, Health Canada and TGA have decided all L-Arginine products must carry a warning on their labels that reflects the current safety information. The DCA agreed that the following warning must be included on labels and package inserts of oral health supplement products containing L-Arginine: ***"Arginine is not recommended for patients following a heart attack"***	**DCA 185 (September 2006)**
ACE Inhibitors	Based on the results of a cohort study on the association between exposure to ACE inhibitors in the 1st trimester of pregnancy and the risk of congenital malformations that was published in the New England Journal of Medicine, USFDA and Health Canada have directed that all ACE Inhibitors should carry a statement of this safety warning and recommend discontinuation of the affected drugs as soon as possible if a patient becomes pregnant. Following this safety concern, the DCA made the decision to strengthen the labeling of ACE inhibitors in Malaysia. All ACE inhibitors products should carry the following statement under "Warning" and "Use in Pregnancy" section :- ***"Increased risk of birth defects, fetal and neonatal morbidity and death when used throughout pregnancy".***	**DCA 186 (October 2006)**

ISSUES OF CURRENT INTEREST

ARCOXIA®(Etoricoxib)

The U.S. Food & Drug Administration (FDA) has issued a non-approvable letter in response to Merck & Co.'s application for ARCOXIA® (etoricoxib) for the treatment of symptomatic osteoarthritis (OA). ARCOXIA has been under review by the FDA since December 2003 for the 60 mg once-daily dosing and since April 2004 for the 30 mg once daily dosing. In the non-approvable letter, the FDA stated that MSD has to provide additional data in support of the benefit-to-risk profile for the proposed doses of ARCOXIA before it can be approved in the United States.

The FDA panel members felt that ARCOXIA could pose damage to the heart and it has not shown any additional benefits over other pain medications available in the market. It has been found that when ARCOXIA was given in 90 mg doses, it could cause elevated blood pressure, tissue swelling leading to heart problems and congestive heart failure. Medical scientists also found that ARCOXIA was found to cause the same cardiovascular side effects that were found in studies of VIOXX® (rofecoxib), which has been withdrawn from the market.

However, based on MSD's results of their Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme, it was shown that patients with arthritis treated with the COX-2 selective NSAID etoricoxib and those given the traditional NSAID diclofenac have nearly identical rates of thrombotic cardiovascular events. ARCOXIA is available in 66 countries in Europe, Latin America, the Asia-Pacific region and Middle East/Northern Africa. However, 8 of the countries do not market it.

Up-to-date, most of the countries are still waiting for new measures in EU. As the Europe-wide review of COX-2 inhibitors is not final, no special restrictions or regulatory measures are imposed. Meanwhile, EMEA/CHMP advises that:

- COX-2 inhibitors should not be used in patients with ischaemic heart disease or stroke.
- Etoricoxib should additionally be contraindicated in patients with hypertension whose blood pressure is not yet under control.
- Prescribers should exercise caution when using COX-2 inhibitors in patients with risk factors for heart disease such as hypertension, hyperlipidaemia, diabetes mellitus and smoking, or peripheral arterial disease.
- Doctors should use the lowest effective dose of the COX-2 medicine for the shortest possible duration of treatment.

Currently, in Malaysia, there are nine products which contain a COX-2 inhibitor; parecoxib (4), celecoxib (2) and etoricoxib (3). Etoricoxib is registered with strengths of 60 mg, 90 mg and 120 mg. Since the year 2005, the Drug Control Authority (DCA) has taken the following actions to ensure the safe use of this group of products:

- suspended the registration of products containing valdecoxib and parecoxib due to serious adverse skin reactions reported by the US FDA. (April 2005)
- reintroduced parecoxib injectable products into the market with some changes in indication, usage and warning in the package insert. (June 2005)
  - Restriction of indication
    "Management of post operative pain in the immediate post operative setting only with the exception of patients undergoing coronary bypass grafting (CABG) procedures and in those patients with cardiovascular risk".
  - Restriction to usage
    "Use should be limited to two (2) days only with a maximum dose of 80mg per day".
  - Boxed warning
    "Contraindicated in patients undergoing coronary bypass grafting (CABG) procedures and in those patients with cardiovascular risk".
- Amended the product inserts for products containing celecoxib and etoricoxib. (April 2005)
  - Included a warning about cardiovascular and gastro-intestinal risk.
  - Contraindication in patients with the risk of ischaemic heart disease and stroke.
  - Prescribed with care in patients predisposed to the risk of hypertension, hyperlipidaemia, heart disease, peripheral arterial disease and in smokers.
  - Encouraged practitioners to use the lowest effective dose for the shortest duration consistent with individual patient treatment goals.

