LOCAL CASE REPORTS

JAMU ASAM URAT JAYA ASLI

During the period 2004-2005, MADRAC received 10 ADR reports associated with the use of a traditional medicine called "Jamu Asam Urat Jaya Asli" mainly from East Malaysia. On investigation, it was found that the product 'Jamu Asam Urat Jaya Asli" is an unregistered product which has never been submitted for registration in Malaysia. This product which is a yellowish powder "jamu" is believed have been imported illegally and it is sold between RM8 – RM10.

From the information on the product label, this product is promoted to treat knee pain and muscular pain, reduce body heat and body tiredness and to increase sexual performance. This product is to be mixed with hot water, honey or lime juice together with an egg yolk and to be taken at least 2 times daily.

The adverse events that were reported associated with the use of this product included hepatic disorders [Hepatitis (3), Jaundice (2), hepatic encephalopathy, liver function test abnormal (2)]; skin reactions [Epidermal Necrolysis (1), Steven Johnson's Syndrome (2), rash (2)]; gastrointestinal disorders [haematemesis (1), vomiting (2), abdominal pain (3), nausea (2)] and other [Eosinophilia (1), DRESS Syndrome (1), fever (2), conjunctivitis (1), stool reddish (1), facial puffiness (1), shortness of breath (1), weakness generalized}

Upon analysis of samples of this product, it tested positive for phenylbutazone. The Pharmacy Enforcement Division was informed and a press release was subsequently made to warn the public to avoid the use of this unregistered product.

MADRAC would like to take this opportunity to thank the reporters who submitted these reports and helped avert other members of the public from using this product.

Note : A similar product was also identified by the Health Sciences Authority, Singapore which was found to contain phenylbutazone

Valproic Acid Induced Pancreatitis in a Child

MADRAC received a report of a 3 year old girl who who was suspected to have developed pancreatitis as a result of the use of sodium valproate which was prescribed to manage her epilepsy.

The child presented with vomiting, abdominal tenderness and poor oral intake which was attributed to loss of apetite. The child had been taking Syrup Sodium Valproate 100mg twice daily but the exact duration was unknown.

On admission, the laboratory findings were suggestive of acute pancreatitis and a laprotomy was done which confirmed the diagnosis.
Sodium valproate was stopped and the patient was switched to Syrup Clonazepam and subsequently recovered.

Valproic Acid has been used extensively as one of the primary anticonvulsants for generalized seizures in children for the past 25 years. It has been stated that drug induced pancreatitis is thought to account for 2-5% of cases of acute pancreatitis with as many as 13% of paediatric cases of acute pancreatitis being drug induced.[1,2]

Prescribers should therefore be always aware of this drug induced adverse reaction in peadiatric patients who are prescribed Valproic Acid and action should be taken early to manage the pancreatitis.

References:

1. Greenberger NJ, Toskes PP. Acute and Chronic Pancreatitis. In Kasper DL, Braunwald e, Fauci AS, et al (Eds) Harrison's Principles of Internal Medicine 16th Ed 2005

2. Pellock JM, Wilder BJ, Deaton R, Sommerville KW. Acute pancreatitis conincident with valproate use: A critical review. Epilepsia 2002;43(11): 1421-1424

ISSUES OF CURRENT INTEREST

Tibolone

TIBOLONE (LIFT STUDY) - *the increased risk of stroke outweighs the benefit of a decreased risk of vertebral fractures*

TThe LIFT Study is a multicenter, multinational randomized study to investigate the effect of Tibolone (Livial) on the incidence of new vertebral fractures in osteoporotic post menopausal women. The secondary endpoints include cardiovascular, gynecological and breast safety. The study enrolled **4538 osteoporotic women of an average of 68 years**, receiving either Tibolone or placebo for 3 to 5 years. **The study started in 2001 but did not include participants from Malaysia.**

The study was overseen by a Data Safety Monitoring Board (DSMB) which bi-annually evaluates the benefits and risks of the participants, based on unblended data. In September 2005, Organon informed regarding the **increased risk of stroke** with Tibolone in the ongoing LIFT Study, based on 23 versus 9 cases of stoke (ischaemic and haemorrhagic) on Tibolone and placebo, respectively. In January 2006, the DSMB informed again that the number of cases was 25 and 11, respectively. The increased risk has thus not changed.

