DECEMBER 2009

# MADRAC

National Pharmaceutical Control Bureau, Ministry of Health Malaysia

Malaysian Adverse Drug Reactions Newsletter

This newsletter is also available on our website: http://www.bpfk.gov.my

## Content



# SAFETY ISSUES OF CURRENT INTEREST

## POTENTIAL MEDICATION ERRORS WITH TAMIFLU FOR ORAL SUSPENSION

The U. S. Food and Drug Administration (USFDA) have received reports of dosing errors with Tamiflu (oseltamivir) for Oral Suspension where dosing instructions for the patient do not match the dosing dispenser. U.S. health care providers usually write prescriptions for liquid medicines in milliliters (mL) or teaspoons, while Tamiflu is dosed in milligrams (mg). The dosing dispenser packaged with Tamiflu has markings only in 30, 45 and 60 mg.

A Dear Healthcare Professional (DHCP) letter by Tamiflu marketing authorization holder (MAH), Roche which was approved by the USFDA suggests the following to health care professionals:

- *If prescription instructions specify administration using milligrams (mg), as per the approved dosing recommendations, then the device included in the Tamiflu® product package should be provided to patients and the prescription label should provide dosing instructions in milligrams (mg).*
  - *For patients prescribed a 75 mg dose, HCPs should counsel patients that to deliver the full dose, the oral dispenser should first be filled to 45 mg and given to the patient, then refilled to 30 mg to give the remainder of the dose.*
- *If prescription instructions specify administration using millilters (mL) or teaspoons (tsp), then the device included in the Tamiflu® product package should be removed and replaced with an appropriate measuring device, such as an oral syringe if the prescribed dose is in milliliters (mL).*

In Malaysia, there are 3 products containing oseltamivir in the form of suspension registered with the Drug Control Authority (DCA) as shown below:

| NAME OF PRODUCT | REGISTRATION NO. |
|---|---|
| Tamiflu Oral Suspension 12mg/ml | MAL20061472A |
| Osmivir Powder for Oral Suspension 12mg/ml | MAL07082972A |
| Fluhalt Oral Suspension 60mg/5ml | MAL07082993A |

The dosage recommendations in the package inserts of all 3 products are given in milligrams (mg). The dosing dispenser packaged with the products also has markings in mg. Therefore, health professionals are required to take this into consideration when prescribing any products containing oseltamivir in the form of suspension. A circular regarding this issue has been sent to all health care professionals including those in the private sector.

**References:**

1. FDA MedWatch: Potential Medication Errors with Tamiflu Oral Suspension. http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm183649.htm. 24/09/2009.
2. Roche Dear Health Care Professional Letter.



**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
P.O. Box 319, 46730 Petaling Jaya, Selangor, Malaysia

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

# UPDATE ON OSELTAMIVIR ADVERSE DRUG REACTIONS

In Malaysia, there are currently 11 oseltamivir products registered with the Drug Control Authority (DCA) as listed below.

| PRODUCT NAME | MAL NO. | HOLDER |
|---|---|---|
| Tamiflu Oral Suspension 12mg/ml | MAL20061472A | Roche |
| Tamiflu Capsules 75mg | MAL20014188A | Roche |
| Tamiflu Capsule 75mg | MAL09082799AS | Roche |
| Tamiflu Capsule 45mg | MAL09100496AR | Roche |
| Tamiflu Capsule 30mg | MAL09100495AR | Roche |
| Omiflu Capsule 75mg | MAL07090926A | Duopharma |
| Osmivir Powder for Oral Suspension 12mg/ml | MAL07082972A | Royce Pharma Manufacturing |
| Osmivir Capsule 75mg | MAL06100581A | Royce Pharma Manufacturing |
| Fluhalt Capsules 75mg | MAL06061317A | Ranbaxy |
| Fluhalt Oral Suspension 60mg/5ml | MAL07082993A | Ranbaxy |
| Oseltamivir Capsule 75 mg | MAL09111816A | Ascent Pharmahealth Asia |

The clinical safety of Tamiflu was evaluated in 2477 infants in US, German and Japanese retrospective and prospective observational and clinical studies and it was found to be generally safe and well tolerated. Based on the Roche safety database, unexpected events did not appear to be causally related to the use of Tamiflu and the safety profile for children less than 1 year of age was found to be consistent to that of older children.

