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

To report an adverse drug reaction:

1. Visit http://www.bpfk.gov.my,
2. Click on "MADRAC (Adverse Drug Reactions)" on the left toolbar; and
3. Click on "Reporting Online".

Alternatively, please contact:

National Centre for Adverse Drug Reactions Monitoring,
Centre for Post Registration
National Pharmaceutical Control Bureau
Ministry of Health
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ADVERSE DRUG REACTIONS (ADR) REPORTS FOR 2007 – AN OVERVIEW

For the year 2007, the National Centre for Adverse Drug Reactions Monitoring received a total of 3068 local spontaneous reports of suspected adverse drug reactions. This was an increase of 525 reports (20.6%) over the 2543 reports received for 2006. The table below shows the reporting rate over the last 2 decades.

(Please refer to **'Figure 1: Analysis of Reporting Rate from Year 1987 – 2007'** *on Page 2)*

Again, the Selangor state hospitals have topped all the other states' hospitals with the number of ADR reports submitted (745). This is followed by the hospitals in Wilayah Persekutuan (466) and Johor (264).

(Please refer to **'Figure 2: Total Number of ADR Reports Received Categorized by State'** *on Page 2)*

During the course of the year 2007, pharmacists and dentists combined submitted the most ADR reports, which was 41.8% of the total number of ADR reports received. It was an increase of 76.7% as compared to the year 2006. However, the number of government doctors reporting ADRs has decreased by 15.6% compared to the year 2006.

(Please refer to **'Figure 3: Total Number of ADR Reports Received Categorized by Reporters'** *on Page 3)*

Among the ADR reports received, the most number of suspected ADRs were attributed to the pharmacological group "anti-infectives".

(Please refer to **'Figure 4: Analyses of Reports by Pharmacological Groups'** *on Page 3)*