The Board on January 28-29, 2006 in Brussels, Belgium reviewed again the LIFT Data as of December 15, 2005 with an average of 33 months of follow-up and about 50% of participants completing the 3-year visit. Based on these findings the DSMB recommended that for the participants taking part in the study, the increased risk of stroke outweighs the benefit of a decreased risk of vertebral fractures and the participants should stop taking their study medication as soon as practical. In summary, the DSMB feels that Tibolone is not an appropriate medication for long term treatment of osteoporosis in older women due to observed risk of stroke.

Organon has decided to end the study as recommended by the DSMB. As a consequence of the findings, Organon also decided not to pursue the indication "Treatment of Osteoporosis". This issue has been announced to the public on Thursday 16 February, 2006.

In Malaysia, the DCA has approved one product containing Tibolone as follows:

Name of Product	:	Livial Tablet 2.5mg
Registration No.	:	MAL19913394A
Registration Holder	:	Organon (M) S/B
Approved Indications	:	*"Treatment of complaints resulting from natural or artificial menopause"*

Comments by Organon (Malaysia):

Women who use Tibolone for the above indications are on average much younger than the patients in the LIFT study group. In these younger patients (average age 55 years), the clinical trial database shows no increased risk for stroke.
However, Organon has submitted a proposal for a label change to the European Health Authorities in October 2005 to reflect the findings of this study. The proposal is still being discussed and as soon as an agreement is reached, a label change will be sent to local companies worldwide for submission to the Health Authorities including Malaysia.

MALAYSIAN ADVERSE DRUG REACTIONS NEWSLETTER

MINISTRY OF HEALTH MALAYSIA w w w . b p f k . g o v . m y MAC 2006

IN THIS ISSUE

ADR MONITORING: A CO-OPERATIVE PROGRAMME FOR ENHANCING THE SAFER USE OF MEDICINES

OVERVIEW OF
ADVERSE DRUG REACTION (ADR) REPORTING IN MALAYSIA FOR THE YEAR 2005

In 2005, there was a marked increase in the number of adverse drug reaction reports received compared to previous years. A total of 2363 reports were received in 2005 vs 1665 reports in 2004 and 1067 reports in 2003, i.e an increase of 41.9% and 121.5% respectively (Figure 1)

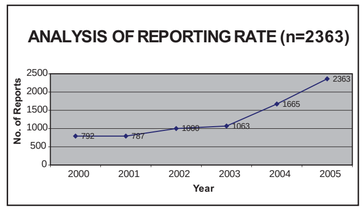


Figure 1

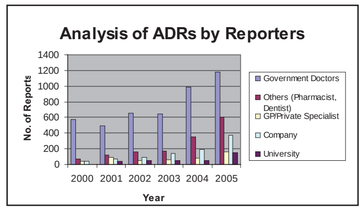
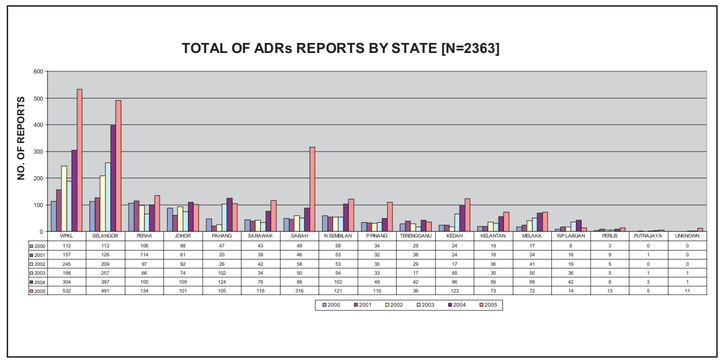


