APRIL 2010

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

ACTIVITIES OF MADRAC FOR 2009

ADR REPORTING FOR 2009: AN OVERVIEW

In year 2009, the National Centre for Adverse Drug Reaction (ADR) Monitoring, National Pharmaceutical Control Bureau (NPCB) had received a total of 5850 reports. This number shows an ascending trend since year 2000 as depicted in Chart 1, with a tremendous increment of nearly 90% from year 2007 to 2009.

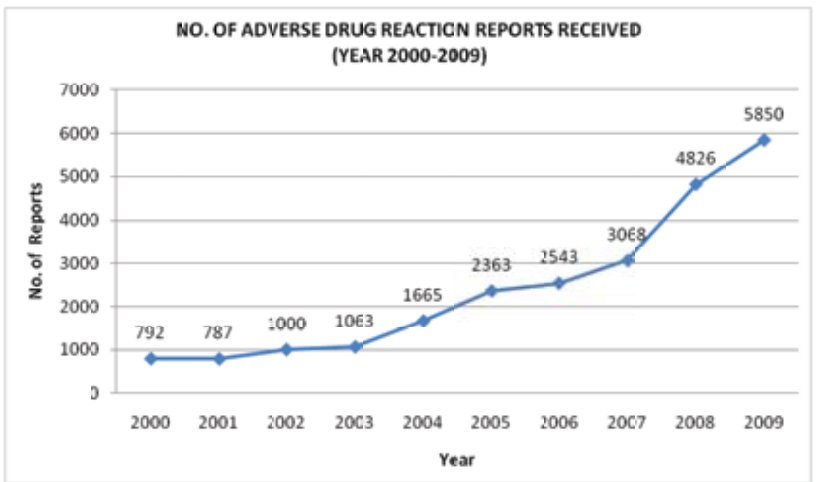

Chart 1

The reports involved 6444 suspected products, of which 6038 (93.7%) were prescription products while 286 (4.4%) were non-prescription products. There were also 97 (1.5%) ADR reports related to consumption of traditional products, and nearly 80% of these products were unregistered. The remaining 0.4% were reports related to cosmetics, food and unregistered products.

(continued)

CONTENT

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 of Products,
National Pharmaceutical Control Bureau,
Ministry of Health,
P.O. Box 319, Jalan Universiti,
46730 Petaling Jaya,
Selangor.

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

ADR Reports by Pharmacological Groups

For prescription products, approximately 50% of the reports had suspected drugs from three major pharmacological groups, namely *Cardiovascular* (1651 reports), *Anti-infectives* (954 reports) and *Analgesics* (566 reports) as per Chart 2.

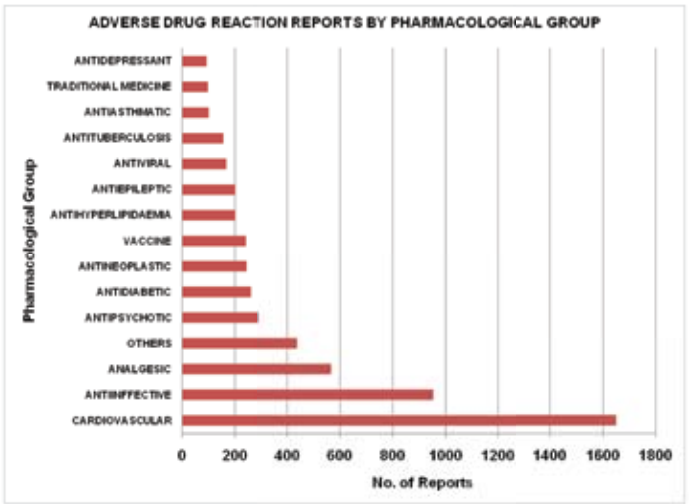

Chart 2

ADR Reporters

A total of 4698 reports were submitted by healthcare professionals in government sector (pharmacists 57.4%, doctors 22.9%), showing an increment from the previous years as in Chart 3. On the other hand, there was a decline in the number of reports from marketing authorisation holders (MAH) and healthcare professionals from private sector (11.7% and 2.5% respectively). Reports from other categories such as nurses, assistant medical officers and consumers constituted 5.5% of the reports.