References:
1. MSD, MEDAL Programme Publication.
2. FDA, News Release, 27 April 2007.
3. Yahoo! News, FDA Refuses Approval for Merck's Painkiller Drug, 4 May 2007.
4. EMEA, Post-Authorisation Evaluation of Medicines for Human Use, Questions and Answers on COX-2 Inhibitors, 17 February 2005

Interaction between Tramadol and Warfarin

According to an article written by Dr. Ruth Savage, Medical Assessor at Centre of Adverse Reactions New Zealand (CARM), there is evidence of an interaction between oral tramadol and warfarin, resulting in an elevated INR and in some cases haemorrhage or bruising, as provided by both international and local case reports, although the mechanism is yet to be determined.

Up to 31st July 2006, CARM received 116 reports of suspected adverse reactions to tramadol. Of these, 3 reports were increased INR, which occurred when oral tramadol was given to warfarin recipients. Two patients were symptomatic, experienced melaena and petechiae. The other patient was found to have haematoma and bruising after 8 days tramadol initiation. Dr. Savage says that it was unclear to what extent tramadol contributed to elevated INR because the patients were also receiving antibacterials and one of the patients had taken an incorrect warfarin dose. But in two of the cases tramadol appeared to be the most likely cause.

Close monitoring should be performed when it is necessary to prescribe tramadol for warfarin recipients, particularly during the first week of treatment.

References:
1. Reaction Weekly, 11 November 2006, No. 1127

Pioglitazone Hydrochloride and Risk of Bone Fracture

Eli Lilly Canada has recently received an analysis of nineteen randomized, controlled, double blind clinical trials, comparing patients treated with pioglitazone to a non-thiazolidinedione (non-TZD) comparator (placebo, or metformin, or sulphonylureas i.e. gliclazide, glyburide or glimepiride). The main study endpoint for sixteen of these trials was glycemic control while three others were liver function, carotid intimamedia thickness, and a combined cardiovascular endpoint.

Based on the analysis, it was found that the number of female patients treated with pioglitazone who experienced at least one event of bone fracture was significantly more as compared to the patients that were treated with non-TZD comparator drugs (other diabetes medications such as metformin or sulphonylureas i.e. gliclazide, glyburide or glimepiride or placebo). However, there was no increase in risk of fracture in men.

Most of the female patients had fractures mostly in the distal upper limb (forearm, hand and wrist) or distal lower limb (foot, ankle, fibula and tibia). These fractures were at different sites from those typically

associated with post-menopausal osteoporosis i.e. fractures in the hip and spine.

Therefore, health professionals should always consider the risk of fractures in type 2 diabetes mellitus female patients who are currently being treated with pioglitazone or when initiation of treatment with pioglitazone is being considered. Health professionals should also assess and help maintain healthy bones in their patients.

In Malaysia, PL Asia Pacific (Singapore), the holder of Actos® has already circulated a Dear Health Care Professional to all Health Care Professionals in April 2007.

Reference:
1. Health Canada Website, Dear Health Care Professional Letter from EliLilly Canada dated April 18, 2007

NOTE: Risk of bone fracture in females is a class effect for the thiazolidinediones

Nimesulide and Hepatic Failure

The Irish Medicines Board (IMB) has recently been made aware of new safety information regarding cases of fulminant hepatic failure (FHF) associated with the use of nimesulide. According to IMB, this reaction appears idiosyncratic in nature, was not reversible despite dechallenging nimesulide and no particular risk group could be identified. The IMB is concerned about the concomitant use of nimesulide with other hepatotoxic medications despite recommendations and advice regarding this combination.

The IMB has informed all relevant companies to suspend their systemic nimesulide products due to companies' inability to provide any additional data/proposals that were considered appropriate to address the IMB's concerns. Therefore, IMB viewed that nimesulide could not be considered as safe under normal conditions of use. This issue will be referred for further European review/assessment.

In Malaysia we have six registered products containing nimesulide; MESULID, NIMOTAS-CD, NIDOL, NIMEGESIC, NIMED and PRECOXI. All of them have included hepato-biliary disorders such as hepatitis, fulminant hepatitis, jaundice and cholestasis as adverse effects in their product information EXCEPT for NIMOTAS-CD and NIMEGESIC.