In addition, there was also a comprehensive report based on post-marketing data, database studies, clinical trial data, surveillance studies, literature reports and the 'Japanese Ministry of Health Labour and Welfare (MHLW) Case Reports of Neuropsychiatric Events with Other Antivirals or No Antiviral Therapy' to evaluate abnormal behavior in influenza patients receiving oseltamivir (Tamiflu). The report concluded that there was no suggestion of an increased risk of neuropsychiatric events with Tamiflu use and that neuropsychiatric events similar to those seen with Tamiflu have been reported in patients with influenza who were not taking Tamiflu. This indicates that influenza itself can be associated with a variety of neuropsychiatric symptoms.

Apart from that, associations between stroke incidence and mortality and influenza epidemics have been demonstrated. However, a summary on Interaction between Tamiflu and Warfarin concluded that changes in blood clotting, such as increases in INR, which may have been seen in influenza patients on warfarin administered Tamiflu may most likely be a manifestation of acute influenza itself rather than related to oseltamivir or any interaction of oseltamivir with influenza.

To date, there have been 52 adverse drug reaction (ADR) reports for oseltamivir. These include reactions such as sleep disturbances, gastrointestinal system disorders (e.g. nausea and vomiting, tongue ulceration, gingival swelling), central and peripheral nervous system disorders (e.g. voice alteration, vertigo, headache, fits NOS), skin disorders (e.g. itching, rashes, urticaria, blisters), respiratory system disorders (e.g. cough aggravated), liver and biliary system disorders (e.g. hepatic enzymes increased, hepatitis), psychiatric disorders (e.g. confusion, claustrophobia, visual and auditory hallucinations, mental concentration difficulty, psychosis acute, disorientation, blank expression face, responses voluntarily reduced) vaccination related events (e.g dizziness, bradychardia), reduced alertness, muscle pain, restlessness marked, crying abnormal and rigors.

None of the patients were taking warfarin concomitantly with oseltamivir and there were two cases with serious adverse effects involving abnormal behavior such as suicidal tendency and aggressiveness. The Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) will continue to monitor on the adverse effects of oseltamivir and propose any further regulatory actions as appropriate.

# EARLY COMMUNICATION ABOUT AN ON GOING SAFETY REVIEW OF ORLISTAT (MARKETED AS ALLI AND XENICAL)

The USFDA is reviewing new safety information regarding reports of liver-related adverse events in patients taking the weight loss drug orlistat. Orlistat is marketed in the United States as a prescription product, Xenical, and as an over-the-counter (OTC) product, Alli.

Between 1999 and 2008, the FDA received 32 reports of serious liver injury in patients taking orlistat. Of those cases, 27 reported hospitalization and 6 resulted in liver failure. Thirty of the adverse events occurred outside the United States. The most commonly reported adverse events included jaundice (yellowing of the skin or whites of the eyes), weakness, and abdominal pain.

In addition to the 32 reported cases, the FDA is reviewing additional data submitted by orlistat manufacturers on suspected cases of liver injury and this issue was discussed at the FDA's Center for Drug Evaluation and Research (CDER) Drug Safety Oversight Board.

The FDA's analysis of these data is ongoing, and no definite association between liver injury and orlistat has been established at this time. As of now, The USFDA is not advising healthcare professionals to change their prescribing practices with orlistat. Consumers taking Xenical should continue to take it as prescribed, and those using over-the-counter Alli should continue to use the product as directed. FDA will communicate its findings to the public as soon as its review of orlistat is complete.

Consumers should consult their health care professional if they are experiencing symptoms possibly associated with the use of orlistat and development of liver injury, particularly weakness or fatigue, fever, jaundice or brown urine. Other symptoms may include abdominal pain, nausea, vomiting, light-colored stools, itching, or loss of appetite.

In Malaysia, 3 orlistat products are registered with the DCA with 2 Xenical products under the marketing authorization holder Roche and 1 Cuvarlix product under Pharmaniaga Manufacturing Berhad. There have been 6 adverse events previously reported related to the use of Xenical and only 1 was related to abnormal liver function tests. The Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) will continue to monitor this issue and the results from the ongoing review will be disseminated to all healthcare professionals once they are available.

