# 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,
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**Alternatively, please contact:**
National Centre for Adverse Drug Reactions Monitoring,
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National Pharmaceutical Control Bureau
Ministry of Health
P.O. Box 319, 46730 Petaling Jaya, Selangor, Malaysia

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

**Editorial Staff**

Advisor : Selvaraja Seerangam
Chief Editor : Tan Lie Sie
Editors : Fuziah Abdul Rashid
Ng Sue Phay
Norleen Mohd Ali
Nafiza Mohd Ismail


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**Issued:**



# SAFETY ISSUES OF CURRENT INTEREST

## CUTANEOUS ADVERSE DRUG REACTION – AN OVERVIEW OF LOCAL ADR REPORTS IN 2008

Drug-induced skin reaction or also known as cutaneous adverse drug reaction (ADR) is a condition whereby a patient suddenly develops an unwanted symmetrical cutaneous eruption after taking medications. In accordance with the World Health Organisation's general definition of adverse drug reactions, it can also be defined as noxious, unintended morphological skin changes with or without systemic involvement, developed after the local or systemic administration of drugs in dosages commonly used for prevention, diagnosis or treatment of disease or modification of physiological functions.

The severity of hypersensitivity drug reactions is often underestimated. However, this adverse drug reaction is in actual fact responsible for significant morbidity, mortality and socioeconomic costs worldwide. For the year 2008, out of the 4,826 spontaneous ADR reports received by MADRAC, 1535 of these reports were due to skin spontaneous reactions. This contributes to about one third (31.8%) of the total ADR cases reported.

The most common manifestations of drug-induced skin reactions reported in Malaysia include itching, pruritis, macula-papular rashes and erythematous rashes. These manifestations were reported in about 95% of the 1535 skin spontaneous reports received in 2008. This type of drug eruptions is usually mild, self-limited, and resolve after the offending medication has been discontinued.

However, more severe and potentially life-threatening cutaneous advese drug reaction may also occur. The two most commonly known are Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). These two conditions not only may cause prolonged hospitalisation, they significantly contribute to higher mortality rates in drug hypersensitivity. A total of 38 cases of SJS and 12 cases of TEN associated with adverse drug reactions were reported in Malaysia last year. These figures contributed to 3.2% of the total skin spontaneous reaction reports received. Fortunately, among these reported cases, none were known to be fatal. However, the socioeconomic cost due to these cases is still yet to be determined.

Figure 1 shows the top ten drugs most commonly reported for cutaneous adverse drug reaction in the year 2008. 50% of these top ten medications reported belong to the antibiotic group and the penicillin-based β-lactam antibiotics are the most commonly implicated drugs. The figures are obtained from random reporting and are not absolute. Hence, the figures should not be interpreted to imply that these drugs are associated with or cause more cutaneous ADRs than the other drugs of the same class.

