MALAYSIAN ADVERSE DRUG REACTIONS NEWSLETTER

National Pharmaceutical Control Bureau, Ministry of Health Malaysia

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CONTENTS

SAFETY UPDATES

Trasylol® (Aprotinin) – Marketing Suspension

A randomized trial in cardiac surgery population (BART) study was in progress to test the hypothesis that aprotinin was superior to epsilon-aminocaproic acid and tranexamic acid in decreasing the occurrence of massive bleeding in association with cardiac surgery. Based on the preliminary findings, it was suggested that aprotinin **increases the risk of death** as compared to epsilon-aminocaproic acid and tranexamic acid.

Hence, on the 25 October 2007, the U.S. Food and Drug Administration (USFDA) stated that re-evaluation of the risk versus benefit of aprotinin and possibly the revision of product information needed to be done. Meanwhile, healthcare professionals who were considering the use of Trasylol® should be aware of the increased risk of death compared to the other antifibrinolytic drugs.

However, on the 5 November 2007, after pending detailed review from a Canadian study that suggested aprotinin increases the risk of death, USFDA announced that as per request, Bayer Pharmaceuticals Corp. has agreed to suspend marketing of Trasylol® in the interest of patient safety. The USFDA stated that it was hard to identify patients for whom the benefits outweigh the risks from the use of Trasylol®.

In Malaysia, the sale of Trasylol® has been suspended pending a thorough evaluation of the final data from the Canadian BART.

Reference:

1. *FDA MedWatch Website, "Trasylol (aprotinin) – FDA requests marketing suspension and Bayer Pharmaceutical Corp. has agreed, pending a detailed review of preliminary results from a Canadian study that suggested an increased risk for death", http://www.fda.gov/medwatchsafety/2007/safety07.htm#Trasylol, 5 November 2007.*

APPROPRIATE USE OF COUGH AND COLD PRODUCTS

Health Canada and the U.S. Food and Drug Administration (USFDA) have raised concerns over the safety of cough and cold medicines (which are sold over-the-counter in these countries), especially in children below 2 years of age, and whether the benefits justify any potential risks from the use of such products.

Recently US federal health advisors also recommended to the USFDA that such medicines do not work and should not be used by children aged below 6. Such cough and cold products typically contain one or more of the following ingredients: decongestants, antihistamines and anti-tussives. Although cough and cold medicines may also contain expectorants, current concerns do not apply to this ingredient.

Despite these concerns, Health Canada and USFDA have yet to make any regulatory decisions regarding these products. However, they have issued the following advice for parents and caregivers:-

Children under 2 years of age

- Do not use cough and cold products, including drugs and natural health products unless instructed to do so by a healthcare practitioner.
- Discuss with your healthcare practitioner before giving cough and cold products even if these products are labeled for use in children under 2 years of age i.e. labeled "for infant".

Children of all ages

- If it is necessary to give a cough and cold product to a child, make sure all labels and instructions are read before doing so. If the product does not contain dosing information for children then it should not be used in children.
- Do not give a child a larger dose or more frequently than it is recommended in the labeling and instructions.
- Take note of the medicinal ingredients in the product especially if more than one product may be given to a child. Be aware that many products contain the same medicinal ingredient(s) and combined use could lead to overdose. Some herbs used in cough and cold products and some over-the-counter products used to control fever may also have medicinal ingredients similar to those in other cough and cold products.
- It is advised not to give more than one cough and cold product to a child as cough and cold products often contain multiple ingredients.
- Talk to your healthcare practitioner if you have questions about the proper use of these products, dosing and administration information, or the medicinal ingredients in the products you are using.
- There is no cure for the common cold. Children will usually recover from coughs and colds in time on their own. The common cold is a mild, viral infection that can be managed by rest, sufficient fluid intake and comfort measures.
- In young children and babies, it is sometimes important to rule out serious illnesses (for e.g. pneumonia or other infections) which may present with cold-like symptoms; this is especially important if symptoms persist or if the child's condition deteriorates.
- If you are concern about the child's health, the child should be brought to a healthcare practitioner for medical evaluation.

Both regulatory authorities are in the midst of determining if the labeling of these cough and cold products is sufficient to ensure that parents, caregivers and prescribers have enough information to make an informed decision regarding the safe use of these products.

In Malaysia, cough and cold products such as decongestants, antihistamines, and anti-tussives are classified as Group C Poison.

The Drug Control Authority (DCA) does not register any cough and cold medicines targeted at children below two years of age. In May 2006, the DCA instructed that all products containing promethazine should not be used in children less than 2 years old due to the reports of serious adverse events in this group of children and a warning statement to that effect was included for all such products. The DCA is currently undertaking a review of scientific data and evidence on the use of cough and cold products in children.