Figure 2

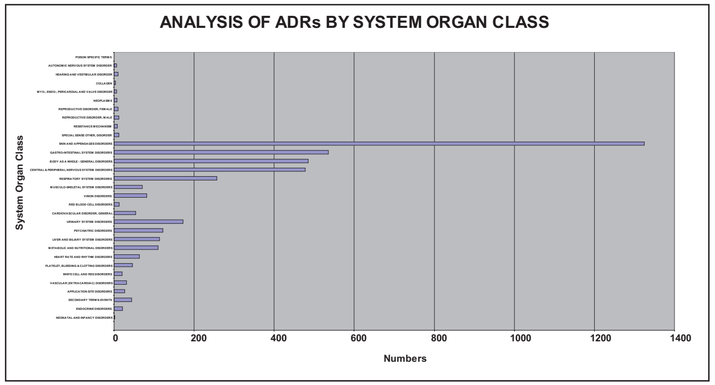
An analysis of the health professionals who submitted ADR reports showed that, as in previous years, doctors based in Government Hospitals submitted the most number of reports constituting 49.9% of the total number of reports received. It is noteworthy that reporting by product registration holders has shown an increasing trend over the years. In 2005, 368 industry driven reports were received which is almost twice the number received in 2004. The number of reports submitted by pharmacist also increased by 72% in 2005 compared to the previous year.The reporting rate from the various states is shown in figure 3. The highest number of reports were submitted from the Kuala Lumpur Hospital followed by the states of Selangor and Sabah.

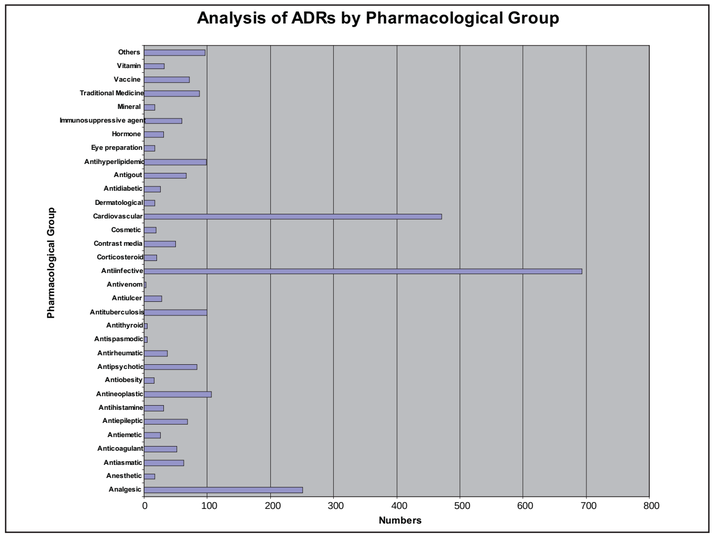


	WPKL	SELANGOR	PERAK	JOHOR	PAHANG	SARAWAK	SABAH	N.SEMBILAN	P.PINANG	TERENGGANU	KEDAH	KELANTAN	MELAKA	WP LABUAN	PERLIS	PUTRAJAYA	UNKNOWN
2000	112	112	106	88	47	43	48	58	34	29	24	19	17	8	3	0	0
2001	157	126	114	61	20	26	46	53	32	36	24	18	24	16	9	1	0
2002	245	209	97	92	26	42	58	53	30	29	17	36	41	16	5	0	0
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	96	56	69	42	8	3	1
2005	532	491	134	101	105	116	316	121	110	36	123	73	72	14	13	5	11

Figure 3

Analysis of the reports recievd by age, system organ class, pharmacological group, gender and race are as shown in the following figures.