As to date, we have received two adverse drug reactions (ADR) reports related to nimesulide. Jaundice was reported in year 2005, in which nimesulide was used as a single agent therapy. In year 2006, Stevens Johnson Syndrome was reported as an adverse drug reaction to using nimesulide and orphenadrine.

References:
1. Irish Medicines Board, "Frequently Asked Questions Relating to Suspension of Marketing of Nimesulide-Containing Medicinal Products For Oral Use".
2. Irish Medicines Board's Announcement, "Immediate Suspension of the Marketing of Medicines Containing Nimesulide".

Trasylol Labelling : Restricted Indications and a Risk of Renal Dysfunction

Trasylol's new prescribing advice follows a newly completed review, which was started early this year after two reports involving Trasylol were published in medical literature. The new advice includes the following:

- Trasylol is now only indicated for prophylactic use to reduce blood transfusion and the loss of blood in patients who are undergoing cardiopulmonary bypass in the course of coronary artery bypass graft (CABG) surgery and are at increased risks of blood transfusion or blood loss.
- Aprotinin could trigger renal dysfunction, especially in patients with pre-existing renal dysfunction. In clinical studies, most cases of post operative renal function were reversible and not severe, but there have been uncommon reports of acute renal failure, oliguria and renal tubular necrosis (<1/100).
- Prior to administering aprotinin; the balance of risk and benefit should be carefully considered, particularly in those with a known risk of renal dysfunction.

Based on this information, the US/FDA requested the manufacturer of Trasylol to review the product prescribing information and also alerted healthcare professionals to the new information as stated below:-

a) Indication and Usage – more limited and focused
Trasylol is now indicated for use only in patients who are at increased risk for blood loss and blood transfusion in association with cardiopulmonary by pass in the course of coronary artery bypass grafting. It should be administered only in the operative setting where cardiopulmonary by pass can be rapidly initiated.

b) A new warning about renal dysfunction
Trasylol administration increases the risk for renal dysfunction and may increase the need for dialysis in the perioperative period.

c) Stronger Warnings about anaphylactic reactions including a new Contraindication for previous aprotinin exposure.
Anaphylactic reactions, including fatal reactions, are one of the important risks associated with Trasylol administration. As a consequence of the higher risk for anaphylactic reactions, administration of Trasylol to patients with known or suspected exposure during the past 12 months is contraindicated.

Reference :
1. Reaction Weekly, 7 October 2006, No.1122

NSAIDs – Cardiovascular, Gastrointestinal and Cutaneous Safety Review

The Australian Drug Evaluation Committee (ADEC) advised that the Package Insert of all the registered prescription NSAID medicines, including topical formulation and those with limited indications, be amended to contain, at a minimum, the following proposed statements on cardiovascular, gastrointestinal and cutaneous safety.

1. Under the Precautions Section

Cardiovascular Thrombotic Events

Observational studies have indicated that non-selective NSAIDs may be associated with an increased risk of serious cardiovascular events, principally myocardial infarction, which may increase with dose or duration of use. Patients with cardiovascular disease or cardiovascular risk of an adverse cardiovascular event in patient taking NSAID, especially in those with cardiovascular risk factors, the lowest effective dose should be used for the shortest possible duration.

There is no consistent evidence that the concurrent use of aspirin mitigates the possible increased risk of serious cardiovascular thrombotic events associated with NSAID use.

Hypertension

NSAIDs may lead to the onset of new hypertension or worsening the pre-existing hypertension and patients taking antihypertensive with NSAIDs may have an impaired anti-hypertensive response. Caution is advised when prescribing NSAIDs to patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.

Heart Failure

Fluid retention and oedema have been observed in some patients taking NSAIDs, therefore caution is advised in patients with fluid retention or heart failure.

Gastrointestinal Events

All NSAIDs can cause gastrointestinal discomfort and rarely serious, potentially fatal gastrointestinal effects such as ulcers, bleeding and perforation which may increase with dose or duration of use, but can occur at any time without warning. Caution is advised in patients with risk factors for gastrointestinal events e.g. the elderly, those with a history of serious gastrointestinal events, smoking and alcoholism. When gastrointestinal bleeding or ulcerations occur in patients receiving NSAIDs, the drug should be withdrawn immediately. Doctors should warn patient about signs and symptoms of serious gastrointestinal toxicity.