**References:**

1. FDA MedWatch: Early Communication about an On-going Safety Review Orlistat (Marketed as Alli and Xenical). http://www.fda.gov/Drugs/DrugSafety/Postmarket-DrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm179166.htm 24/8/2009.

# UPDATE ON PANDEMRIX H1N1 VACCINE

From 1st November 2009, Pandemrix H1N1 vaccine has been distributed in Malaysia and to date, the Malaysian Adverse Drug Reaction Advisory Committee (MADRAC) has received 20 ADR reports related to Pandemrix. (Table 1)

This vaccine contains antigen A/Carlifornia/7/20209(H1N1)v – like strain (X-179). It was mixed together with the adjuvant which is composed of squalene, DL-α-tocopherol and polysorbate. From the 20 reports, only 1 report was clearly recognized as a serious adverse event as the patient developed anaphylaxis reaction.

The most frequently reported adverse events were minor which included injection site reactions, lethargy, fever, headache, nausea and minor skin reactions. From the Summary of Product Characteristic (SPC), the adverse reactions reported were considered as very common (>1/10) for headache injection site reaction, fever, lethargy and uncommon (1/1000 to 1/100) for rash, nausea, and abdominal cramps.

There were 32 reports of fainting from the Swedish Medical Products Agency for Pandemrix (until 10th November 2009). Information was also received from the Irish Medicine Board on the update of their National Monitoring Experience with Pandemic H1N1 Vaccine for Pandemrix which classified reactions such as headache, dizziness, fainting, fatigue and gastrointestinal symptoms as expected reactions and common to any vaccination. There are also 24 confirmed reports of anaphylaxis in Canada with Influenza AH1N1 vaccine.

Up to 4th December 2009, a total of 7516 doses of vaccine have been given to the front liners of the Ministry of Health, Malaysia. As this vaccine is considered as a new vaccine, please be advised that all healthcare providers have to report all adverse events following immunization (AEFI) including the minor and known reactions.

**Table 1 : Summary of ADR reports related to Pandemrix H1N1 Vaccine**

| No. | Age | ADR |
|---|---|---|
| 1 | 27 | a) Fever<br>b) Headache<br>c) Urticaria<br>d) Myalgia |
| 2 | 27 | a) Syncope<br>b) Chest tightness<br>c) Rash<br>d) Headache<br>e) Nausea<br>f) Taste metallic<br>g) Abdominal pain |
| 3 | 28 | a) Fever<br>b) Giddiness<br>c) Vomiting<br>d) Sweating increased<br>e) Itching |
| 4 | 25 | a) Urticaria |
| 5 | 27 | a) Fever<br>b) Weakness generalized<br>c) Chills<br>d) Myalgia<br>e) Nausea |
| 6 | 50 | a) Bloating |
| 7 | 27 | a) Injection site pain |
| 8 | 26 | a) Injection site pain |
| 9 | 25 | a) Injection site pain |
| 10 | 25 | a) Injection site pain |
| 11 | 27 | a) Injection site pain<br>b) Injection site tenderness |
| 12 | 25 | a) Fever |
| 13 | 34 | a) Headache |
| 14 | 31 | a) Fever<br>b) Headache |
| 15 | 28 | a) Fever<br>b) Lethargy |
| 17 | 33 | a) Fever<br>b) Injection site swelling |
| 16 | 26 | a) Fever<br>b) Lethargy<br>c) Weakness generalized<br>d) Injection site pain |
| 18 | 39 | a) Fever<br>b) Diarrhoea<br>c) Injection site swelling<br>d) Lethargy |
| 19 | 33 | a) Fever<br>b) Flu-like syndrome<br>c) Throat sore<br>d) Coughing<br>e) Phlegm<br>f) Breathing irregular<br>g) Injection site swelling |
| 20 | 46 | a) Shivering<br>b) Headache<br>c) Nausea |

# REGULATORY MATTERS

## IMMUNOSUPPRESSANTS AND INCREASED RISK FOR OPPORTUNISTIC INFECTIONS SUCH AS ACTIVATION OF LATENT VIRAL INFECTIONS INCLUDING BK VIRUS-ASSOCIATED NEPHROPATHY

The U.S. Food and Drug Administration (FDA) is requiring the makers of certain immunosuppressant drugs to update their labeling to reflect that immunosuppressed patients are at increased risk for opportunistic infections, such as activation of latent viral infections, including BK virus-associated nephropathy. These immunosuppressant drugs are used to protect against the rejection of certain organ transplants.

