AUGUST 2012

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

HIGHLIGHTS

ALLOPURINOL: AN UPDATE ON USAGE IN THE MINISTRY OF HEALTH FACILITIES AND RELATED ADVERSE CUTANEOUS DRUG REACTIONS

By Vidhya Hariraj

Background

In year 2010, *CK Lee, A. Mohd Affandi et al.* retrospectively reviewed all adverse cutaneous drug reactions (ACDR) reports associated with ingestion of allopurinol received by MADRAC from January 2001 till December 2009. Published in the MADRAC Bulletin in December 2010, the results showed a significant proportion of patients experienced serious ACDRs with a fraction of them succumbing to their complications. Allopurinol induced ACDRs were reported in 437 patients, accounting for 3.75% of the total ACDRs reported to MADRAC. The incidence in Malaysia was 15 cases per hundred thousand population years. The commonest ACDRs described were Steven Johnson Syndrome (27.3%), followed by maculopapular exanthem (23.1%) and Toxic Epidermal Necrolysis (5.7%).

CONTENT

HIGHLGHTS
- Allopurinol: An Update On Usage In The Ministry Of Health Facilities and Related Adverse Cutaneous Drug Reactions

REGULATORY MATTERS
- Cipram® (Citalopram Hydrobromide): Abnormal Heart Rhythms Associated With Doses More Than 40mg per Day

SAFETY ISSUE OF CURRENT INTEREST
- Varicella Vaccines: A Review on Breakthrough-Varicella Infections

To report an adverse drug reaction:
1. Visit http://www.bpfk.gov.my
2. Click on the red box, ADR Reporting and Product Complaints.
3. Go to report as a healthcare professional via online or hardcopy.
4. Submit the form once completed.

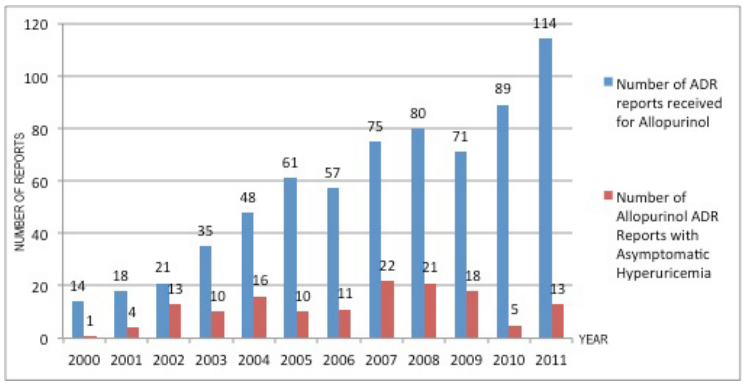
Alternatively, please contact:

National Centre for Adverse Drug Reactions Monitoring
Centre for Post Registration of Products
National Pharmaceutical Control Bureau
Ministry of Health
Peti Surat 319, Jalan Sultan,
46730 Petaling Jaya,
Selangor.

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

Further analysis of data by MADRAC shows that 21% of total ADR reports received since year 2000 were due to use of allopurinol for asymptomatic hyperuricemia. **Chart 1** shows a breakdown from year 2000 till 2011 of ADR reports received for allopurinol and number of cases associated with asymptomatic hyperuricemia. An alarming 60% of ADR reports received for allopurinol in 2002 was related to its inappropriate use. In 2004, an advisory was disseminated to remind prescribers of allopurinol indication following which, a decline was seen in 2005 and 2006. However, from 2007 to 2009 an increasing trend of 25-30% was observed. The figures triggered a signal for risk minimisation actions which is explained further in the next section. Although the number of cases showed a decreasing trend and dropped to 5 (5.6%) and 13 (11.4%) cases in 2010 and 2011 respectively this still remain a cause for concern.