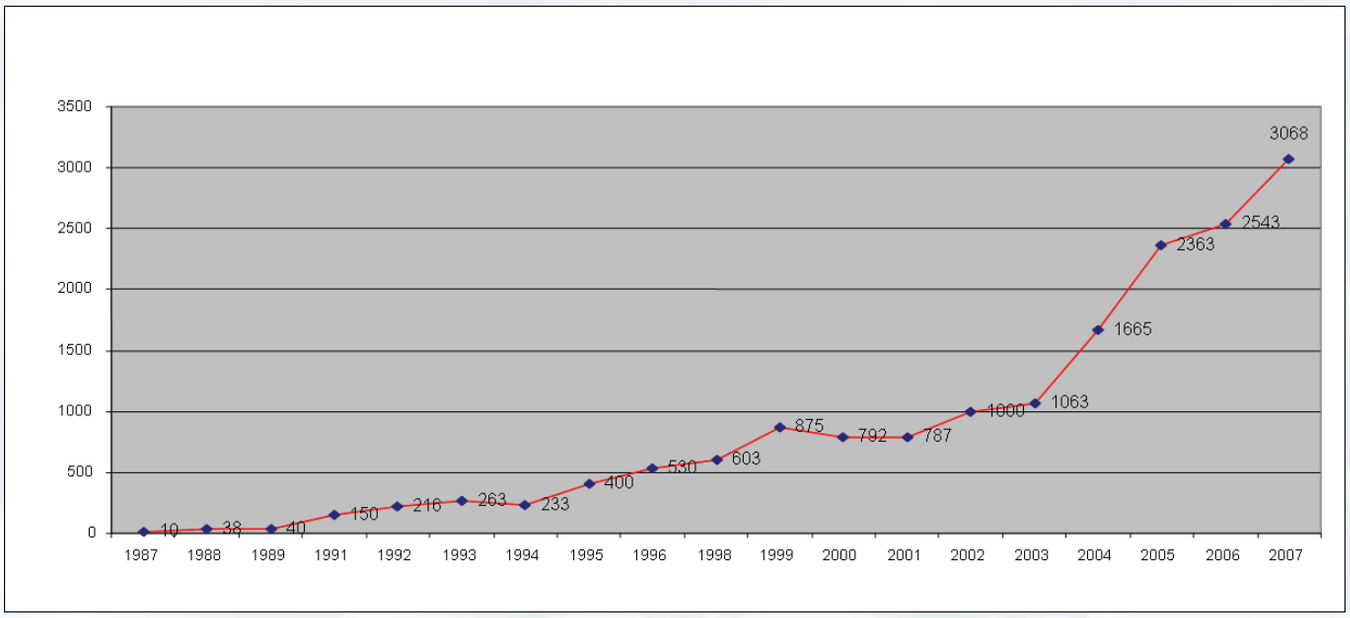
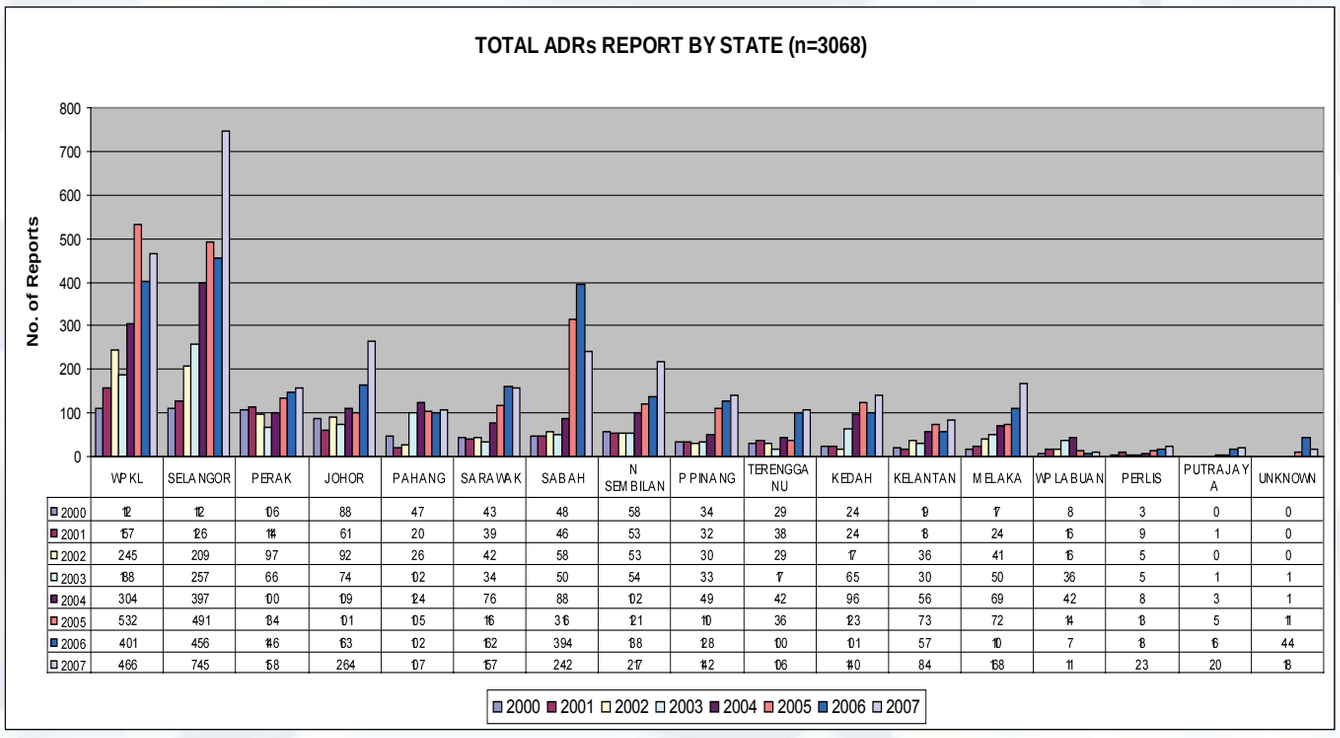
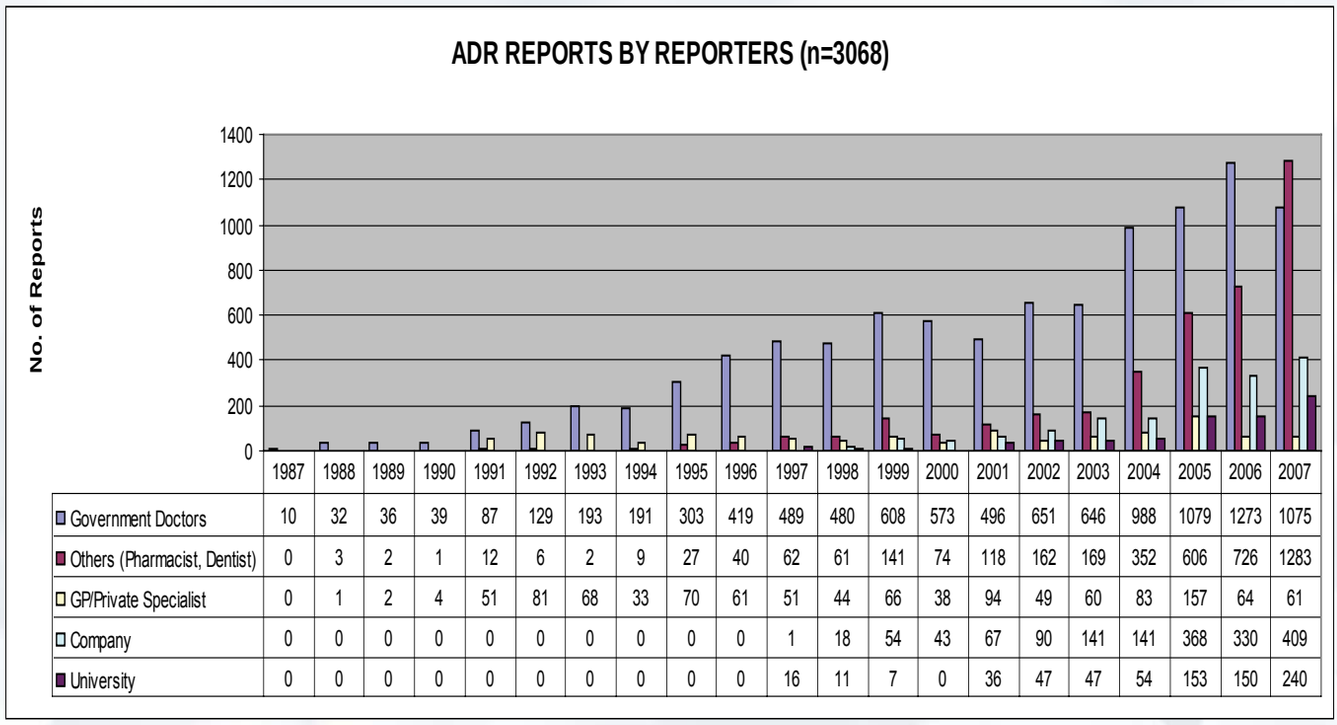