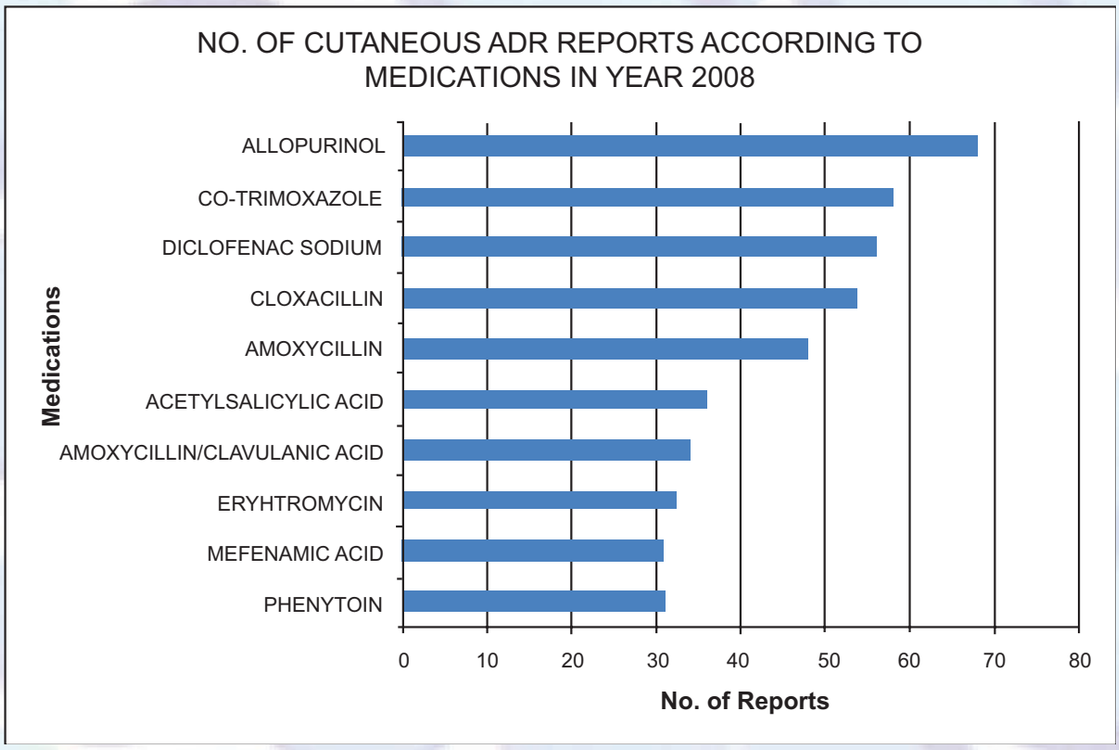


**Figure 1**

Cutaneous adverse drug reaction may not have as high a fatality rate as some other medical conditions, but it is proven to be a distressing issue in the medical field because instead of providing medication relief to patients, it causes another problem to arise. However with the number of new drugs which are being developed and entering the market on a daily basis, this is inevitable.

Therefore, it is the responsibility of all health professionals to be alert to these potential adverse events and if possible, prevent them from happening. It is also the responsibility of all health professionals to report the relevant cases to the regulatory authority. This medical issue should not be taken lightly or ignored.

## Reference:

1. MADRAC Database

**CELLCEPT® (MYCOPHENOLATE MOFETIL) AND PURE RED CELL APLASIA (PRCA)**

CellCept® is an immunosuppressive agent indicated for the prophylaxis of acute transplant rejection in adults receiving allogeneic renal, cardiac or hepatic transplants, and in children and adolescents (2-18 years) receiving renal transplants. It should be used concomitantly with cyclosporine and corticosteroids.

Hoffmann-La Roche Limited (Roche), in consultation with Health Canada, provided important new safety information regarding reports of pure red cell aplasia in patients treated with CellCept® when used in combination with other immunosuppressants.

The marketing authorization holder of CellCept® in Malaysia, Roche (M) Sdn Bhd, has already updated the product package insert to include the following 'Warnings and Precautions':-

- *Cases of PRCA have been reported in patients treated with CellCept in combination with other immunosuppressive agents.*
- *The mechanism for mycophenolate mofetil induced PRCA is unknown. In some cases PRCA was found to be reversible with dose reduction or cessation of CellCept therapy. In transplant patients however reduced immunosuppression may place the graft at risk.*

- *PRCA is usually treated by treating the underlying condition (disease) or discontinuing the drug that causes PRCA.*

A Dear Healthcare Professional (DHCP) letter has been issued to update healthcare professionals on this safety information.

To date, there are no such ADR reports that have been received in Malaysia.

## Reference:

1. Health Canada: Advisories, Warnings and Recalls for Health Professionals. http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2009/cellcept_2_hpc-cps-eng.php. 3 June 2009.

### RAPAMUNE® - INCREASE IN MORTALITY IN STABLE LIVER TRANSPLANT PATIENTS

Wyeth has submitted to the USFDA results of a clinical trial, titled *A Randomised, Open-Label, Comparative Evaluation of Conversion From Calcineurin Inhibitor (CNI) Treatment to Sirolimus Treatment Versus Continuation of Calcineurin Inhibitor Treatment In Liver Allograft Recipients Undergoing Maintenance Therapy*. Based on the clinical trial, the USFDA has notified healthcare professionals that the data suggested an increase in mortality in stable liver transplant patients after conversion from a CNI-based immunosuppressive regimen to sirolimus (Rapamune®).