Chart 1: Number of adverse events reports received by NPCB associated with allopurinol 2000-2011



Source: National Centre for Adverse Drug Reaction Monitoring

Asymptomatic Hyperuricemia And Allopurinol Associated Adverse Cutaneous Drug Reactions (ACDRs)

Allopurinol is used for reducing uric acid formation in conditions where uric acid deposition has already occurred or is a predictable clinical risk. Almost 10% of adults are documented to have hyperuricemia at least once in their lifetime. There are many causes that lead to hyperuricemia involving overproduction, undersecretion or both. Asymptomatic hyperuricemia is common and does not in itself constitute a disease.[2]

Allopurinol use in patients with asymptomatic hyperuricemia has been acknowledged as a suggested contributory risk factor for allopurinol hypersensitivity syndrome. Other factors include recent onset (several months) of allopurinol therapy, HLA-B58 allele in subjects of Han Chinese, European ancestry and chronic kidney disease, concomitant thiazide diuretic therapy and high allopurinol dose relative to renal function.[3]

Risk Minimisation Actions of Allopurinol Associated ACDRs

MADRAC subsequently made recommendations on risk minimisation strategies and the following actions have been taken to curb the inappropriate use of allopurinol in light of these serious cutaneous adverse events:

- In November 2008, the Director General of Health issued a circular to all State Health Directors to remind prescribers on allopurinol **prescribing indications** (KKM 87/91/19/1/0(12).
- In August 2011, another circular (KKM 87/P1/19/1/0(25)) was issued to inform all healthcare professionals that **uric acid test should no longer be included as part of routine renal function test but conducted only when patient presents with clinical symptoms of gout**.
- Concurrently, in August 2011, the Ministry's Medicine List Review Panel Meeting (No.2/2011) **raised the category of allopurinol prescribers from Category B (by Medical Officer) to Category A/AKK (by Consultant/Specialist/Family Physician specialist only)**

The National Centre for Adverse Drug Reaction Monitoring will continue to monitor the adverse cutaneous drug reactions associated with allopurinol. Cutaneous drug reactions associated with inappropriate use of allopurinol need to be reduced and prevented as they cause significant morbidity and mortality. A progress report will be provided in 2013.

Reminder to healthcare professionals:

- Primary prescribers are reminded to inform patients treated with allopurinol to **discontinue the drug at the first appearance of skin rash or other signs which may indicate an allergic reaction and seek immediate medical attention.**
- Pharmacists should screen prescriptions for allopurinol to verify its indication.
- All healthcare professionals are required to report any adverse event associated with allopurinol to NPCB.

Special Advice to Healthcare Professionals

The indications approved for allopurinol in Malaysia are listed as below:

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

1) Warnings and Precautions For the Use of Allopurinol[4] are as follows:

WARNINGS AND PRECAUTIONS FOR USE OF ALLOPURINOL

- ✓ Allopurinol should be withdrawn **immediately** if a skin rash or other evidence of sensitivity occurs as this could result in more serious hypersensitivity reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis).
- ✓ Reduced doses should be used in patients with hepatic or renal impairment. Patients under treatment for hypertension or cardiac insufficiency, for example with diuretics or ACE inhibitors, may have some concomitant impairment of renal function and allopurinol should be used with care in this group.
- ✓ Asymptomatic hyperuricemia per se is generally not considered an indication for use of allopurinol. Fluid and dietary modification with management of the underlying cause may correct the condition.
- ✓ Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine.

Acute gouty attacks

Allopurinol treatment should not be started until an acute attack of gout has completely subsided, as further attacks may be precipitated. In the early stages of treatment with allopurinol, as with uricosuric agents, an acute attack of gouty arthritis may be precipitated.

Therefore it is advisable to give prophylaxis with a suitable anti-inflammatory agent or colchicine for at least one month. The literature should be referred for details of appropriate dosage and precautions and warnings.

If acute attacks develop in patients receiving allopurinol, treatment should continue at the same dosage while the acute attack is treated with a suitable anti-inflammatory agent.

2) The table below provides recommendations for diet, lifestyle modification and non-pharmacological management of gout:[5]

Recommendations for diet, lifestyle modification and non-pharmacological management of gout:	
Encourage patients to:	**Recommend patients to:**
• Maintain an ideal weight • Consume low fat dairy, vegetable sources of protein and foods rich in vitamin C • Drink water > 2 L/day • Exercise moderately • Elevate and cool affected joints	• Avoid (or limit) alcohol, particularly beer • Avoid (or limit) high purine foods such as red meat, shellfish, oily fish, liver, kidney, yeast extracts, sucrose and fructose containing soft drinks • Avoid high protein, low carbohydrate diets • Avoid dehydration • Avoid intense exercise and joint trauma