Figure 1: Analysis of Reporting Rate from Year 1987 – 2007



	WP KL	SELANGOR	PERAK	JOHOR	PAHANG	SARAWAK	SABAH	N SEMBILAN	P PINANG	TERENGGANU	KEDAH	KELANTAN	MELAKA	WP LABUAN	PERLIS	PUTRAJAYA	UNKNOWN
2000	12	12	06	88	47	43	48	58	34	29	24	9	7	8	3	0	0
2001	57	26	14	61	20	39	46	53	32	38	24	8	24	6	9	1	0
2002	245	209	97	92	26	42	58	53	30	29	7	36	41	6	5	0	0
2003	68	257	66	74	02	34	50	54	33	7	65	30	50	36	5	1	1
2004	304	397	00	09	24	76	88	02	49	42	96	56	69	42	8	3	1
2005	532	491	64	01	05	6	36	21	0	36	23	73	72	4	8	5	1
2006	401	456	46	63	02	62	394	68	28	00	01	57	0	7	8	6	44
2007	466	745	58	264	07	57	242	27	42	06	40	84	68	1	23	20	8

Figure 2: Total Number of ADR Reports Received Categorized by State



	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
Government Doctors	10	32	36	39	87	129	193	191	303	419	489	480	608	573	496	651	646	988	1079	1273	1075
Others (Pharmacist, Dentist)	0	3	2	1	12	6	2	9	27	40	62	61	141	74	118	162	169	352	606	726	1283
GP/Private Specialist	0	1	2	4	51	81	68	33	70	61	51	44	66	38	94	49	60	83	157	64	61
Company	0	0	0	0	0	0	0	0	0	0	1	18	54	43	67	90	141	141	368	330	409
University	0	0	0	0	0	0	0	0	0	0	16	11	7	0	36	47	47	54	153	150	240