References:

1. *Health Canada website, "Recommendations for the Appropriate Use of Cough and Cold Products in Children", http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2007/2007_147 e.html, 11 October 2007.*
2. *FDA website, "Public Health Advisory: Nonprescription Cough and Cold Medicine Use in Children", http://www.fda.gov/cder/drug/advisory/cough_cold.htm, 15 August 2007.*

AVANDIA® (ROSIGLITAZONE) UPDATE

On the 1 November 2007, the European Medicines Agency (EMEA) has announced their finalization on the review of the benefits and risks of the thiazolidinediones, namely rosiglitazone (Avandia®) and pioglitazone (Actos®) through a press release. The Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that the benefits in the treatment of Type 2 diabetes mellitus still outweigh the risks. However, the prescribing information should be updated to include a warning for patients with ischaemic heart disease.

The CHMP recommended that the prescribing information should state that rosiglitazone and rosiglitazone-containing products should only be used after careful individual evaluation in patients with ischaemic heart disease. The combination of rosiglitazone and insulin should only be used in exceptional cases and under close supervision.

In Canada, Rosiglitazone (AVANDIA®) is no longer approved as monotherapy for Type 2 diabetes mellitus, except when metformin use is contraindicated or not tolerated. Rosiglitazone is also no longer approved for use in combination with a sulfonylurea, except when metformin is contraindicated or not tolerated. In addition, treatment with all rosiglitazone products is now contraindicated in patients with ***any*** stage of heart failure (i.e., NYHA Class I, II, III or IV).

GlaxoSmithKline also reminded prescribers that **"rosiglitazone is not indicated for use with insulin"**. This combination is associated with an increased risk of heart failure and rosiglitazone is **not indicated for triple therapy** (i.e., therapy with rosiglitazone in combination with both metformin and a sulfonylurea). There have been increased in cases of congestive heart failure and other fluid retention-related events reported in patients receiving rosiglitazone as part of the triple therapy.

In Malaysia, GlaxoSmithKline has issued a "Dear Healthcare Professional" letter to address the upcoming label changes once the updated Product Monographs are available.

Reference:

1. *Health Canada Website, "New restrictions on the use of rosiglitazone products due to cardiac safety concerns (AVANDIA®, AVANDAMET® and AVANDARYLTM)", http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis_prof/2007/avandia_hpc-cps_5_e.html, 1 November 2007.*

2. *AVANDIA UPDATE: EMEA issues press release on outcome of benefit/risk review of TZDs.*

BYETTA® (EXENATIDE) – ACUTE PANCREATITIS

Byetta® (Exenatide) is a drug indicated to treat adults with type 2 diabetes. The U.S. Food and Drug Administration has reviewed 30 post marketing adverse drug reaction reports related to Byetta®. It was found that there was a suspected association between Byetta® and acute pancreatitis in some of the reports. Hence, new information regarding acute pancreatitis has been included in the PRECAUTION section of the product information: -

Recommendations and Considerations

- **Healthcare providers should be alert to the signs and symptoms of acute pancreatitis.**
  Symptoms include persistent severe abdominal pain that can radiate to the back and may be accompanied by nausea and vomiting. Acute pancreatitis is typically confirmed by the presence of elevated levels of serum amylase and/or lipase and characteristic findings by radiological imaging.

- **Discontinue Byetta if pancreatitis is suspected.**
  If pancreatitis is confirmed, do not restart Byetta® unless an alternative etiology for the pancreatitis is identified.

Patients are informed prior starting of Byetta® that the commonly reported side effects of Byetta® are nausea, vomiting, diarrhea, indigestion and upper abdominal discomfort. However, the presence of unexplained, severe abdominal pain, with or without nausea and vomiting, raises the suspicion of acute pancreatitis, a potentially serious condition that requires prompt medical attention. Therefore, patients taking Byetta® should promptly seek medical care if they experience unexplained severe abdominal pain with or without nausea and vomiting.

In Malaysia, no adverse reaction report has been received on exenatide to date. However, Eli Lilly, the product holder of Byetta® has been instructed to include this new warning into the product information.

Reference:

1. *FDA MedWatch website, "Byetta (exenatide) and Postmarketing Reports of Acute Pancreatitis", http://www.fda.gov/cder/drug/InfoSheets/HCP/exenatideHCP.htm, October 2007.*

HALOPERIDOL – NEW WARNINGS AND REVISED PRESCRIPTION INFORMATION

In the United States, injectable haloperidol is only approved by the U.S. Food Drug and Administration (USFDA) for intramuscular injection. However, intravenous administration of haloperidol is a common off-label clinical practice. Therefore, Johnson and Johnson in the United States has revised the prescribing information for haloperidol (marketed as Haldol®, Haldol Decanoate® and Haldol Lactate®) to include a new Cardiovascular subsection regarding cases of sudden death, QT prolongation and Torsades de Pointes (TdP) especially given intravenously, or at doses higher than recommended.