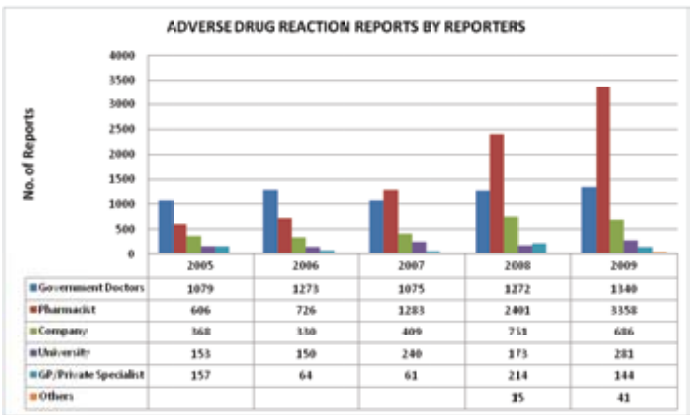

Chart 3

Selangor emerged as the most active state in ADR reporting, with 1352 (23.1%) reports submitted in year 2009 (23.1%). This was followed by Federal Territory Kuala Lumpur with 827 (14.1%) reports and Sabah with 606 (10.4%) reports. Other states such as Perak, Negeri Sembilan, Pahang, Pulau Pinang and Kelantan had all exhibited an encouraging increase in the reporting of adverse events.

ADR Reporting by System Organ Class (SOC)

Classification of reports according to SOC indicated that the most reported adverse events, i.e. 2337 events, were *Skin and appendages disorders*. Other SOC that recorded high number of adverse events were *Central & peripheral nervous system* and *Gastro-intestinal system*, with 1548 and 1342 events respectively.

Pharmacovigilance Activities: Promoting ADR Reporting

Six Adverse Drug Reaction (ADR) & Adverse Events Following Immunisation (AEFI) workshops were held in collaboration with Pharmaceutical Services Division in year 2009.

No.	Zone Covered	Date	Venue
1	East Malaysia Zone	March 2009	Kota Kinabalu
2	National level	June 2009	NPCB
3	Northern Zone	July 2009	Alor Setar
4	National level	July 2009	NPCB
5	East Coast Zone	October 2009	Kuala Terengganu
6	Central & Southern Zone	November 2009	Negeri Sembilan

Apart from these, talks were also conducted following invitations by some institutions and universities. These workshops and talks were aimed at increasing the awareness of the importance of reporting adverse events of drugs and vaccines, as well as improving the quality of ADR reports submitted.

No.	Workshop	Date	Organizer
1	Pharmacovigilance in Malaysia	February 2009 November 2009	Cyberjaya University College of Medical Sciences
2	Pharmacovigilance: Safety of Vaccines	May 2009	Jabatan Hal Ehwal Orang Asli Hospital
3	Adverse Drug Reaction Reporting & Monitoring	July 2009	Hospital Port Dickson
4	Adverse Drug Reaction & Adverse Event Following Immunisation Workshop	October 2009	JKWPKL / Putrajaya

SUMMARY OF MADRAC RECOMMENDATIONS FOR REGULATORY ACTIONS: YEAR 2009

Suspension Lifted

Suspensions on two registered products were lifted by the Drug Control Authority (DCA) following reviews of the result of investigation conducted by the National Pharmaceutical Control Bureau (NPCB) and marketing authorisation holders (MAHs). Nevertheless, NPCB will continue to closely monitor these products to ensure their safety and quality.