Class labeling changes are required for the following immunosuppressant drugs:

- sirolimus marketed as Rapamune
- cyclosporine marketed as Sandimmune and generics
- cyclosporine modified marketed as Neoral and generics
- mycophenolate mofetil marketed as Cellcept and generics
- mycophenolic acid marketed as Myfortic

The FDA conducted analyses of its Adverse Event Reporting System (AERS) to characterize the association between BK virus-associated nephropathy and the use of these immunosuppressant drugs. The occurrence of BK virus-associated nephropathy is primarily observed in renal transplant patients.

BK virus-associated nephropathy can progress to renal allograft loss. Monitoring for this serious risk and early intervention by the health care provider is critical. Adjustments in immunosuppressant therapy should be considered for patients who develop BK virus-associated nephropathy.

The association of BK virus-associated nephropathy has previously been reported for another immunosuppressant drug, tacrolimus (marketed as Prograf).

Based on this new safety information, FDA is requiring, that manufacturers of these immunosuppressants update their prescribing information to include stronger warnings about the risk of BK virus-associated nephropathy.
This information reflects FDA's current analysis of data available to FDA concerning these products. FDA intends to update this document when additional information or analyses become available. As of now, FDA is continuing to review the safety of immunosuppressant drug products used in renal transplantation.

In Malaysia, there are 19 immunosuppressant products registered with the Drug Control Authority (DCA):

- Sirolimus (3 products)
- Cyclosporin (8 products)
- Mycophenolate mofetil (2 products)
- Mycophenolic acid (2 products)
- Tacrolimus (4 products)

The DCA has instructed the product holders to include the following safety information into the current package inserts:

***WARNINGS AND PRECAUTIONS***

*Immunosuppressed patients are at increased risk for opportunistic infections, including activation of latent viral infections. These include BK virus associated nephropathy which has been observed in patients receiving immunosuppresants. These infections may lead to serious, including fatal, outcomes.*

**References**

1. FDA MedWatch. Information for Healthcare Professionals: Immunosuppressant Drugs: Required Labelling Changes. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm171654.htm 14 July 2009.

# SEVERE DRUG INTERACTION BETWEEN COLCHICINE AND P-GLYCOPROTEIN OR STRONG CYP3A4 INHIBITORS

The United States Food and Drug Administration (USFDA) has informed Health Care Professionals regarding severe drug interactions in certain patients treated with colchicine and concomitant P-glycoprotein (P-gp) or strong CYP3A4 inhibitors.

According to a drug application review, FDA analysed safety data for colchicine-related deaths described in the published literature, adverse events reported to FDA's Adverse Event Reporting System (AERS), and company-sponsored pharmacokinetic and drug interaction studies. The analysis found 169 deaths associated with the use of oral colchicine.

117 out of the 169 deaths were not reported as overdoses which means the majority of reported deaths had colchicine doses within the therapeutic range of less than or equal to 2 mg per day. The reported death cases did not contain information regarding patients' renal or hepatic function. Sixty or 51% of the 117 reported deaths involved patients who were concomitantly using clarithromycin. These reports suggest alterations in the pharmacokinetics of colchicine played a central role in the development of toxicity.

The pharmacokinetics of colchicine may be affected in several ways. The absorption of colchicine from the gastrointestinal tract is thought to be limited by the multidrug resistance efflux transporter P-glycoprotein (P-gp). Additionally, colchicine is a substrate of intestinal and hepatic cytochrome P450 3A4 (CYP3A4), which catalyzes demethylation of colchicine to inactive metabolites. Colchicine is primarily eliminated by hepatobiliary excretion through the stool. Renal excretion accounts for 10-20% of colchicine elimination in patients with normal renal function.

Consistent with the current understanding of colchicine metabolism, certain drugs increase the potential for colchicine toxicity via modulation of P-gp and CYP3A4 activity. Life-threatening and fatal drug interactions have been reported in patients treated with colchicine when P-gp and strong CYP3A4 inhibitors, particularly clarithromycin, were also being used. In the majority of cases, the doses of colchicine were within the therapeutic range.