The trial also provided additional safety and efficacy information on sirolimus:

- *The overall treatment failure rates at one year, defined as the occurrence of acute rejection or premature discontinuation for any reason, for the Intent-to-Treat population were significantly higher for the cohort of stable liver transplant patients converted to sirolimus compared to the cohort that continued on CNIs.*
- *Drug discontinuation due to an adverse event was also more frequent in the sirolimus cohort compared to those patients continued on CNI.*
- *Peripheral edema, stomatitis, rash and mouth ulceration were the most frequent adverse events resulting in discontinuation in the trial.*
- *Mean fasting lipid concentrations increased significantly after the sirolimus conversion and remained elevated throughout the one year follow-up evaluation period*

Sirolimus is indicated for the prophylaxis of organ rejection in patients aged 13 years or older who are receiving kidney transplants. The safety and efficacy of this drug in liver or lung transplant patients have not been established. Therefore, the USFDA is determining whether a labeling change is needed. In the interim, physicians are advised to continue using the drug's professional labeling as a guide to therapy. The Agency will continue to examine the data on mortality and other adverse events in this study and will make further recommendations as appropriate.

In Malaysia, there are three Rapamune® products which are registered with the DCA. The product holder, Wyeth Sdn. Bhd. has agreed to issue a 'Dear Healthcare Professional' letter regarding this safety information. MADRAC will continue to monitor on this issue and propose any further regulatory actions as appropriate.

## Reference:

1. FDA MedWatch: Sirolimus (marketed as Rapamune). http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm165015.htm. 11 June 2009.

### CEFEPIME: UPDATE OF AN ONGOING SAFETY REVIEW

In November 2007, the USFDA announced that it was reviewing safety data about the potential increased mortality in patients treated with cefepime (which is a cephalosporin antibacterial and a member of the β–lactam class of antibacterial drugs) compared to other β–lactam antibacterials noted in a meta-analysis published by Yahav et al. In order to evaluate the finding from this meta-analysis, the FDA requested data from sponsor, Bristol-Myers Squibb (BMS) to perform additional analyses. Following this, in June 2009, the FDA issued a communication to share information on this issue based on meta-analyses which included additional data beyond those found in the Yahav et al. publication.

In the Yahav et al. meta-analysis which was based on a limited number of clinical trials, the 30 day all-cause mortality was higher with cefepime compared to other β–lactams. The authors also reported a statistically significant increase in risk of 30-day all-cause mortality associated with cefepime in the subset of febrile neutropenia. However, this meta-analysis only evaluated trial-level data and did not include patient-level data.

On the other hand, in the USFDA analyses, it was reported that there were no statistically significant differences or no increase in mortality was observed between cefepime and the comparators at trial-level, patient-level and febrile neutropenia trials. The data from clinical trials used in the meta-analysis carried out by the USFDA included those in the Yahav et al. meta-analysis. Additional analyses of cefepime comparative febrile neutropenia trials were also performed to further understand the causes of death and to identify potential risk factors for mortality. A review of all deaths in these febrile neutropenia trials revealed that most patients appeared to have died from their underlying malignancies and/or co-morbid conditions.

As of now, the FDA has determined that cefepime remains an appropriate therapy for its approved indications. However, it is continuing to review the safety of cefepime. As part of the ongoing review, both the FDA and BMS are conducting separate analyses of mortality associated with cefepime using hospital drug utilization data.

In Malaysia, cefepime is marketed as Maxipime® and Megapime®. The Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) will continue to monitor this issue and will inform all healthcare professionals on the latest updates.

## Reference:

1. FDA MedWatch: Information for Healthcare Professionals: Cefepime (marketed as Maxipime). http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm167254.htm. 17 June 2009.

## EARLY COMMUNICATION ABOUT SAFETY OF LANTUS® (INSULIN GLARGINE)

The USFDA and the EMEA have recently notified healthcare professionals and patients regarding four recently-published observational studies that looked at the use of insulin glargine and possible risk for cancer in patients with diabetes. These four observational studies evaluated large patient databases. It was suggested in three of the four studies that an increased risk of cancer was associated with the use of insulin glargine.