No.	MADRAC Meeting	Product Name	Issues	DCA Meeting
1	112 (10/12/09)	**Hydroxycut®** MAL06061641TC (a traditional product used to reduce body weight)	The product available in the US market was found to be associated with serious liver injuries. Suspension was lifted because: • the active ingredients used in the products in US and Malaysia were different; • the safety data for the product marketed in Malaysia was good and did not contribute to any adverse events; • it was free from adulteration.	223 (24/12/09)
2	112 (10/12/09)	**Cardiamed®** MAL20051326A (noradrenaline injection)	A number of ADR reports related to *gangrene* and *peripheral cyanosis* were received in a short time frame. Suspension was lifted because: • potential and quality of active pharmaceutical ingredient (API) were within specification; • the same API was also supplied to European countries and the manufacturing site was audited by the local regulatory agency according to the WHO guidelines; • supplier was classified as 'satisfactory' according to PIC/S guidelines (Annex II).	224 (28/01/10)

Package Insert Safety Updates

Pharmacovigilance Section, Centre of Post-Registration of Product, NPCB regularly reviews Periodic Safety Update Reports (PSUR) received from MAHs as a post-approval commitment between DCA and MAHs, as well as global safety updates of medicinal products. Equipped with the information, Malaysian Adverse Drug Reaction Advisory Committee (MADRAC) would then make recommendations for DCA action. In year 2009, the major amendments made to package inserts following DCA's directive were as follows:

No.	MADRAC Meeting	Product Name	Changes	DCA Meeting
1	108 (12/03/09)	**Cough & cold products**	**Additional Warnings for Use in Children** • Not to be used in children less than 2 years of age. • To be used with caution and doctor's advice in children 2 to 6 years of age.	216 (28/05/09)
2	110 (23/07/09)	**Propylthiouracil**	**Additional Warnings on Potential Risk of Hepatotoxicity** • Potential risk of serious hepatotoxicity or liver injury including liver failure and death. • Not to be used in pediatric patients unless the patient is allergic to or intolerant of the alternatives available.	218 (30/07/09)
3	110 (23/07/09)	**Clopidogrel**	**Additional Warnings on Possible Interaction with Proton Pump Inhibitors** • Concomitant use of drugs that inhibit CYP2C19 (e.g. proton pump inhibitors) should be discouraged.	218 (30/07/09)
4	110 (23/07/09)	**Antiepileptics**	**Additional Warnings on Potential Risk of Suicidal Thoughts or Behaviour** • Potential for an increase in risk of suicidal thoughts or behaviours.	218 (30/07/09)
5	111 (10/09/09)	**Colchicine**	**Additional Warnings on Severe Drug Interaction with P-glycoprotein or Strong CYP3A4 Inhibitors** • Potential risk of severe drug interactions, including death, in certain patients treated with colchicine and concomitant P-glycoprotein or strong CYP3A4 inhibitors. • P-glycoprotein or strong CYP3A4 inhibitors are not to be used in patients with renal or hepatic impairment who are taking colchicines. • A dose reduction or interruption of colchicines treatment should be considered in patients with normal renal and hepatic function if treatment with a P-glycoprotein or a strong CYP3A4 inhibitor is required. • Avoid consuming grapefruit and grapefruit juice while using colchicines.	220 (01/10/09)
6	111 (10/09/09)	**Immunosuppressant**	**Additional Warnings on Increased Risk for Opportunistic Infections** • Immunosuppressed patients are at increased risk for opportunistic infections, including activation of latent viral infections. These include BK virus associated nephropathy, which may lead to serious, including fatal, outcomes.	220 (01/10/09)
7	112 (10/12/09)	**Ceftriaxone**	**Update to the Previous Warning on Potential Interaction with Calcium-containing Intravenous Solutions** • Ceftriaxone is contraindicated in neonates (≤ 28 days of age) if they require treatment with calcium-containing intravenous solutions because of the risk of ceftriaxone-calcium precipitation. • In patients other than neonates, ceftriaxone and calcium-containing solutions may be administered sequentially if the infusion lines are thoroughly flushed between infusions with a compatible fluid.	223 (24/12/09)

REGULATORY MATTERS

SIBUTRAMINE: A SAFETY CONCERN

In January 2010, a notification was received by the National Centre of ADR Monitoring regarding the safety of sibutramine, an appetite-suppressant. It was based on a review of results from the **SCOUT** study (**S**ibutramine **C**ardiovascular **OUT**come Trial) conducted by Abbott for its product Reductil®.