Fatal and non-fatal cases of colchicine toxicity have also been reported in the literature with concomitant use of other CYP3A4 and P-gp inhibitors, such as cyclosporine, erythromycin, and calcium channel antagonists such as verapamil and diltiazem. Other examples of P-gp and strong CYP3A4 inhibitors include telithromycin, ketoconazole, itraconazole, HIV protease inhibitors, and nefazodone. Toxicity has also been reported in a patient who began to regularly consume a litre of grapefruit juice daily while being treated chronically with colchicine. Additionally, cases of myopathy and/or rhabdomyolysis in patients receiving colchicine have been reported with concomitant use of statins, fenofibrate/gemfibrozil, cyclosporine, or digoxin.

Based on this information, FDA concludes there is a risk for severe drug interactions in certain patients treated with colchicine and concomitant P-gp or strong CYP3A4 inhibitors. FDA recommends that:

- P-gp or strong CYP3A4 inhibitors not be used in patients with renal or hepatic impairment who are currently taking colchicine.
- Healthcare professionals consider a dose reduction or interruption of colchicine in patients with normal renal and hepatic function if treatment with a P-gp or a strong CYP3A4 inhibitor is required.

In Malaysia, there are 4 colchicine products registered with the Drug Control Authority (DCA). However, no reports associated with colchicines toxicity have been received by MADRAC so far.

The DCA has decided that all products containing colchicines must have the following updates in the package inserts:

***INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION***

- *Potential risk of severe drug interactions, including death, in certain patients treated with colchicines and concomitant P-glycoprotein or strong CYP3A4 inhibitors such as clarithromycin, cyclosporin, erythromycin, calcium channel antagonists (e.g. verapamil and diltiazem), telithromycin, ketoconazole, itraconazole, HIV protease inhibitors and nefazodone.*
- *P-glycoprotein or strong CYP3A4 inhibitors are not to be used in patients with renal or hepatic impairment who are taking colchicine.*
- *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.*

**References**

1. FDA MedWatch. Information for Healthcare Professionals: New Safety Information for Colchicine (marketed as Colcrys). http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm174315.htm 30 July 2009.

# ALENDRONATES AND ATYPICAL STRESS FRACTURES

The Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom has notified healthcare professionals regarding the use of products containing alendronate or alendronic acid and the risk of atypical stress fractures.

The notification was based on a Europe-wide review of biphosphonates and atypical stress fractures which analysed preclinical data, clinical trial data, post marketing spontaneous reports of adverse drug reactions, published literature and information from other drug regulatory authorities.

MHRA has issued the following information and advice to healthcare professionals:

- Atypical stress fractures or insufficiency fractures of the proximal femoral shaft have been reported in patients treated long term with alendronate (in most cases, time to onset ranged from 18 months to 10 years)
- Fractures occurred after minimal or no trauma, and some patients experienced thigh pain weeks to months before presenting with a completed femoral fracture. Fractures were frequently bilateral; therefore the contralateral femur should be examined in patients treated with alendronic acid who have a femoral shaft fracture. Poor healing of these fractures was also reported
- Patients who develop atypical stress fractures should discontinue alendronic acid and receive no further bisphosphonate treatment unless the benefits of continued treatment are thought to clearly outweigh the risks to the individual
- Product information for alendronic acid will be updated to include a warning about atypical stress fractures

At the moment, there is limited data available for the other bisphosphonates in support of a causal association with atypical stress fractures. This might reflect their lower usage and the limited long-term data that exist for other bisphosphonates. However, the possibility that other bisphosphonates may be associated with an increased risk of atypical stress fractures cannot be excluded.

The MHRA will continue to keep a close review on the risk of atypical stress fractures with all bisphosphonates, including consideration of further epidemiological research and will issue further information for healthcare professionals when available.