Figure 3: Total Number of ADR Reports Received Categorized by Reporters

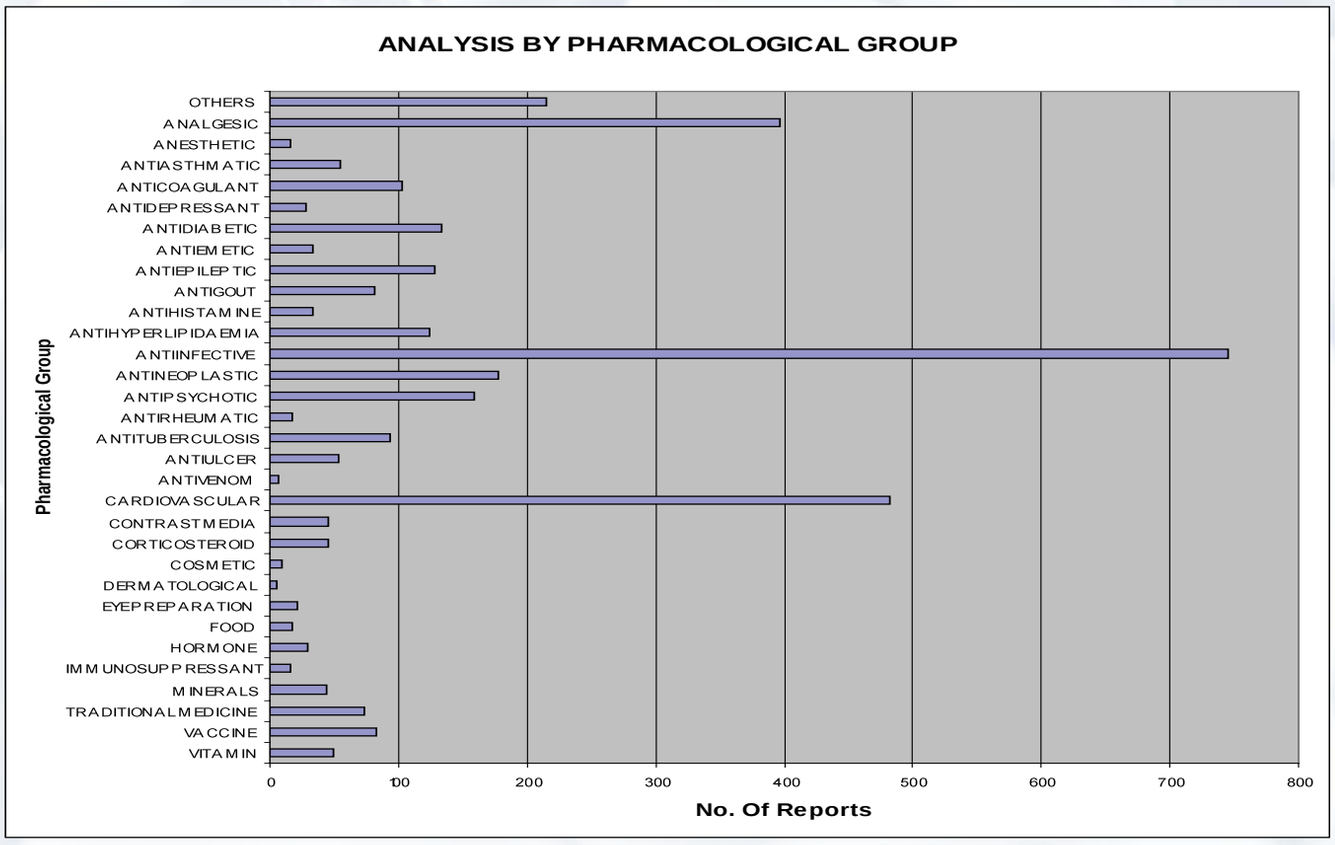


Figure 4: Analyses of Reports by Pharmacological Group

TEN DRUGS WITH THE MOST REPORTED ADVERSE DRUG REACTIONS (YEAR 2002-2007)

In 2007, the suspected drug which contributed to the highest number of ADR reports was perindopril. The ADR reports were mainly related to respiratory system disorders such as coughing/dry cough. The other suspected drugs among the top 10 which contributed to the most number of ADR reports were allopurinol, cloxacillin, diclofenac, metformin, aspirin, ticlopidine, rifampicin, phenytoin and amoxycillin. The ADR reports related were mostly skin and appendages disorders.

Figure 5 displays the ten drugs with the most ADR reports received from year 2002 to 2007. The figures are obtained from random reporting and are not absolute. Hence, the figures should not be interpreted to imply that these drugs were associated with or cause more ADRs than the other drugs of the same class.

NO	2002	2003	2004	2005	2006	2007
1	CO – TRIMOXAZOLE (47)	ALLOPURINOL (33)	ALLOPURINOL (37)	CAPTOPRIL (52)	TRADITIONAL MEDICINE (68)	PERINDOPRIL (97)
2	CARBAMAZEPINE (32)	CLOXACILLIN (30)	PARACETAMOL (29)	ALLOPURINOL (51)	DICLOFENAC (65)	ALLOPURINOL (75)
3	CLOXACILLIN (31)	MEFENAMIC ACID (25)	CARBAMAZEPINE (29)	CLOXACILLIN (50)	CARBAMAZEPINE (62)	CLOXACILLIN (71)
4	AMOXYCILLIN (28)	DICLOFENAC (24)	NIFEDIPINE (28)	DICLOFENAC (44)	NIFEDIPINE (58)	DICLOFENC (71)
5	ALLOPURINOL (22)	CHLOROTHIAZIDE (22)	CO – TRIMOXAZOLE (28)	NIFEDIPINE (44)	ALLOPURINOL (57)	METFORMIN (69)
6	TRADITIONAL MEDICINE (22)	CARBAMAZEPINE (19)	ERYTHROMYCIN (23)	METFORMIN (39)	PERINDOPRIL (57)	ASPIRIN (67)
7	ALENDRONATE (19)	TRADITIONAL MEDICINE (18)	AMOXYCILLIN (23)	PARACETAMOL (38)	CO – TRIMOXAZOLE (55)	TICLOPIDINE (50)
8	DICLOFENAC (19)	AMOXYCILLIN (18)	MEFENAMIC ACID (21)	CO – TRIMOXAZOLE (37)	ASPIRIN (41)	RIFAMPICIN (46)
9	ISOSORBIDE DINITRATE (18)	PENICILLIN G SODIUM (15)	ASPIRIN (19)	ATENOLOL (37)	ERYTHROMYCIN (40)	PHENYTOIN (44)
10	LOVASTATIN (13)	VANCOMYCIN (15)	CLOXACILLIN (18)	CEFUROXIME (36)	PHENYTOIN (39)	AMOXYCILLIN (43)

Figure 5: Ten Drugs with the Most ADR Reports

TEN BEST REPORTING HOSPITALS

In the year 2007, the National Pharmaceutical Control Bureau received the most adverse drug reactions reports from Hospital Selayang which contributed 6.42% of the total reports. This was followed by Hospital Kuala Lumpur (5.54%) and University Malaya Medical Centre (5.08%). The other reporting hospitals that were among the top ten were Hospital Duchess of Kent, Hospital Tuanku Jaafar, Hospital Pulau Pinang, Hospital Sultanah Aminah, Hospital Melaka, Hospital Umum Sarawak and Hospital Pakar Sultanah Fatimah. (Figure 6)

The National Pharmaceutical Control Bureau appreciates the contribution made by all reporters and would like to thank all hospitals and clinics which took the initiative to report suspected adverse events.