The purpose of the study was to evaluate cardiovascular safety of long-term treatment with sibutramine in high risk patients. Approximately 10,000 patients were actively recruited. The inclusion criteria were over 55 years of age, overweight or obese, and had a history of heart disease and/or type II diabetes plus one additional cardiovascular risk factor. In the current clinical practice, sibutramine would have been contraindicated in majority of cases. The study showed that patients treated with sibutramine experienced 16% increased risk of a primary outcome event of non-fatal myocardial infarction, non-fatal stroke, resuscitated cardiac arrest or cardiovascular death (561/4906, 11.4%) compared with placebo-treated patients (490/4808, 10.0%) (hazard ratio 1.161 [95% CI 1.029, 1.311]; p = 0.016).

Local Scenario

There are eight products containing sibutramine that are registered with the Drug Control Authority (DCA). Package inserts for all products have incorporated the following *Contraindications/Warnings and Precautions*.

- History of coronary artery disease, congestive heart failure, tachycardia, peripheral arterial occlusive disease, arrhythmia or cerebrovascular disease (stroke or TIA)
- Inadequately controlled hypertension >145/90mmHg.

Up to March 2010, the National Centre of ADR Monitoring had received 38 reports related to the use of products containing sibutramine, of which five involved cardiovascular events (total: 6 events). The cardiovascular events reported were myocardial infarction (2), palpitation (3) and ST segment elevation (1).

Actions by DCA

The following recommendations were proposed by MADRAC regarding this issue.

- **Inclusion of SCOUT study summary description in package inserts for all products containing sibutramine to strengthen the safety information.**
- **Instruction to all product holders to circulate Dear Health Care Professional (DHCP) letter to inform about the new information.**

A press statement was released on 25 January 2010 to inform the public regarding this issue. The DCA approved the proposal by MADRAC in its 224th meeting on 28 January 2010.

Reference:

1. EMA. Press Release: European Medicines Agency recommends suspension of marketing authorisations for sibutramine.
http://www.ema.europa.eu/pdfs/human/referral/sibutramine/3940810en.pdf [21 Jan 2010]

CARDIAMED®: SUSPENSION OF MARKETING AUTHORISATION LIFTED

Injection Cardiamed® (noradrenaline) is a product supplied to government hospitals under tender since end of year 2006. It is used in the treatment of shock which persists after adequate fluid volume replacement. The common adverse events related to the use of this product are as follows:

- **Cardiovascular** : arrhythmias, bradycardia, peripheral (digital) ischaemia
- **Central nervous system** : anxiety, headache (transient)
- **Local** : skin necrosis (with extravasation)
- **Respiratory** : dyspnoea, respiratory difficulty

From November 2007 to February 2008, the National Centre of ADR Monitoring received seven reports involving three batches of this product submitted by two hospitals, reporting on *gangrene* and *cyanosis peripheral*. The marketing authorisation holder, Duopharma Sdn Bhd conducted an investigation and reported that the product fulfilled all the quality specifications. Nonetheless, considering the severity of the issue, Duopharma carried out a voluntary recall of the three batches in April 2008.

Suspension of Cardiamed®

Pharmacovigilance Section, Centre for Post-Registration of Product, NPCB continued to investigate the issue. Feedback was received from all government hospitals using Cardiamed®. Within three months after the voluntary recall, there were another eight reports of Cardiamed®, also involving other events such as *peripheral ischaemia*, *skin necrosis* and *neck oedema*. In view of this, MADRAC made a recommendation for suspension of the marketing authorisation of Cardiamed®. This was accepted by the Drug Control Authority (DCA) in its 206th meeting in July 2008.