References:

1. CK Lee, A Mohd Affandi, YY Lee, CC Chang and R Baba. Allopurinol Induced Adverse Cutaneous Drug Reactions (ACDRs): A Review of MADRAC (Malaysian Adverse Drug Reaction Advisory Committee) Report from 2000-2009.
2. HE Dincer, AP Dincer, DJ Levinson, et al. Asymptomatic hyperuricemia: To treat or not to treat. Cleveland Clinic Journal Of Medicine August 2002; Volume 69, 8: 594-608.
3. Jeannie Chao and Robert Terkeltaub. A Critical Reappraisal of Allopurinol Dosing, Safety, and Efficacy for Hyperuricemia in Gout. Current Rheumatology Reports 2009; 11:135–140.
4. Zyloric Package Insert. Malaysia. [September 2011]
5. Bpac nz. The Management of Gout Revisited. Best Practice Journal, August 2011; 37: 34-40. http://www.bpac.org.nz/magazine/2011/august/gout.asp

REGULATORY MATTERS

CIPRAM® (CITALOPRAM HYDROBROMIDE): ABNORMAL HEART RHYTHMS ASSOCIATED WITH DOSES MORE THAN 40MG PER DAY

By Lee Sing Chet

Two studies were compared to assess the effects of doses of citalopram and its active S-isomer escitalopram (Lexapro®) on the QT interval in adults. The studies showed that citalopram causes dose-dependent QT interval prolongation that is clinically significant with the 60mg daily dose. Additionally, there is no added effectiveness of citalopram at 60mg/day compared to 40mg/day.[1]

MADRAC in its 127th meeting, concluded that the benefits of citalopram continue to outweigh their risks. However, healthcare professionals are reminded that **the maximum daily dose for citalopram is 40mg.**[2]

LF Asia (Malaysia) Sdn Bhd, the innovator product holder for citalopram, is currently updating the local package insert with the new recommendations on dosing and QT interval prolongation. These safety updates will be extended to all generic products.

Comparatively, for escitalopram, a dose dependent increase in QT interval was seen particularly with 30mg/day when given to healthy volunteers at doses of 10mg and 30mg. When used below **20mg (maximum dose)** which is indicated for major depressive disorder, escitalopram showed substantially lower risk for QT prolongation.

There are **no safety information changes planned for escitalopram** at this time. Nevertheless, escitalopram should also be used with caution in patients with pre-existing cardiac disease. **Table 3** shows the comparative differences between citalopram and escitalopram.

Healthcare professionals should be cautious when prescribing citalopram to patients who have a higher risk of developing prolongation of QT interval including those who have congestive heart failure, bradyarrythmias, predisposition to hypokalemia, hypomagnesemia and those who are concurrently taking medicines that can prolong QT interval. Any adverse events associated with citalopram and its analogues should be reported to the National Centre for Adverse Drug Reactions Monitoring.

Table 3: Comparison of Citalopram with Escitalopram

	Citalopram[3]	Escitalopram[4]
Indication	Treatment of depression and prevention of depression relapse/recurrence. It is also indicated for panic disorder with or without agoraphobia and obsessive-compulsive disorder.	Treatment of major depressive episodes, panic disorder with or without agoraphobia, social anxiety disorder (social phobia), generalised anxiety disorder and obsessive-compulsive disorder.
Recommended Dose	20-40mg daily	10-20mg daily
Pharmacodynamics	Citalopram is a very Selective Serotonin Reuptake Inhibitor (SSRI) with no, or minimal, effect on noradrenaline (NA), dopamine (DA) and gamma aminobutyric acid (GABA) uptake. It enhances serotonergic activity in the central nervous system (CNS) as a result of its inhibition of serotonin (5-HT) reuptake in CNS neurons. It has no or very low affinity for a series of receptors including 5-HT 1A, -HT2, DA D1 and D2 receptors, α1-, α2-, β-adrenoceptors, histamine H 1 muscarine cholinergic, benzodiazepine and opioid receptors.	Escitalopram is the S-enantiomer of the racemate (citalopram) and is the enantiomer to which the therapeutic activity is attributed. Pharmacological studies have shown that the R-enantiomer is not inert but counteracts the serotonin-enhancing and consequent pharmacological properties of the S-enantiomer.
Pharmacokinetics	**Absorption:** Tmax: 3 hours Effect of food: no effect **Distribution:** Vd: 12-17 L/kg **Biotransformation:** Liver: Metabolised to the active demethylcitalopram, didemethylcitalopram, citalopram-N-oxide and an inactive deaminated propionic acid derivative. The biotransformation of citalopram to demethylcitalopram is mediated by CYP2C19 (approx. 38%), CYP3A4 (approx. 31%) and CYP2D6 (approx.31%). **Elimination:** $T_{1/2}$: 1 ½ days **Excretion:** Liver: 85% Kidney: 15%	**Absorption:** Tmax: 4 hours Effect of food: no effect **Distribution:** Vd: 12-26 L/kg **Biotransformation:** Liver: Metabolised to the demethylated and didemethylated metabolites, mediated primarily by CYP2C19. Some contribution by the enzymes CYP3A4 and CYP2D6 is possible. **Elimination:** $T_{1/2}$: 30 hours **Excretion:** Liver Kidney