NO.	HOSPITAL NAME	NO. OF REPORTS
1.	HOSP. SELAYANG	197
2.	HOSP. KUALA LUMPUR	170
3.	UNIVERSITY MALAYA MEDICAL CENTRE	156
4.	HOSP. DUCHESS OF KENT	140
5.	HOSP. TUANKU JAAFAR	137
6.	HOSP. PULAU PINANG	126

7.	HOSP. SULTANAH AMINAH	122
8.	HOSP. MELAKA	121
9.	HOSP. UMUM SARAWAK	97
10.	HOSP. PAKAR SULTANAH FATIMAH	95

Figure 6: Ten Best Reporting Hospitals

* The ten best reporting hospitals were based purely on quantity of the reports sent in and not the quality.

SUMMARY OF REGULATORY ACTIONS TAKEN IN 2007

During the course of the year MADRAC proposed a number of recommendations based on safety concerns for the consideration of the Drug Control Authority (DCA).

The table below reflects the regulatory actions taken by the DCA for the year 2007:

No	Product	Regulatory Action Implemented	DCA Meeting
1.	Glucosamine	Due to the increasing number of adverse drug reactions reported locally, the DCA decided to update the information on side effects of all products containing glucosamine, by standardizing labeling of all glucosamine containing products to include the following statement under “Side Effects” : *Cardiovascular :* Peripheral oedema, tachycardia were reported in a few patients following larger clinical trials investigating oral administration in osteoarthritis. Causal relationship has not been established. *Central nervous system:* Drowsiness, headache, insomnia have been observed rarely during therapy (less then 1%) *Gastrointestinal:* Nausea, vomiting, diarrhea, dyspepsia or epigastric pain, constipation, heartburn and anorexia have been described rarely during oral therapy with glucosamine. *Skin :* Skin reaction such as erythema and pruritus has been reported with therapeutic administration of glucosamine.	DCA 193 (24.05.07)
2.	Tegaserod	Both the U.S. Food & Drug Administration (USFDA)-and Health Canada reported on 30 Mac 2007 that a new safety analysis on tegaserod found a higher chance of heart attack, stroke, and worsening heart chest pain that can become a heart attack in patients treated with it compared to those treated with placebo. A decision was taken on 2 April 2007 to suspend the importation, sale and distribution of the product Zelmac which contains tegaserod with immediate effect and a press release was made . In May 2007, the DCA at its 193rd meeting decided on the following actions: • To cancel the registration of product containing tegaserod (marketed as Zelmac 6mg tablet by Novartis Corporation) • Products containing tegaserod will no longer be registered in Malaysia • Novartis, the registration holder of Zelmac is given a grace period of 6 months to ensure this product is removed from the market • Novartis may import tegaserod upon request by prescribers on named patient basis when no suitable alternative drugs are available	DCA 193 (24.05.07)

3.	Sedative – Hypnotic Products	Based on post-marketing adverse events reported, the USFDA directed that the labeling of several sleep disorder products be strengthened The DCA at its 193rd meeting decided that the following warning statements should be added to products containing *zolpidem, flurazepam, triazolam and midazolam* After reviewing the range of products approved as sedative-hypnotics in the local market and sourcing the WHO databank for reported ADRs related to the products, another 7 ingredients were added to the list of products that need to carry the warnings at its 195th meeting , namely *nitrazepam, alprazolam, zopiclone, diazepam, bromazepam, clobazam and lorazepam*: • *Anaphylaxis (severe allergic reaction) and angioedema (severe facial swelling) which can occur as early as the first time the product is taken.* • *Complex sleep related behaviors which may include sleep driving, making phone calls, preparing and eating food while asleep.*	DCA 193 (24.05.07) DCA 195 (07.08.07)
4.	Pergolide	Based on the studies which showed that patients with Parkinson's disease who were treated with pergolide had an increased chance of serious damage to their heart valves, the USFDA requested all manufacturers to voluntarily remove their products from the market. Due to this safety concern, the DCA has decided on the following: • To cancel the registration of all products containing pergolide • Not to register any product containing pergolide in the future.	DCA 195 (07.08.07)