As a consequence, hospitals resorted to using Levophed® (Hospira Sdn Bhd) as an alternative. Pharmacovigilance Section continued to monitor and compile information such as method of administration and dosage from all hospitals. From December 2008 to September 2009, 15 reports were received. Adverse events involved were similar to that of Cardiamed®, with the most reported ones being *peripheral gangrene* and *cyanosis peripheral*, as well as a case of *ST depression*.

Appeal by Product Holder

In September 2009, Duopharma submitted an appeal to lift the suspension of the product based on the following reasons:

- Potential and quality of active pharmaceutical ingredient (API) were within specifications.
- The same API was also supplied to a few countries in Europe and the manufacturing site was audited by the local regulatory agency according to the WHO guidelines.
- Supplier was classified as 'satisfactory' according to PIC/S guidelines (Annex II).

Duopharma also committed to the following actions:

- Increase the awareness of users on the possible adverse events following overdosage.
- Conduct trainings on the use of Cardiamed® injection.
- Encourage ADR reporting to MADRAC.
- Appoint a pharmacist to deal with ADR reporting.

DCA Decision

As this is a product for emergency use and the same adverse reactions are seen in innovator product, MADRAC suggested that the suspension of marketing authorisation for Cardiamed® be lifted. The suggestion was accepted by the DCA in its 224th meeting on 28 January 2010.

SAFETY ISSUES OF CURRENT INTEREST

ROTARIX™ VACCINE: PRESENCE OF DNA FRAGMENTS FROM PCV-1

In March 2010, GlaxoSmithKline (GSK) reported the presence of DNA fragments from Porcine Circovirus Type 1 (PCV-1) in its Human Rotavirus (HRV) vaccine, Rotarix™. This was based on findings from an independent academic research team, led by Prof. Eric Delwart from the Department of Laboratory Medicine, UCSF, USA. The presence of PCV-1 DNA fragments was then confirmed by additional tests conducted by GSK.

PCV-1 is not known to replicate and cause illness in humans and animals. Commonly found in meat products, this virus is not of porcine origin. Although DNA fragments from PCV-1 have been detected in Rotarix™, it is not yet known whether this means that intact virus is present.

Reassessment of all the adverse reaction reports found that no adverse event was identified to be related to the presence of components of the extraneous virus in the vaccine.

WHO Statement

The World Health Organization (WHO) concurred that the findings did not present a threat to public health. Moreover, rotaviruses are the most common cause of severe diarrhoeal disease in young children throughout the world, with an estimated 527,000 deaths among children under five years old, most of whom live in low-income countries. Therefore, WHO concluded that no changes was necessary at this point. All countries were encouraged to carefully consider the significant benefits of continued use of the vaccine in any decisions about further use.

Local Scenario

The Drug Control Authority (DCA) has registered three rotavirus vaccines, namely Rotarix Oral Vaccine and Rotarix Rotavirus Vaccine from GSK, as well as Rotateq® from MSD. These products are indicated to protect against gastroenteritis due to rotavirus infection, which can cause severe diarrhoea and dehydration.

A total of 14 reports had been received by the National Centre of ADR Monitoring relating to the use of Rotarix™. The adverse reactions involved were as follows:

Adverse Reaction	No. of Reports
Diarrhoea	6
Gastroenteritis	5
Fever	2
Vomiting	2
Intussusceptions	1
Appetite loss	1

DCA Action

The DCA decided that no regulatory action is warranted at this moment. A press statement was issued on 24 March 2010 to inform the public about the issue.

Reference:

1. WHO. Rotavirus Vaccination: WHO does not recommend any change to use of Rotarix vaccine. http://www.who.int/immunization/newsroom/news_rotavirus_vaccine_use/en/ [22 Mar 2010]

AVANDIA®: THE CURRENT SAFETY STATUS

The dispute regarding the safety of an antidiabetic agent, Avandia® (rosiglitazone) resurfaced following a report issued by the United States Senate Committee on Finance early this year.

In consideration of the safety of this medication, the US Food and Drug Administration (FDA), in May 2007, had instructed the issuance of Dear Health Care Professional (DHCP) letter by marketing authorisation holders (MAHs) that described the potential cardiovascular risks in patients taking rosiglitazone. Several other regulatory actions were also taken to further strengthen the safety information in the package insert.