In Malaysia, there are 15 products registered with the DCA. So far, 7 cases of fractures relating to the use of alendronate have been reported. Therefore, the DCA has decided that all products containing alendronate must have the following updates in the package inserts:

***WARNINGS AND PRECAUTIONS***

*Atypical stress fractures (insufficiency fractures) of the proximal femoral shaft occurring after minimal or no trauma have been reported in patients treated long-term with alendronic acid. Some patients experienced thigh pain for weeks to months before a complete fracture occurred. Patients who develop stress fractures should discontinue alendronic acid and receive no further bisphosphonate treatment unless the benefits for the individual clearly outweigh the risk of harm. An increased risk of atypical stress fractures with other bisphosphonates cannot be excluded*

**References**

1. UK MHRA. Biphosphonates: atypical stress fractures. Drug Safety Update 2: 8, No.8, Mar 2009.

# HYDROXYCUT® - WITHDRAWAL OF SUSPENSION

On 1st May 2009, the U.S Food and Drug Administration (USFDA) warned consumers and health care professionals to immediately stop using Hydroxycut® products due to the potential risk of serious liver injuries. Hydroxycut® products are dietary supplements that are marketed for weight-loss, as fat burners, as energy-enhancers, as low carb diet aids, and for water loss.

The decision was based on a report from the *Health Hazard Evaluation Board* which studied information from 3 sources:

- Cases reported in the *Centre for Food Safety and Applied Nutrition's (CFSAN)* adverse monitoring system, *CAERS*;
- Reports of Hydroxycut®-associated liver toxicity in peer-reviewed literature; and
- Discussions with hepatologists

In 2002, CAERS began receiving reports of liver-related illnesses in persons who reported consuming the dietary supplement Hydroxycut® for periods ranging from as short as a week to months.

To-date, 23 case reports of Hydroxycut®-associated liver toxicity has been identified in CAERS. Of these 23 cases, 16 cases (70%) were hospitalized. The severity of illness ranged from asymptomatic elevations in serum bilirubin to acute liver failure. So far, 1 case where patient required liver transplantation and 1 death due to liver failure has been reported to the FDA concerning the use of Hydroxycut®.

All three sources studied suggest that Hydroxycut® causes idiosyncratic hepatotoxicity due to:
- The majority of cases reported no history of liver disease or risk factors for liver disease (e.g., alcohol consumption, previous viral infection, hereditary factors, etc.) prior to experiencing liver injury following the ingestion of Hydroxycut®
- In many subjects, thorough diagnostic evaluations performed in multiple settings ruled out a number of known causes of liver disease, including viral hepatitis, autoimmune diseases, and metabolic/inherited disorders.
- Prompt resolution of liver disease occurred in a number of patients following cessation of Hydroxycut® ingestion.

Furthermore, while some adverse event reports involved users who had consumed more than the daily dosage recommended on the products' labelling, if these reports were excluded from consideration, the remaining evidence demonstrates liver-related adverse effects following exposure to Hydroxycut®. In addition to Hydroxycut®-associated liver-related adverse effects, the Board is aware of a number of CAERS reports that describe seizures, rhabdomyolysis, and cardiovascular signs and symptoms.

At the moment, The Board does not know what ingredient(s) of Hydroxycut® are responsible for producing liver toxicity. In addition, there is insufficient information to determine whether there is a dose-response effect between Hydroxycut® ingestion and liver disease or whether its effects are cumulative over time. However, based on the totality of evidence presented above, the Board concludes that the ingestion of the dietary supplement, Hydroxycut®, presents a severe potentially life-threatening hazard to some users. Although Hydroxycut®–induced hepatotoxicity has been reversible in most patients that have come to the attention of CFSAN, in certain instances acute liver failure has resulted that has required liver transplantation to ensure survival and death occurred in one instance prior to transplantation.

According to the action taken by USFDA, a discussion was held with Nutri-Active Sdn Bhd, the marketing authorization holder (MAH) of Hydroxycut® in Malaysia. On 5th May 2009, Nutri-Active Sdn Bhd. voluntarily agreed to suspend the sale, distribution and import of Hydroxycut® until investigations and safety information has been obtained.

Recently, Nutri-Active Sdn. Bhd. has requested for the suspension of Hydroxycut® to be lifted and has provided the safety evaluation data for the ingredients in Hydroxycut®. In comparison, there are a few differences between the

Hydroxycut® in the US and Hydroxycut® in Malaysia. In US, there are 14 products registered under the brand name Hydroxycut® whereas in Malaysia, there is only 1 Hydroxycut® product registered with DCA.