The concurrent use of aspirin and NSAIDs also increases the risk of serious gastrointestinal adverse events.

Severe Skin Reactions

NSAIDs may very rarely cause serious cutaneous adverse events such as exfoliative dermatitis, toxic epidermal necrolysis (TEN) and Stevens-Johnson Syndrome (SJS), which can be fatal and occur without warning. These serious adverse events are idiosyncratic and are independent of dose or duration of use. Patients should be advised of the signs and symptoms of serious skin reactions and to consult their doctor at the first appearance of a skin rash or any other sign of hypersensitivity.

REPORTS FROM JOURNAL

In-Utero Case Report

In May 2002, a 24-year-old Malay female was diagnosed with cervical and mediastinal lymphadenopathy due to Hodgkin's Disease of mixed cellularity variation. She did not receive any treatment until December 2004. Her last menstrual period was 24 weeks before admission. She had hepatomegaly and gravid uterus which was consistent with 18 weeks gestation. Ultrasound of abdomen confirmed a viable foetus weighing 0.87kg with no foetal abnormality.

Therapy was started from 25 weeks gestation onwards with a two-day course of chemotherapy regimen consisting of doxorubicin, bleomycin, vinblastine and decarbazine in the usual dose with granisetron as anti-emetic, thereafter every 3-4 weeks. The mother did not experience any significant adverse effect due to the chemotherapy. The mother delivered a healthy baby boy after 38 weeks of gestation by caesarean section. The baby weighed 1.65kg with a good Apgar score of 1 min 9, 5 min 10. The baby was admitted to intensive care unit for observation and discharged well with normal blood counts after a week.

Both the mother and baby remained well after ten months (at the time of reporting).

Reference:
1. Med J Malaysia Vol 61 No s August 2006

CURRENT REGULATORY ISSUES

Tegaserod Maleate and Risk of Cardiovascular Adverse Events

In February and March 2007, Novartis reported to the US FDA the results of new analysis of 29 short – term (1-3 months) randomized, controlled clinical studies of Zelnorm (marketed in Malaysia as Zelmac). The US FDA concluded, based on these data that for most patients the benefits of this drug no longer outweigh the risks.

The analysis included more than 11,600 patients treated with Zelnorm and over 7000 patients treated with placebo. The data showed that the risk of serious cardiovascular adverse events (e.g. angina, heart attacks and strokes) associated with Zelnorm is higher than with placebo treatment. Thirteen Zelnorm – treated patients (0.1%) had serious and life-threatening cardiovascular side effects; among these, four patients had a heart attack (one died), six had a type of severe heart chest pain which can quickly turn into a heart attack, and three had a stroke. Of the patients taking placebo, one (0.01%) had symptoms suggesting the beginning of a stroke that went away without complications.

Based on this analysis, the US FDA and Health Canada requested Novartis to suspend the sales of the Zelnorm immediately and initiate product recall. TGA, Australia and Medsafe, New Zealand also followed the same action.

Swissmedic, Switzerland, instructed that women with cardiovascular risk factors or cardiovascular disease should stop using the drug, whilst those without cardiovascular risk factors could continue to take the drug if they have good response to it. Therapy was not to be initiated in new patients.

The European Medicines Agency (EMEA) had all along refused to grant marketing authorization on the ground that Zelnorm's benefits are not greater than its risks (adopted the final negative opinion recommending refusal of marketing authorization on 23 March 2006).

In Malaysia, Zelmac had been registered with the DCA for use as a **"symptomatic treatment of female patients with abdominal pain and constipation associated with irritable bowel syndrome (IBS)"**
On 2nd April 2007 the DCA made the following decisions :-

- Requested to Novartis Corporation to suspend the importation, sales and distribution of Zelmac immediately and to issue a Dear Healthcare Professional Letter advising prescribers not to initiate treatment for new patients and to review treatment options for patients already on Zelmac
- Made a press release to advise the Public on the above matter
- Review the product registration for Zelmac in the light of current available information on its benefit -risks profile.

Product Registration for Zelmac was subsequently cancelled by the DCA at its May Meeting.

For any query, complaint and reporting adverse drug reaction, please contact :

Adverse Drug Reaction Monitoring Centre
National Pharmaceutical Control Bureau
Ministry of Health
P.O. Box 319, Petaling Jaya
Selangor

Tel : 03 - 7957 3611
Fax : 03 - 7956 7151

Also available at : www.bpfk.gov.my