In line with the action taken by the FDA, the Drug Control Authority (DCA) had requested GSK Malaysia to revise several sections in the package insert for all products containing rosiglitazone. The updates, as below, were approved in December 2007 and May 2008.

- A new *Boxed Warning* and changes to the *Warnings*, *Precautions* and *Contraindications*.
- Emphasis of the risk of rosiglitazone causing or exacerbating heart failure, and that rosiglitazone is contraindicated in patients with established NYHA Class III or Class IV heart failure.
- Request of the close monitoring for signs and symptoms of heart failure after initiation or dose increment.

Recent Updates

In the years following FDA notifications of potential cardiovascular risk of Avandia®, seven large, prospective, randomized clinical trials, including a meta-analysis (164 clinical trials) had been conducted. None of these established a statistically significant association between Avandia® and myocardial infarction or other ischaemic cardiovascular events.

Local Scenario

To date, the DCA has registered 11 products containing rosiglitazone.

Up to March 2010, the National Centre of ADR Monitoring had received 34 reports related to the use of rosiglitazone, of which two reports were linked to myocardial ischaemia and congestive heart failure. Nevertheless, these patients also suffered from concurrent cardiovascular diseases such as hypertension, which can contribute to the occurrence of these adverse events. Both adverse events resolved after discontinuation of rosiglitazone.

Product Name	Active Ingredient	No. of Strength Available
Avandia®	Rosiglitazone	3
Avandamet®	Rosiglitazone / Metformin	5
Avandaryl®	Rosiglitazone / Glimipride	3

Actions by DCA

The DCA had released a press statement on 23 February 2010 to inform healthcare professionals and patients taking rosiglitazone that the current safety information available is valid and sufficient. The DCA decided that no other action is necessary at the moment. To date, no country has taken any regulatory action on the product.

Reference:

1. FDA MedWatch. FDA Drug Safety Communication: Ongoing review of Avandia® (rosiglitazone) and cardiovascular safety. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm201418.htm [22 Feb 2010]

INVIRASE®: CARDIOVASCULAR RISK WITH CONCURRENT USE OF NORVIR®

In February 2010, the National Centre of ADR Monitoring received a notification from the US Food and Drug Administration (FDA) regarding a review of clinical trial data about a potentially serious effect on the heart from the combined use of Invirase® (saquinavir) and Norvir® (ritonavir) in the treatment of HIV infection.

The data suggested that these two drugs, when used concomitantly, may affect the electrical activity of the heart, known as prolonged QT or PR intervals.

- Prolonged QT interval can increase the risk for torsades de points, a serious abnormal heart rhythm condition.
- Prolonged PR interval can cause the slowing or stopping of the electrical signal responsible for generating a heartbeat, also known as a heart block.

Local Scenario

In Malaysia, there are 2 saquinavir products and 5 ritonavir products registered with the Drug Control Authority (DCA) as below:

No.	Product Name	Active Ingredient & Strength
1.	Invirase film-coated tablet	Saquinavir 500mg
2.	Invirase hard-gelatin capsule	Saquinavir 200mg
3.	Norvir oral solution	Ritonavir 80mg/ml
4.	Norvir sec (capsule)	Ritonavir 100mg
5.	Kaletra capsule	Ritonavir 33.3mg / Lopinavir 133.3mg
6.	Kaletra film-coated tablet	Ritonavir 50mg / Lopinavir 200mg
7.	Kaletra oral solution	Ritonavir 20mg/ml / Lopinavir 80mg/ml

A warning on the possible cardiac conduction abnormalities caused by concomitant use of saquinavir and ritonavir is described in the current package insert of Invirase®.

- Dose-dependent prolongations of QT and PR intervals have been observed in healthy volunteers receiving ritonavir-boosted Invirase®.
- Caution should be taken when administering ritonavir-boosted Invirase® to patients with a known history of QT prolongation or patients who are taking Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic medications.