Apart from that, the ingredients contained in the Hydroxycut® products in US also differs from the ingredients declared in the Hydroxycut® in Malaysia as shown in Table 1:

**Table 1**

| Hydroxycut® US | Hydroxycut® Malaysia |
|---|---|
| *Garcinia cambogia* | *Garcinia cambogia* |
| *Camellia sinensis* | *Camellia Sinesis leaf extract* |
| *Gymnema sylvestre* | *Gymnema sylvestre* |
| *Rhodiola rosea* | *Rhodiola rosea extract* |
| *Guarana* | *Withania somnifera* |

The safety data produced by Nutri-Active is based on the formulation of Hydroxycut® in Malaysia. From the analysis of the safety data, providing that the recommended dosage is adhered to, the ingredients contained in Hydroxycut® does not cause any adverse effects on health and is safe to use as a health supplement in healthy adults.

The Traditional Section in the Centre for Registration of Products has also confirmed that the safety of all the ingredients in Hydroxycut® is accepted as their use has been documented.

- *Garcinia Cambogia, Gymnema Sylvestre and Withania Somnifera* are Indian herbs and is documented in the "Indian Pharmacopeia";
- *Camelia Sinensis* is documented in "PDR for Herbal"; whereas
- *Rhodiola Rosea* is traditionally used in cold countries such as the Siberia and Alps and has been registered in Malaysia for quite some time.

The ingredients are also listed in several other products registered with DCA as shown in Table 2:

**Table 2**

| Name of Ingredient | Number of Products |
|---|---|
| Garcinia Cambogia | 127 |
| Camelia Sinensis (Green tea) | 282 |
| Gymnema Sylvestre | 55 |
| Rhodiola Rosea | 17 |
| Withania Somnifera | 79 |

Tests conducted showed that Hydroxycut® was free from fefluramine, phentermine and sibutramine but detected the presence of caffeine. However, the Centre for Quality Control has clarified that caffeine can be sourced from the plants used in the formulation. Therefore, Hydroxycut® does not have any issues in terms of safety and quality.

So far, the Malaysian Adverse Drug Reaction Advisory Committee (MADRAC) has yet to receive any adverse drug reaction reports relating to the use of Hydroxycut®.

Based on the above discussion, the Drug Control Authority (DCA) has agreed to withdraw the suspension of Hydroxycut®. However, the marketing authorization holder, Nutri-Active Sdn. Bhd. is required to continue to monitor the adverse effects received from consumers and to immediately report any serious adverse events to the DCA.

**References**

1. FDA MedWatch. Hydroxycut Products. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm144316.htm
2. Health Hazard Evaluation Board. Liver toxicity following consumption of dietary supplement, Hydroxycut.

# POTENTIAL RISK ASSOCIATED WITH CONCOMITANT USE OF CEFTRIAXONE WITH CALCIUM-CONTAINING INTRAVENOUS SOLUTIONS

In the 196th Drug Control Meeting (DCA) meeting, a decision was made to include the following updates regarding the use of ceftriaxone with calcium or calcium-containing products into the package inserts of all products containing ceftriaxone:

***WARNINGS***

*Ceftriaxone must not be mixed or administered simultaneously with calcium-containing solutions or products, even via different infusion lines. Calcium containing solutions must not be administered within 48 hours of last administration of Ceftriaxone.*

*Cases of fatal reactions with calcium-ceftriaxone precipitates in lung 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.*

***DOSAGE AND ADMINISTRATION***

*Do not use diluents containing calcium, such as Ringer's Solution or Hartmann's Solution, to reconstitute Ceftriaxone. Particulate formation can result.*

Recently, Health Canada, U. S. Food and Drug Administration (USFDA) and the Medicines and Healthcare products Regulatory Agency (MHRA) announced to all healthcare professionals regarding a revision on products containing ceftriaxone. The revision was made based on 2 in-vitro studies which studies the interaction between ceftriaxone and calcium using adult plasma and plasma from neonates.