	Citalopram[3]	Escitalopram[4]
Local Products	There are 10 citalopram-containing products registered in Malaysia. A total of 3 strengths are available, namely 10mg, 20mg and 40mg.	For escitalopram, there are 11 registered products, which are available in 4 strengths, i.e. 5mg, 10mg, 15mg and 20mg.
National Centre for ADR Reporting in Malaysia's Database	Since year 2000: No ADR reports received.	Since year 2004: Supraventricular tachycardia: 1 (dose: 30mg)
WHO Vigibase*	Report since year 1989: • QT prolonged: 357 • Torsade de pointes: 152 • Ventricular tachycardia: 66 • Supraventricular tachycardia: 27	Report since year 2003: • QT prolonged: 140 • Torsade de pointes: 29 • Ventricular tachycardia: 34 • Supraventricular tachycardia: 17

**WHO Vigibase is a global individual case safety report (ICSR) database system which is contributed by more than 80 member countries worldwide, including Malaysia. The information comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases and it does not represent the opinion of WHO.*

Reference:

1. FDA Drug Safety Communication: Revised recommendations for Celexa (citalopram hydrobromide) related to a potential risk of abnormal heart rhythms with high doses. http://www.fda.gov/Drugs/DrugSafety/ucm297391.htm [28 March 2012]
2. Summary report for Citalopram. MADRAC 127 (April 2012).
3. Cipram (citalopram hydrobromide) Package Insert. Malaysia. [May 2012]
4. Lexapro Package Insert. Malaysia. [15 Sept 2008 based on Core SPC ESC 26 Feb 2007]

SAFETY ISSUE OF CURRENT INTEREST

VARICELLA VACCINES: A REVIEW ON BREAKTHROUGH-VARICELLA INFECTIONS

By Nurulhuda Hamdan and Vidhya Hariraj

Background

Varicella (chickenpox) is a highly communicable viral disease. Varicella-zoster virus (VZV), the causative agent in susceptible individuals is a double-stranded DNA virus of the herpes family. Humans are the only reservoir and only one serotype is known. VZV can be transmitted via droplets, aerosols or direct contact with respiratory secretions and patients are usually contagious from a few days before rash onset until the rash has crusted over.

After primary infection, the virus remains latent in the neural ganglia for the lifetime of the individual. In about 10%-20% of the cases, with waning of cellular immunity later in life or during immunocompromised periods, the virus is reactivated and may cause herpes zoster (shingles) that can be painful, severe and debilitating in the elderly. [1]

Prevention of varicella infection

Individual cases may be prevented or modified by varicella-zoster immune globulin or treated with antiviral drugs, however, control can only be achieved by widespread vaccination. The original strain of varicella virus, the Oka strain, was derived from the parental strain of wild-type VZV isolated in Japan in 1971 from a healthy child named Oka infected with varicella by Takahashi and colleagues.