To date, no report related to the use of saquinavir or combination of saquinavir/ritonavir had been received by the National Centre of ADR Monitoring. There were six reports on products containing ritonavir, but none of them was related to cardiovascular events.

Recommendation

Healthcare professionals should be aware of this potential cardiovascular risk and are encouraged to report adverse events related to the use of these products to the National Centre of ADR Monitoring.

References:

1. FDA MedWatch. Invirase (Saquinavir): Ongoing safety review of clinical trial data. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm201563.htm [23 Feb 2010]

WHO RECOMMENDATIONS ON ANTIRETROVIRAL THERAPY

The World Health Organization (WHO) has revised its guidelines on antiretroviral therapy (ART) for adults and adolescents.

The revised guideline recommends an earlier start to treatment and transition to less toxic first-line drugs. In fact, most high-income countries have revised their national ART guidelines to adopt this policy.

Main Revisions

1. *Eligibility for treatment*

The **2006 guidelines** recommended that ART be started for all patients with advanced clinical disease and/or a CD4 count of **200 cells/mm^3 or less**.

The **2009 recommendations** promote earlier treatment for all patients, when their CD4 count falls to **350 cells/mm^3 or less**, irrespective of clinical symptoms.

CD4 count measures the strength of immune system.

2. *Treatment regimens*

The **2006 guidelines** recognized the critical role of Stavudine (d4T)-containing regimens due to its low cost, limited need for laboratory monitoring, initial tolerability and widespread availability. However, they recommended that countries plan to move away from d4T.

The **2009 recommendations** propose that countries progressively phase out the use of Stavudine as a preferred first-line therapy option and move to less toxic alternatives such as Zidovudine (AZT) and Tenofovir (TDF).

Long term, cumulative and irreversible toxicities of Stavudine include peripheral neuropathy (numbness, weakness and burning pain of hands and feet) and lipoatrophy (loss of fat from specific parts of the body).

3. *Laboratory testing*

The **2009 recommendations** outline an expanded role of laboratory testing, including CD4 testing and viral load monitoring.

Expanding CD4 testing enables people to access earlier treatment. This is critical to HIV-positive pregnant women and would help in preventing mother-to-child transmission (MTCT) of HIV.

The revised guidelines also outline the treatment regimens for different populations, which include adults, adolescents, pregnant women, HIV/tuberculosis co-infected individuals and HIV/hepatitis B co-infected individuals. The full guidelines are now available in the WHO website.

References:

1. WHO. Rapid Advice: Antiretroviral therapy for HIV infection in adults and adolescents. http://www.who.int/hiv/pub/arv/rapid_advice_art.pdf [30 Nov 2009]

2. WHO. New WHO Recommendations: Antiretroviral therapy for adults and adolescents. http://www.who.int/hiv/pub/arv/art_key_mess.pdf [30 Nov 2009]

LOCAL CASE REPORTS

ALLOPURINOL: PRESCRIBING FOR THE RIGHT INDICATIONS

Allopurinol is an effective drug extensively used in the treatment of gout. However, the substantial amount of adverse reaction reports has triggered the concern on the safety of this drug. Since year 2000, the National Centre of ADR Monitoring had received 493 reports on allopurinol. More than 90% of these reports are related to the *Skin and appendages disorders*. 16 reports ended up with a fatal outcome, of which in some of these cases, allopurinol might be a contributory factor. The adverse reactions can manifest at different degrees of severity, ranging anywhere from mild itching to life-threatening conditions such as Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN).

Gout & Allopurinol

Gout is an inflammatory joint disorder resulting from deposition of monosodium urate (MSU) monohydrate crystals in joints and periarticular tissues. Serum and urinary uric acid levels have limited value in the diagnosis of gout. However, serum levels over 6mg/dL increase the risk for developing gout. Therefore, gout should not be confused with hyperuricaemia.