5.	Gadolinium – Based Contrast Agent	In view of the findings of the review of gadolinium-based contrast agents, the USFDA has directed to add a boxed warning and new warnings about risk of nephrogenic systemic fibrosis (NSF) to the full prescribing information of these products. Based on this information, the DCA has made the decision to strengthen the warnings of all gadolinium-based contrast agents. The following warnings must be included in their package inserts: <u>*Boxed warning*</u> • *Exposure to gadolinium – based contrast agents (CBCAs) increases the risks for nephrogenic systemic fibrosis (NSF) in patient with :* • *Acute chronic severe renal insufficiency (glomerular filtration <30mL/min/1.73m^2), or* • *Acute renal insufficiency of any severity due to the hepato – renal syndrome or in the preoperative liver transplantation period.* • *NSF is a debilitating and sometimes fatal disease affecting the skin, muscle and internal organs.* • *Avoid use of GBCAs unless the diagnostic information is essential and not available with non – contrast enhanced magnetic resonance imaging (MRI)* • *Screen all patients for renal dysfunction by obtaining a history and / or laboratory tests.* • *When administering GBCAs, do not exceed the dose recommended in product labeling. Allow sufficient time for elimination of the GBCA prior to any administration.* <u>*Additional new warnings*</u> • *Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of GBCA.* • *For patients receiving haemodialysis, healthcare professionals may consider prompt haemodialysis following GBCA administration in order to enhance the contrast agent elimination. However, it is unknown if haemodialysis prevents NSF.* • *Determine the renal function of patients by obtaining a medical history of conducting laboratory tests that measure renal function prior to using GBCA.* • *The risk, if any, for developing NSF among patients with mild to moderate renal insufficiency or normal renal function is unknown.* • *Post marketing reports have identified the development of NSF following single and multiple administrations of GBCAs.*	DCA 195 (07.08.07)
6.	Nimesulide	The Irish Medicines Board (IMB) suspended the sales of nimesulide-containing products and recalled them from the market due to concerns over a number of serious adverse events (fulminant hepatic failure) reported associated with nimesulide. The risk-benefit profile of nimesulide is deemed unfavorable as the potential of an increased risk of serious hepatic reactions is not predictable. Based on this safety concern, the DCA suspended the sales of all products containing nimesulide in Malaysia until further reviews from other regulatory agencies and feedback from local experts were received. In September 2007, the European Medicines Agency (EMEA) concluded the benefits of these medicines outweigh their risks. The Committee for Medicinal Products for Human Use (CHMP) therefore recommended that treatment with nimesulide should be limited to a maximum of 15 days and all packs containing more than 30 doses should be removed from the market. However, after reviewing the safety profile of nimesulide, availability of other alternatives and expert's opinion, the DCA decided to cancel the registration of all products containing nimesulide and not to register this ingredient in the future. All registration holders have been given a grace period of 3 months to recall their products from the market.	DCA 195 (07.08.07) DCA 199 (04.12.07)

7.	Ceftriaxone	New safety information was alerted by the USFDA on the interaction of ceftriaxone with calcium-containing products based on reports of fatal cases in neonates. Although there are no reported cases of ceftriaxone-calcium precipitates in patients other than neonates, the potential for this interaction exists in patients of any age. Hence, the DCA at its 196th meeting has decided the following precautionary statement should be included in the package inserts of all products containing ceftriaxone: <u>*Warning*</u> *Ceftriaxone must not be mixed or administered simultaneously with calcium containing solutions or products, even via different infusion lines.* *Calcium containing solutions or products must not be administered within 48 hours of last administration of ceftriaxone.* *Cases of fatal reactions with calcium – ceftriaxone precipitates in lungs and kidneys in both term and premature neonates have been described.* *In some cases the infusion lines and times of administration and calcium – containing solutions differed.* <u>*Dosage and Administration : Direction for Use*</u> *Do not use diluents containing calcium, such as Ringer's Solution or Hartmann's Solution, to reconstitute ceftriaxone. Particulate formation can result.*	DCA 196 (30.08.07)
8.	Piroxicam	The EMEA has alerted all healthcare professionals on the restrictions of systemic piroxicam-containing products due to the risk of gastrointestinal side effects and serious skin reactions. Based on these issues the CHMP concluded that piroxicam should no longer be used for treatment of short term painful and inflammatory conditions. However, it can be used to treat osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. The DCA has agreed to MADRAC's proposal to restrict the indications of all systemic piroxicam as follows: *For symptomatic relief of pain and inflammation in patients with osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.* *However it should not be the first choice of non-steroidal anti-inflammatory drug (NSAID) treatment in these conditions.* The following warnings, precautions and contraindications must be included in their package inserts: <u>*Warning and Precautions*</u> • *Treatment should always be initiated by a physician experienced in the treatment of rheumatic diseases.* • *Use the lowest dose (No more than 20mg per day) and for the shortest duration possible. Treatment should be reviewed after 14 days.* • *Always consider prescribing a gastroprotective agent.* <u>*Contraindication*</u> • *Piroxicam should not be prescribed to patients who are more likely to develop side effects, such as those with a history of gastro – intestinal disorders associated with bleeding, or those who had skin reactions to other medicines.* • *Piroxicam should not be prescribed in association with any other NSAIDs or an anticoagulant.*	DCA 199 (04.12.07)