However, according to an expert statement by a multidisciplinary board of renowned international experts who have assessed these publications, it was concluded that all four studies have significant methodological limitations and shortcomings. It was also noted that the results provided regarding to a potential link between insulin glargine and an increased risk of cancer were inconsistent and inconclusive.

Based on the currently available data, a relationship between insulin glargine and cancer cannot be confirmed or excluded. Thus, the USFDA and the EMEA recommend that patients should not stop taking their insulin therapy without consulting a physician, since uncontrolled blood sugar levels can have both immediate and long-term serious adverse effects.

The EMEA's Committee for Medicinal Products for Human Use (CHMP) also issued a press release stating that the available data does not provide a cause for concern and that changes to the prescribing advice are therefore not necessary. In the mean time, due to the limitations of the existing evidence, the CHMP has requested the marketing authorisation holder to develop a strategy for generation of further research in this area.

The USFDA is also reviewing many sources of safety data for insulin glargine, including these newly published observational studies, data from all completed controlled clinical trials and information about ongoing controlled clinical trials, to better understand the risk, if any, for cancer associated with use of insulin glargine. Discussions are also ongoing between the USFDA and the manufacturer of insulin glargine as to whether any additional studies evaluating the safety and efficacy of this drug will need to be performed. The USFDA will communicate the results on its ongoing review, if any, to the public.

In Malaysia, insulin glargine is marketed as Lantus® by Sanofi-Aventis and there are currently four Lantus® products which are registered with the DCA. Since the current available data on this safety issue is inconclusive and inconsistent, the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) is not proposing any regulatory actions nor any changes in the current prescribing information. However, MADRAC will continue to monitor this issue and any safety updates will be disseminated to all healthcare professionals once they are available.

## References:

1. European Medicines Agency Press Release: EMEA Update on Safety of Insulin Glargine. http://www.emea.europa.eu/humandocs/PDFs/EPAR/Lantus/40847409en.pdf. 29 June 2009.
2. European Medicines Agency Press Release: EMEA Update on Safety of Insulin Glargine http://www.emea.europa.eu/humandocs/PDFs/EPAR/Lantus/47063209en.pdf. 23 July 2009.
3. FDA MedWatch: Early Communication about Safety of Lantus (Insulin Glargine). http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm169722.htm. 01 July 2009.
4. Reactions Weekly, Uppsala Monitoring Centre: Insulin Glargine Increases Cancer Risk? 04 July 2009, No. 1259.
5. Sanofi-Aventis Press Release: Sanofi-Aventis Stands behind the Safety of Lantus. 26 June 2009.
6. Sanofi-Aventis Press Release: Expert Statement Issued about Lantus Following Recent Publications in Diabetologia. 15 July 2009.


# REGULATORY MATTERS

### SECONDARY EXPOSURE TO ANDROGEL

The USFDA has received reports of adverse effects in children ranging in age from nine months to five years who were inadvertently exposed to testosterone through contact with another person being treated with these products (secondary exposure). Included among the adverse events reported in these children were inappropriate enlargement of the genitalia (penis or clitoris), premature development of pubic hair, advanced bone age, increased libido and aggressive behavior.

The USFDA therefore announced that it is requiring manufacturers of topical testosterone gel products to include the following proposed changes on the products labels.

***WARNINGS AND PRECAUTIONS***

***Potential for Secondary Exposure to Testosterone***

*Secondary exposure to testosterone (including in children and women) can occur with Androgel use in men. Cases of secondary exposure resulting in virilization of children have been reported in postmarketing surveillance. Signs and symptoms have included enlargement of the penis or clitoris, development of pubic hair, increased erections and libido, aggressive behavior, and advanced bone age. In most cases, these signs and symptoms regressed with removal of exposure to Androgel. In a few cases, however, enlarged genitalia did not fully return to age-appropriate normal size, and bone age remained modestly greater than chronological age. The risk of transfer was increased in some of these cases by not adhering to precautions for the appropriate use of Androgel.*

*Inappropriate changes in genital size or development of pubic hair or libido in children, or changes in body hair distribution, significant increase in acne, or other signs of virilization in adult women and the possibility of secondary exposure to Androgel should be brought to the attention of a physician. Androgel should be promptly discontinued at least until the cause of virilization has been identified.*