Being a potent xanthine oxidase inhibitor, allopurinol decreases the production of uric acid by inhibiting the action of xanthine oxidase. Allopurinol is also able to promote resolution of existing urate crystals and deposits, thus reducing the frequency of acute gout attacks in patients with chronic gout. It is indicated for reducing uric acid formation in conditions where uric acid deposition has already occurred or is a predictable clinical risk.

No.	Registered Indications
1.	Chronic gout / Gouty arthritis
2.	Uric acid nephropathy
3.	Calcium oxalate renal calculi / Uric acid renal calculi
4.	Hyperuricaemia 2° cancer chemotherapy / radiation therapy
5.	Hyperuricaemia 2° blood dyscrasias
6.	Hyperuricaemia 2° enzyme disorders

Facts & Figures of Allopurinol

As stated in the Ministry of Health Drug Formulary, allopurinol is contraindicated in acute gout and asymptomatic hyperuricaemia. Despite the clear instruction, it has been noted that healthcare professionals do not adhere to the prescribing information. Throughout the years, the National Centre of ADR Monitoring received many reports associated with inappropriately prescribed allopurinol.

Indication as Stated in Reports	No. of Reports	Percentage
Registered indications	**267**	**54.2%**
• Gout / Arthritis / Gouty arthritis	249	
• Chemotherapy	10	
• Renal calculi	8	
Inappropriate indications	**149**	**30.2%**
• Acute gout / Joint pain	12	
• Asymptomatic hyperuricaemia	3	
• Hyperuricaemia	131	
• Others	3	
Unknown	**77**	**15.6%**
Total	**493**	**100%**

(continued)

The common adverse events associated with allopurinol include maculopapular eruption and pruritus. The serious listed reactions are as below:

System Organ Class	Serious Undesirable Effects
Dermatologic	Rash (<1%), Steven Johnson's syndrome (<1%), Toxic epidermal necrolysis (<1%)
Haematologic	Agranulocytosis, Aplastic anaemia, Eosinophilia, Myelosuppression, Thrombocytopenia (0.6%)
Hepatic	Granulomatous hepatitis (<1%), Hepatic necrosis (<1%), Hepatotoxicity
Immunologic	Immune sensitivity reaction
Renal	Renal failure (<1%)

In light of the serious reactions that may occur, allopurinol **should not be used indiscriminately in all conditions involving high serum uric acid levels**.

The drug is **not effective in the treatment of acute gout attacks** since it has no anti-inflammatory action. In fact, it may intensify and prolong inflammation during the acute phase. Other drugs, such as colchicine, analgesics or steroids should be used instead.

Exercise Caution

Allopurinol should be discontinued at the first appearance of skin rash or other signs which may indicate an allergic reaction. If an acute attack occurs when the patient is on allopurinol, the drug has to be continued without any alteration in dosage, together with the treatment for the acute attack. This is very important in order to prevent future gouty attacks.

AMLODIPINE: INCIDENCE OF COUGHING

Since year 2008, the National Centre of ADR Monitoring received 15 reports on amlodipine-associated coughing, of which 10 of these reports were received in year 2009. It was a finding that triggered interest as such adverse event has never been reported prior to year 2008. The breakdown of reports according to the brand of amlodipine is as below.

Product Name	No. of Reports
Covasc ®	2
Norvasc ®	2
Vamlo ®	9
Unknown	2
Total	15

The time to onset of reaction varied from 30 minutes to as long as two weeks. 11 cases reported a positive dechallenge while four patients suffered from coughing again after restarting the medication. No rechallenge was performed in the remaining seven cases. Most of the patients reported a positive outcome.

Local Case Report

In February 2010, a 64-year-old female presented with moderate coughing after taking amlodipine for three days. She discontinued the medication nine days later and consequently, the reaction subsided. The medication was never re-introduced. Causality proposed by the reporter was *possible*.

Objective Evidence

A look up in the literature shows that amlodipine can *very rarely* be associated with cough. WHO database received 278 cases of *cough* and six cases of *productive cough*. Healthcare professionals are advised to look out for this adverse event in patients taking amlodipine.