Results of the study showed that there was an increased risk of precipitation of ceftriaxone-calcium in neonatal plasma whereas in patients other than neonates, no precipitation is expected with intravenous calcium solutions not exceeding concentrations of 4.0 mmol/L (160 mcg/ml calcium). Based on these results, new precautions have replaced the previous requirement for a 48-hour interval between the administration of IV ceftriaxone and IV calcium-containing solutions.

Although there have been no reports of intravascular calcium-ceftriaxone precipitates in patients other than neonates treated with ceftriaxone and calcium-containing IV products, caution is warranted during IV treatment of patients outside the neonatal period.

There have been no reports of an interaction between ceftriaxone and oral calcium-containing products or interactions between intramuscular ceftriaxone and calcium-containing products (IV or oral).

In Malaysia, there are 39 ceftriaxone products registered with the DCA. All are in the form of injections.
The following regulatory actions were taken by the DCA:

1) Product holders of ceftriaxone-containing products are instructed to update their product package inserts regarding the potential risk associated with concomitant use of ceftriaxone with calcium-containing intravenous solutions in the following sections:

***CONTRAINDICATION***

- *Ceftriaxone in contraindicated in neonates (≤28 days of age) if they require (or are expected to require) treatment with calcium-containing intravenous solutions, including calcium-containing infusions such as parenteral nutrition, because of the risk of precipitation of ceftriaxone-calcium.*

***WARNINGS***

- *In patients other than neonates, Ceftriaxone and calcium-containing solutions may be administered sequentially to one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid.*
- *Diluents containing calcium, such as Ringer's solution or Hartmann's solution, are not to be used to reconstitute Ceftriaxone vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form. Ceftriaxone must not be administered simultaneously with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site, because precipitation can occur.*

2) A circular was sent to all healthcare professionals to inform them of the changes

**References**

1. FDA MedWatch. Information for Healthcare Professionals: Ceftriaxone (marketed as Rocephin and generics). http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm084263.htm 21 April 2009.
2. Health Canada. Health Canada Issued Important Safety Information on Ceftriaxone. http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2009/ceftriaxone_2_nth-aah-eng.php 15 October 2009.
3. UK MHRA. *MHRA highlights interaction between ceftriaxone and calcium*. Drug Safety Update 3: 3, No.2, Oct 2009.

# LOCAL CASE REPORTS

## DRUG EXPOSURE DURING PREGNANCY - GARDASIL®

Since 2007, MADRAC has received a total of 13 reports regarding the exposure of Quadrivalent Human Papillomavirus (Types 6, 11, 16 and 18) Recombinant Vaccine (Gardasil®) during pregnancy. Among these reports, only 5 cases were completed with final outcomes, 7 cases were unable to be followed up due to several reasons and the remaining case is still pending. Out of those 5 cases for which MADRAC had received the final reports, 4 of the patients delivered healthy babies. The remaining patient had elective termination of the pregnancy as the fetus had no heart beat due to unknown causes. One of the patients who delivered a healthy baby had previously had a miscarriage before during exposure to Gardasil. The summary of the case is as below.

The aforementioned case involves a 28 year old malay female with a history of 2 pregnancies and 1 live birth who was vaccinated with the first dose of HPV on 14 February 2007 and the second dose on 13 April 2007. The patient had her "last normal menstrual period (LNMP)" on 1 May 2007 and approximately 8 weeks after (1 July 2007), the patient started bleeding for days with clots and had a miscarriage. On 21 July 2007, the patient experienced menstruation again and subsequently became pregnant. The reporter felt that the miscarriage was not due to therapy with HPV vaccine and the cause of the miscarriage was unknown. Upon internal review, miscarriage was considered an important medical event.

In a follow-up report, the patient was given folic acid 5mg daily from the beginning of pregnancy, iron tablets (Obimin) and calcium carbonate tablet (Caltrate) from 12 weeks onwards, diosmin + hesperidine (Daflon) for varicose vein, acetaminophen + codeine phosphate (Panadeine) and paracetamol for migraine, and loratadine + pseudoephedrine sulfate (Clarinase) and azithromycin (Zithromax) for sinusitis at 28 weeks. There were no complications during the pregnancy, labor or delivery. On April 18 2008, the patient delivered a normal, healthy female baby weighing 3.05 kg without any congenital anomalies or any other complications. On approximately 24 July 2009, the patient was given the third dose of HPV Vaccine.