***ADVERSE REACTIONS***

*Cases of testosterone secondary exposure resulting in virilization of children have been reported. Signs and symptoms have included inappropriate enlargement of the penis or clitoris, premature development of pubic hair, increased erections and libido, aggressive behavior, and advanced bone age. In most cases, these signs and symptoms regressed with removal of the exposure to Androgel. In a few cases, however, enlarged genitalia did not fully return to age-appropriate normal size and bone age remained modestly greater than chronological age.*

In Malaysia, there are two Androgel® registered products; 50mg gel of testosterone 1% and 25mg gel of testosterone 1%. To date, MADRAC has yet to receive any reports regarding this issue. However, the marketing authorisation holder, Orient Europharma (M) Sdn Bhd has been requested to include this warning into the local prescribing information.


## Reference:

1. USFDA News Release: Testosterone Gel Safety Concerns Prompt FDA to Require Label Changes, Medication Guide.http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm149580.htm. 7 May 2009.

## PROPYLTHIOURACIL (PTU)-INDUCED LIVER FAILURE

The USFDA has alerted healthcare professionals of the risk of serious liver injury, including liver failure and death, with the use of PTU in adult and pediatric patients. Reports to FDA's Adverse Event Reporting System (AERS) suggested that there is an increased risk of hepatotoxicity with PTU when compared to methimazole (MMI). Methimazole is the active form of carbimazole which is a pro-drug. Although both PTU and MMI are indicated for the treatment of hyperthyroidism due to Grave's disease, healthcare professionals should carefully consider which drug to initiate in a patient recently diagnosed with Grave's disease.

At present, FDA has identified 32 AERS cases (22 adult and 10 pediatric) of serious liver injury associated with PTU use. Of the adult cases, 12 deaths and 5 liver transplants had occurred. Among the pediatric patients, 1 case resulted in death and 6 in liver transplants.

As of now, FDA will continue to monitor these serious reported adverse events and work to make changes to the PTU prescribing information, particularly for use in pediatric patients. The American Thyroid Association also plans to update its treatment guidelines for Grave's disease in the upcoming months. The FDA intends to update any additional information or analyses when they are available.

In Malaysia, there are currently 3 propylthiouracil registered products. They are all indicated for the treatment of hyperthyroidism. A Dear Healthcare Professional letter has been issued by MADRAC to alert practitioners regarding this safety update and advise them on appropriate PTU use and monitoring. Since the 'Warnings and Precautions' on hepatotoxicity in the package inserts for all 3 propylthiouracil products are incomplete and inadequate, the DCA has instructed all three product holders of PTU to include the following safety information into the current package inserts:

***WARNINGS AND PRECAUTIONS***

*Potential risk of serious hepatotoxicity or liver injury including liver failure and death. Patients who are initiated with propylthiouracil should be closely monitored for signs and symptoms of liver injury (e.g. fatigue, weakness, vague abdominal pain, loss of appetite, itching, easy bruising or yellowing of the eyes or skin) especially during the first six months. If liver injury is suspected, promptly discontinue propylthiouracil therapy.*

*Propylthiouracil should not be used in pediatric patients unless the patient is allergic to or intolerant of the alternatives available.*

### Reference:

1. FDA MedWatch: Propylthiouracil (PTU)-Induced Liver Failure. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm162701.htm. 6 March 2009.

## POSSIBLE INTERACTION BETWEEN CLOPIDOGREL AND PROTON PUMP INHIBITORS

On 26 January 2009, the United States Food and Drug Administration (USFDA) issued an early communication about an ongoing safety review of clopidogrel following reports of decreased effectiveness in some patients. Following this, on 12 May 2009, the Irish Medicines Board alerted its healthcare professionals to be aware of the potential interaction between clopidogrel and proton pump inhibitors (PPIs). On 29 May 2009, the European Medicines Agency (EMEA) has also issued a public statement that it is aware of suggestions about clopidogrel being less effective in patients receiving PPI. This new concern is related to several recently published studies examining clinical outcomes of clopidogrel users. These studies suggested that a significant interaction might occur between clopidogrel and PPIs, making clopidogrel less effective when given with these medicines. This could result in patients being at an increased risk of thrombotic events, including acute myocardial infarction (heart attack).