9.	Red 2G Colouring Agent	In October 2007, the Ministry of Health Malaysia has announced to ban the use of Red 2G with immediate effect. This is based on the issuance of a European Commission Directive in July 2007 which directed a ban on the use of Red 2G in food due to safety concerns that this colorant could be genotoxic and carcinogenic. Therefore, the DCA has decided to ban the usage of Red 2G in oral preparation products and also in all products that come in contact with mucous membrane. All product registration holders are advised to reformulate their formulations with other colorants.	DCA 199 (04.12.07)
10	"Diluluskan oleh KKM (Approved by the MOH)"	In 2006, traditional medicines as a group were identified as one of the top among ten drugs with the most reported adverse drug reactions. Traditional medicines are easily available in the market and can be purchased without prescription. Most of the reports received are serious and some of the products taken from the market / submitted with the ADR reports were found to be adulterated with scheduled poisons. MADRAC has expressed concerns about this trend and suggested that the statement "Diluluskan oleh KKM (Approved by the MOH)" may mislead the consumers into thinking that such products are without safety concerns since these are "natural" products and have the KKM endorsement. Consumers can always identify the registered products based on the registration number and hologram labels which are mandatory to be stated on their labels. Based on this concern, MADRAC proposed to the DCA to delete this statement from the label of all categories of products already in the market and not to allow the same statement to be included in labels for new registration of products. A period of 6 months has been given to registration holders to comply with this requirement.	DCA 199 (04.12.07)

ISSUES OF CURRENT INTERESTS

SEVERE HYPONATRAEMIA AND SEIZURES ASSOCIATED WITH THE USE OF DESMOPRESSIN

The U.S. Food & Drug Administration (USFDA) has requested the product holders to update the prescribing information to include new information for desmopressin containing products in relations to severe hyponatraemia and seizures.

It was found that children treated with desmopressin intranasal formulations for primary nocturnal enuresis (PNE) are particularly susceptible to severe hyponatraemia and seizures. Therefore, desmopressin intranasal formulations are no longer indicated for the treatment of primary nocturnal enuresis and should not be used in hyponatraemia patients or patients with history of hyponatraemia. USFDA also advised that PNE treatment with desmopressin tablets should be interrupted during acute illnesses that may lead to fluid and/or electrolyte imbalance. All desmopressin formulations should be used cautiously in patients at risk for water intoxication with hyponatraemia.

USFDA recommended

- *Desmopressin **intranasal** formulations are no longer indicated for the treatment of primary nocturnal enuresis due to serious hyponatraemia that may result in seizures and death. Doctors should consider other options for managing this condition.*
- *Desmopressin **tablets**:*
    - *Treatment for primary nocturnal enuresis should be interrupted during episodes of fluid and/or electrolyte imbalance, such as fever, recurrent vomiting or diarrhea, vigorous exercise, or other conditions associated with increased water consumption.*
    - *Fluid intake should be restricted from 1 hour before to 8 hours after administration of desmopressin tablets.*
- *All desmopressin formulations should be used cautiously in patients with habitual or psychogenic polydipsia or in patients who are taking drugs that may cause them to drink more fluids, such as tricyclic antidepressants and selective serotonin re-uptake inhibitors (SSRIs). Patients taking desmopressin and consuming excessive fluids are at higher risk of developing hyponatraemia.*

In Malaysia, there are six products containing desmopressin that are registered by the Drug Control Authority (DCA). The DCA has informed the product holders; United Italian Trading (M) Sdn. Bhd. and Pahang Pharmacy Sdn. Bhd. to include the important new information into their products' information leaflet.

BOTULINUM TOXIN

The U.S. Food and Drug Administration (USFDA) has received reports of systemic adverse reactions including respiratory compromise and death following the use of botulinum toxins types A and B for both USFDA-approved and unapproved indications. The reactions reported are suggestive of botulism, which occurs when botulinum toxin spreads in the body beyond the site where it was injected. The most serious cases had outcomes that included hospitalization and death, and occurred mostly in children treated for cerebral palsy-associated limb spasticity. Use of botulinum toxins for treatment of limb spasticity (severe arm and leg muscle spasms) in children or adults is not an approved use in the U.S. These serious systemic adverse reactions occurred following treatment of a variety of conditions using a wide range of botulinum toxin doses.

There are 3 registered botulinum toxin products in the United States; Botox®, Botox Cosmetic® and Myobloc®. Both Botox® and Botox Cosmetic® contain botulinum toxin type A while Myobloc® contains botulinum toxin type B. Botox® is approved for treatment of conditions such as blepharospasm, cervical dystonia and severe primary axilary hyperhydrosis. Botox Cosmetic® is approved for temporary improvement in the appearance of moderate to severe facial frown lines. Myobloc® is approved for the treatment of adults with cervical dystonia.

The USFDA is currently reviewing safety data from clinical studies submitted by the manufacturers of Botox®, Botox Cosmetic® and Myobloc®, post-marketing adverse event reports and medical literature. Meanwhile, healthcare professionals who use medicinal botulinum toxins were advised to:

- Understand that potency determinations expressed in "Units" or "U" are different among the botulinum toxin products; clinical doses expressed in units are not comparable from one botulinum product to the next
- Be alert to the potential for systemic effects following administration of botulinum toxins such as: dysphagia, dysphonia, weakness, dyspnea or respiratory distress
- Understand that these effects have been reported as early as one day and as late as several weeks after treatment
- Provide patients and caregivers with the information they need to be able to identify the signs and symptoms of systemic effects after receiving an injection of a botulinum toxin
- Tell patients they should receive immediate medical attention if they have worsening or unexpected difficulty swallowing or talking, trouble breathing, or muscle weakness

In Malaysia, there are two botulinum toxin products registered. Both Botox® and Dysport® contain clostridium botulinum toxin type A.