ABOUT VARICELLA (CHICKENPOX) VACCINATION [1-4]

- Varicella vaccine is recommended as 1 dose from the age of 12 months up to 12 years of age and 2 doses with an interval of 6 to 10 weeks in 13 years and above.
- It must not be administered intradermally or intravenously.
- The schedule and administration may vary from country to country.
- Side effects reported include minor injection site complaints (such as pain, swelling, or redness).
- Less than 5% of recipients develop a localised or generalised varicella-like rash 5-26 days after vaccination. These rashes have an average of 2-5 lesions, and may be maculopapular rather than vesicular.
- When given at separate sites and with separate syringes, simultaneous vaccination of varicella with other vaccines is safe and immunogenic.
- In order to induce the same immune response as the monovalent varicella vaccines, the dose of the varicella component had to be increased when included in a tetravalent vaccine with the combined measles-mumps-rubella vaccine.
- Varicella vaccine is effective in preventing chickenpox or reducing the severity of the disease if used within 72 hours (3 days), and possibly up to 5 days, after exposure. However, not every exposure to varicella leads to infection, so for future immunity, varicella vaccine should be given, even if more than 5 days have passed since an exposure.
- Varicella vaccine is contraindicated in patients with a known systemic hypersensitivity to neomycin and for patients suffering from acute, severe febrile illnesses and pregnancy.
- Although this vaccine is approved for use in immunocompromised patients, in some countries, the vaccine may cause viremia and a varicella-like illness in some high-risk patients and therefore must be used with caution in this clinical situation.
- The duration of protection against varicella and zoster without natural exposure to the virus, the epidemiological impact of childhood vaccination at various levels of coverage, and the zoster-preventive effect of vaccination of people with a history of varicella need to be better understood.

Local Scenario

In Malaysia, varicella vaccine is not listed under a government funded programme. The Drug Control Authority (DCA) has registered 5 varicella-containing vaccines which indicated for immunisation against varicella as shown in the table 4 below:

Table 4: Varicella-containing vaccines registered in Malaysia[4]

No.	Product Name	Product Registration Number	Marketing Authorisation Holder
Single Active Ingredient Varicella Vaccine:			
1	Varilrix™	MAL19970631A	GlaxoSmithKline(M) Sdn Bhd
2	Varivax™	MAL19970632AR	MSD(M) Sdn Bhd
3	Okavax™	MAL20001542A	Sanofi-Aventis(M) Sdn Bhd
Combined Vaccine (Measles, Mumps, Rubella, Varicella):			
4	Priorix-tetra™	MAL20081816A	GlaxoSmithKline(M)Sdn Bhd
5	ProQuad™	MAL20061601AR	MSD(M)Sdn Bhd

Since year 2000 till May 2012, the National Centre of ADR Monitoring has received a total of 164 Adverse Events Following Immunisation (AEFI) reports associated with the use of varicella vaccine. Out of these, 149 (91%) reports were related to post-vaccination varicella (breakthrough varicella infections). Although the breakthrough infection is the most commonly reported adverse events for varicella vaccines, it is attributed to various factors including local reporting rates and vaccine schedules. Varicella in persons who have received the vaccine ("break-through varicella") is substantially less severe than the disease in unvaccinated individuals.[2]

Globally, since year 1996 to May 2012, 7,332,991 ADR reports associated with varicella vaccine have been reported to the World Health Organisation (WHO) Vigibase* system. Out of these, a total of 12,800 reports were reported on post-vaccination varicella.

**WHO Vigibase is a global individual case safety report (ICSR) database system which is contributed by more than 80 member countries worldwide, including Malaysia. The information comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases and it does not represent the opinion of WHO.*

Conclusion

The benefit-risk ratio for varicella vaccines remain positive and no regulatory action has been taken against the varicella vaccines used in Malaysia. The National Centre of ADR Monitoring will continue to monitor the safety profile of the varicella vaccines and healthcare professionals are encouraged to report any adverse events related to the use of vaccines.

Reference:

1. WHO Weekly Epidemiological Record, 7 Aug 1998.
2. World Health Organization (WHO). International travel and health: Varicella. http://www.who.int/ith/diseases/varicella/en/ index.html [5 June 2012]
3. Selected references: WHO Position Paper on Varicella Vaccines, (WER March 1998). http://www.who.int/immunization/Refs_Varicella_Mar_1998.pdf [5 Oct 2012]
4. Vaccine Package Inserts_Approved Malaysia