Clopidogrel is an antiplatelet medicine that is used to prevent a further heart attack in patients who have recently had an attack and also in patients who have had other problems caused by blood clots, such as ischaemic strokes or acute coronary syndromes. Heartburn and stomach ulcers can occur as side effects of clopidogrel. Therefore, patients taking this medication often also take PPIs which are medicines used to prevent and ease these symptoms. Several PPIs are available in the market and include omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole.

Since some PPIs inhibit one of the liver enzymes, CYP2C19 which converts clopidogrel into its active form in the body, this process of conversion may be prevented if both drugs are taken concomitantly, thus reducing its effectiveness

and increasing the risk of heart attack or other conditions involving harmful clotting (e.g. strokes). However, different PPIs may have different capacity to affect the metabolism of clopidogrel.

Taking into account all these data, the innovator of clopidogrel (Plavix®), Sanofi-Aventis, has agreed to work with the USFDA to conduct studies to obtain additional information that will allow a better understanding of the effects of other drugs (especially the PPIs) on the effectiveness of clopidogrel. The Agency's Committee for Medicinal Products for Human Use (CHMP) has also recommended that the product information for all clopidogrel-containing medicines be amended to discourage concomitant use of PPI and clopidogrel-containing medicines unless necessary. It is also recommended that further information is needed in relation to the inhibition of clopidogrel metabolism by other medicines and in relation to the implications of genetic variation which results in a small proportion of individuals (so called 'CYP2C19' poor metabolisers) being unable to fully convert clopidogrel to its active form, regardless of interactions with other medicines.

In Malaysia, there are 6 clopidogrel-containing products which are registered with the DCA. Since 2003 till now, 36 adverse drug reactions reports associated with the use of clopidogrel have been received. Among these 36 ADR reports, 5 involved a concomitant use with a PPI product. However, none of these 5 cases reported were due to a consequence of a possible interaction between clopidogrel and PPIs.

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

***SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE***

*Pharmacogenetics: Based on literature data, patients with genetically reduced CYP2C19 function (intermediate or poor metabolisers) have lower systemic exposure to the active metabolite of clopidogrel and diminished antiplatelet responses, and generally exhibit higher cardiovascular event rates following myocardial infarction than do patients with normal CYP2C19 function.*

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

*Since clopidogrel is metabolised to its active metabolite by CYP2C19, use of drugs that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel and a reduction in clinical efficacy. Concomitant use of drugs that inhibit CYP2C19 (e.g., proton pump inhibitors) should be discouraged.*

***PHARMACOKINETIC PROPERTIES***

*The oxidative step is regulated primarily by Cytochrome P450 isoenzymes 2B6, 3A4, 1A1, 1A2 and 2C19.*

## References:


1. European Medicines Agency: Public Statement on Possible Interaction between Clopidogrel and Proton Pump Inhibitors. 29 May 2009.
2. FDA MedWatch: Early Communication about an Ongoing Safety Review of Clopidogrel Bisulfate (marketed as Plavix).http://www.fda.gov/cder/drug/early_comm/clopidogrel_bisulfate.htm. 26 January 2009.
3. Irish Medicines Board: Safety review of Clopidogrel – IMB interim advice on the concurrent use of Proton Pump Inhibitors in patients treated with Clopidogrel. 12 May 2009.
4. Letter from Sanofi-Aventis (Malaysia) Sdn. Bhd. Plavix 75mg Tablet (MAL19992344A). 8 May 2009.


# LOCAL CASE REPORTS

**DRUG EXPOSURE DURING PREGNANACY – GARDASIL®**

Since year 2007 till now, MADRAC has received a total of 12 reports regarding the exposure of Quadrivalent Human Papillomavirus (Types 6, 11, 16, and 18) Recombinant Vaccine (Gardasil®) during pregnancy. Among these reports, only 4 cases were completed with final outcomes, 3 cases are still pending and 5 cases were unable to be followed up due to several reasons. Out of those 4 cases for which MADRAC had received the final reports, 3 of the patients delivered healthy babies. However, there was one single case whereby the pregnancy was terminated (refer Case 2 below).