Botox® is indicated for the

- Treatment of blepharospasm associated with dystonia, including benign essential blepharospasm, hemifacial spasm and VIIth nerve disorders in patients 12 years or older.
- Correction of strabismus in patients 12 years of age or older.
- Treatment of spasmodic torticollis (cervical dystonia) in adults.
- Treatment of dynamic equinus foot deformity due to spasticity in paediatric cerebral palsy patients, two years of age or older.
- Management of focal spasticity, including wrist and hand disability due to upper limb spasticity associated with stroke in adults.
- Temporary treatment of glabellar lines associated with corrugator and/ or procerus muscle activity in adult patients below 65 years of age.
- Management of severe hyperhidrosis of the axillae which does not respond to topical treatment with antiperspirant or antihidrotics.

Dysport® is indicated for the treatment of:

- Dynamic equinus foot deformity due to spasticity in ambulant paediatric cerebral palsy patients, two years of age or older, only in hospital specialist centres with appropriately trained personnel
- Spasmodic torticollis in adults
- Blepharospasm in adults
- Hemifacial spasm in adults

The recommended doses of Botox® and Dysport® for different conditions vary due to the difference in expression of potency determination. The table below reflects so:

Condition	Botox®	Dysport®
Blepharospasm	Initially 25U/eye. Should not exceed 100U every 12 weeks	120 units/eye.
Hemifacial spasm	Initially 25U/eye. Should not exceed 200U in 2 months.	120 units/eye.
Strabismus	1.25 – 5U depending on muscle deviation. Maximum dose as a single injection for any one muscle is 25U.	N/A
Spasmodic torticollis (cervical dystonia)	6U/kg body weight. Frequency: ≤2 months.	250 – 1000 units/patient given in divided dose and administered to two or three most active neck muscles.
Paediatric cerebral palsy	4U/kg. Maximum of 200U at any single treatment session.	10 – 30 units/kg body weight as a divided dose between both calf muscles. Maximum dose ≤1000 units/patient.
Focal Spasticity in Adults	≤360U divided among selected muscles.	N/A
Glabellar Lines	Total dose: 20U	N/A
Hyperhidrosis of the axilla	50U/axilla distributed evenly in multiple sites approximately 1-2 cm apart. Frequency: ≤2 months.	N/A

The National Pharmaceutical Control Bureau has received one adverse drug reaction report in which the patient developed fever and breathing difficulty five hours post injection of Dysport®.

LOCAL CASE REPORTS

TONIK WARISAN BANJAR

A 69-year-old male patient of Malay ethnicity developed “moon face” and “excessive weight gain” in March 2007 after a few months of consuming an **unregistered** traditional liquid preparation, “Tonik Warisan Banjar” at an unknown dosage. “Tonik Warisan Banjar” is manufactured by **Perusahaan Jamu Warisan Banjar for Syarikat Senyum, Kampong Sri Ledong, Gua Musang**. It is indicated as per label to

- strengthen muscles/veins and energy (menguatkan urat – urat dan tenaga)
- remove toxins in the body (menghilangkan toksin dalam badan)
- increase appetite (menambah selera makan)

A 100mL sample was provided along with the adverse drug reaction report. The sample was tested by the Centre for Quality Control, NPCB for steroids adulteration, and found to **contain dexamethasone**. As the preparation is an unregistered product, the report was forwarded to the Pharmaceutical Enforcement Division for further action.

CARDIAMED® (NORADRENALINE) INJECTION

The National Pharmaceutical Control Bureau recently received 7 adverse drug reactions reports related to the use of noradrenaline (Cardiamed®) from two different hospitals. The patients developed gangrene on the toe(s)/ finger(s)/leg and/or peripheral cyanosis 2 to 5 days post injection. Three batches were involved. Risk of gangrene of the extremities and/or peripheral cyanosis is documented as rare adverse events in the product information leaflet as well as in health search engines such as Lexi-Comp® and Micromedex®.

It was initially suspected that the dosing and/or method of administration could be possible contributory factors towards the adverse events reported. However, after gathering more information from the reporters, it was found that the dosing and method of administration was as per recommendation: 0.13mcg/kg/min to 0.3mcg/kg/min diluted in 5% dextrose saline infused via a dedicated central line. No other drugs were infused concomitantly.

The National Pharmaceutical Control Bureau (NPCB) conducted further investigations and requested information from other hospitals which were supplied with Cardiamed® to check if such adverse events had occurred in their hospitals. Another hospital was found to have experienced similar adverse events. However, it was not reported by the doctor at that time.

Discussions were conducted with the manufacturer of Cardiamed® who agreed to do a voluntary recall of Cardiamed® with the batches KKM 27177, KKM 27162 and KKM 27165 in view of potential patient safety concerns due to the reported adverse events. This was duly done on the 10 April 2008. In the meantime, the Drug Control Authority will continue its investigations and monitor the situation. Further regulatory action will be taken if deemed necessary. Healthcare professionals are encouraged to report suspected adverse events.