REGULATORY ISSUES
SUMMARY OF REGULATORY ACTIONS TAKEN IN 2005

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
1	**Nevirapine**	In view of the findings of the review of Nevirapine by the US Food & Drugs Administration, the DCA agreed with MADRAC's proposal that the indication and usage section in the Product Insert (PI) of all products containing Nevirapine should be include the following statement: ***Indications and Usage section of the Viramune label now recommends against starting Nevirapine treatment in women with CD4+cell counts greater than 250 cells/mm3 unless benefits clearly outweigh risks.*** The product registration holders were required to inform prescribers of this change to the PI	DCA 166 (January 2005)
2	**COX-2 Inhibitors**	**1. Valdecoxib, Parecoxib** The registration of products containing Valdecoxib and Parecoxib were suspended based on the issue of serious adverse skin reactions reported by the US FDA in March 2005. **2. Parecoxib** Products containing Parecoxib injectible were allowed to be reintroduced in the market following certain changes which were made to the product: **i. 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" **ii.Restriction to usage** "Use should be limited to two (2) days only with a maximum dose of 80mg per day" **iii.Boxed warning** "Contraindicated in patients undergoing coronary bypass grafting (CABG) procedures and in those patients with cardiovascular risk" **3. Celecoxib, Etoricoxib** The following changes were proposed by the DCA to the product insert for products containing Celecoxib, Etoricoxib **i.** Include a warning about Cardiovascular and Gastro-intestinal risk. Contraindication in patients with the risk of ischemic heart disease and stroke. Prescribed with care in patients predisposed to the risk of hypertension, hyperlipidaemia, heart disease, peripheral arterial disease and in smokers **ii.** Encourage practitioners to use the lowest effective dose for the shortest duration consistent with individual patient treatment goals.	DCA 169 (April 2005) DCA 171 (Jun 2005) DCA 169 (April 2005)
3	**Thioridazine**	Following the voluntary cancellation of registration for MelleriIR by Novartis (M) due to adverse cardiovascular events and poor benefit risk profile, a risk-benefit analysis of other generic products containing thioridazine was conducted. Based on this review, the DCA took the decision to disallow the continued use of Thioridazine in Malaysia and the registration of these products be cancelled. However, a grace period was given for patients to be switched to other safer antipsychotic agents before the products are fully withdrawn from the market.	DCA 169 (April 2005)
4	**Products containing Ginseng**	For traditional products containing Ginseng, the existing labeling requirement ● Safe use of Ginseng in pregnant women and children has not been established. ● Do not exceed the stated dose. ● Continous use exceeding three months is not advisable. was modified as follows: ● Safe use of Ginseng in pregnant women and children has not been established. ● Do not exceed the stated dose. ● ***"Safety on long term use has not been established"***	DCA 169 (April 2005)
5	**Propolis and Royal Jelly**	Based on a review done for products containing bee products, it was decided that products containing royal jelly and propolis for topical use should carry the following precautionary statements on the product label: **Royal Jelly** ***"Royal Jelly may cause allergic reactions. Most reports have been in asthma sufferers"*** **Propolis (topical)** ***"Propolis may cause allergic skin reactions"***	DCA 170 (May 2005)
6	**Gingko Biloba/Gingko Biloba extracts**	In order to reduce the risk of untoward events such as prolonged bleeding time, the DCA proposed that all traditional medicines containing Gingko should carry the following precautionary statement: ***As the use of Ginkgo may increase the tendency of bleeding, please consult your physician/pharmacist if you are on or intend to start using any other medicines and before you undergo any surgical/dental procedure***	DCA 171 (Jun 2005)
7	**Products derived from seafood/marine source**	As it has been reported that products derived from seafood/marine source could trigger an allergic response in susceptible users who are allergic to seafood, it was proposed that products containing active ingredients derived from seafood/marine source such as glucosamine, chitosan etc should state the source clearly on the label. Products for which is obvious that it is from a marine source such as fish oil products are exempted from this labeling requirement.	DCA 175 (October 2005)