The following are the two most recent cases reported to MADRAC.

**CASE 1**

A 36 year old Asian (Chinese) female patient was reported to have been vaccinated with the first dose of Gardasil®, 0.5ml, intramuscular injection on 9 September 2008.

It was reported that the patient's last menstrual period was on 3 September 2008. However, on 15 October 2008, a urine pregnancy test was carried out and the result was positive. Subsequently, the second dose of the vaccine was not given to the patient.

On 18 June 2009, the patient delivered a healthy baby.

**CASE 2**

A 29 year old Asian (Chinese) female patient with a history of 1 pregnancy and 1 live birth was vaccinated with the third dose Gardasil®, intramuscularly, on the 12 April 2009. Details of the first and second doses of the vaccine are unknown. The patient is also not on any other therapy.

It was reported that her last menstrual period was on the 20 March 2009 and the physician only found out later that the patient was 4 days pregnant when she received the last dose (third dose). The estimated delivery date given is 29 December 2009.

During the patient's first visit to the obstetrician, the foetus was reported to be "fine" and "the limbs were ok". On either the second or third visit which was approximately on 5 June 2009, it was reported that the foetus had no heart beat. Subsequently, the pregnancy was terminated. The foetus was found not to be suffering from any congenital anomaly. Upon internal review, no heart beat for the foetus and termination of pregnancy-elective were considered to be important medical events. However, causality for the elective termination (for the mother) and no heart beat (for the foetus) were unknown.

**DIPHTHERIA, TETANUS, ACELLULAR PERTUSSIS, INACTIVATED POLIOMYELITIS VACCINE, ADSORBED AND HAEMOPHILUS INFLUENZAE TYPE B CONJUGATE VACCINE (PENTAXIM®)**

Two cases of ADR reports associated with Pentaxim® which is also known in short as DTAP-IPV/Hib were reported to MADRAC this year.

In the first case, a 2 month old male infant was given the **first dose** of DTAP-IPV/Hib on 12 January 2009 (time was unknown). The baby then developed low grade fever on the same day and was given 1.5ml of paracetamol syrup. The baby fed as usual after that. The baby's mother then noticed that he had an injection site swelling and thus put a warm compression at the injection site.

Subsequently the baby was given another 2 doses of paracetamol syrup at an 8 hour interval for his fever. It was reported that the infant choked a little after the last dose of the paracetamol syrup and the baby's mother fed him immediately after administering the medicine. On 13 January 2009, at around 6 am the baby was found to be "not moving, looked pale and had bleeding from the ears and nose". The parents immediately brought the baby to the hospital A&E Department and the baby was found to have already stopped breathing. The cause of death was unknown as the parents refused to do a post-mortem.

In another case, a 3 month old baby boy was given a **second dose** of DTAP-IPV/Hib on 8 June 2009. The baby then developed low grade fever at night time on the same day and was given paracetamol syrup. The baby recovered from the fever the next day. However, in the afternoon, the baby was continuously crying and his whole body was reported to have turned 'blue'. He was immediately sent to the hospital and was intubated and placed in the Intensive Care Unit (ICU). It is noted that no ADR was reported after the first dose of vaccination for this baby.

Blood cultures were done in the hospital as there was suspected infection and the baby was treated as presumed meningitis. Later on, the baby was transferred to the normal ward and was no longer on any support. However, he was reported to be "sleepy, drowsy and unable to focus with his eyes well".
Unfortunately, the baby died on 6 July 2009. The primary cause of death was reported as bronchopulmonary pneumonia secondary to hypoxic encephalopathy. The child's parents refused to do a post-mortem for further investigation.

MADRAC has given a causality grading of C2 (probable) for both cases as the incidences of ADRs reported (e.g. fever, ear/nose bleeding, injection site induration, crying abnormal, unconsciousness) were consistent with those expected of the vaccine.

Investigations carried out by the registration holder, Sanofi Pasteur did not reveal any quality issues which could have a link with the reported serious adverse event. No other similar ADR reports were received for the batches involved in both cases.

To date, no regulatory actions were taken against the batches of the product involved.