Based on clinical data, there were at least 28 case reports of QT prolongation and TdP in the medical literature, some with fatal outcome due to the use of off-label intravenous use of haloperidol. Case control studies have also demonstrated a dose-response relationship between intravenous administration of haloperidol and TdP. There is also a biologic plausibility of QT prolongation in association with intravenous haloperidol. Hence, the USFDA has strengthened warnings to include:-

Warnings

- Higher doses and intravenous administration of haloperidol appear to be associated with a higher risk of QT prolongation and TdP.

- Although cases of sudden death, TdP and QT prolongation have been reported even in the absence of predisposing factors, particular caution is advised in treating patients using any formulation of haloperidol who:

  - Have other QT-prolonging conditions, including electrolyte imbalance (particularly hypokalaemia and hypomagnesemia.
  - Have underlying cardiac abnormalities, hypothyroidism, or familial long QT syndrome, or
  - Are taking drugs known to prolong the QT interval.

- because of this risk of TdP and QT prolongation, ECG monitoring is recommended if haloperidol is given intravenously.

- Haloperidol is not approved for intravenous administration.

In Malaysia, there is one registered injectable haloperidol, "Manace Injection" by Duopharma (M) Sdn. Bhd. This product can be used either via intravenous or intramuscular as the formulation is in accordance to a New Zealand product "Serenace", which can also be used via intravenous or intramuscular routes. The Drug Control Authority (DCA) has advised Duopharma (M) Sdn. Bhd. to include new warnings as per USFDA's recommendations.

Reference:

1. *USFDA website, "Information for Healthcare Professionals: Haloperidol (marketed as Haldol, Haldol Decanoate and Haldol Lactate)", http://www.fda.gov/cder/drug/Infosheets/HCP/haloperidol.htm, 1 November 2007.*

CURRENT REGULATORY ISSUES

Ban on Red 2G Colouring Agent

On October 11, 2007, the Ministry of Health, Malaysia announced a ban on the use of the colouring agent, Red 2G, in all food with immediate effect. This action was based on the issuance of a European Commission Directive on July 26, 2007 which enforced a ban on the use of Red 2G in food due to safety concerns.

Red 2G or *disodium 8-acetamido-1-hydroxy-2-2phenylazo-napthalene-3, 6-disulphonate* is a synthethic colouring agent of red coal tar or azo dye. The synonym of Red 2G includes CI Food Red 10, Azogeranine,

CI (1975) No.18050, E 128. This colouring agent was exclusively permitted for use in breakfast sausages and burger meat. The Acceptable Daily Intake (ADI) allocated for Red 2G was 0.1mg/kg bodyweight. Red 2G is extensively metabolised to aniline and both genotoxic and carcinogenic effects have been observed in rodents treated with aniline.

In view of this safety concern, the DCA at its 199th meeting decided to ban the use of Red 2G coloring agent in all medicines for oral administration and in those products which come in contact with the mucous membranes.

Reference :

1. *Press release: Y.B. Menteri Kesihatan, "Pengharaman Penambahan Bahan Pewarna Red 2G Dalam Semua Makanan".*

2. *Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on the food colour Red 2G (E128). The EFSA Journal (2007) 515, 1-28.*

3. *Commission Regulation (EC) No. 884/2007 of 26 July 2007 on Emergency Measures Suspending the use of E128 Red 2G as Food Colour. Official Journal of the European Union.*

DEREGISTRATION OF NIMESULIDE

The Irish Medicine Board (IMB) suspended the sales of all oral nimesulide containing products in Ireland following signals of increased risk of liver toxicity: "fulminant hepatic failure" associated with the use of nimesulide. This reaction appears idiosyncratic in nature, was not reversible despite discontinuation of nimesulide and no particular risk group could be identified.

Data obtained from the National Liver Transplant Unit showed that 6 patients required liver transplants following treatment with nimesulide. Since nimesulide was first licensed in Ireland in 1995, a total of 53 hepatic related reactions have been reported. The IMB viewed that nimesulide could not be considered as safe under normal conditions of use.

In Malaysia, the DCA has registered 6 products containing nimesulide. MADRAC received 3 ADR reports associated with nimesulide and two (2) of these were associated with liver problems (jaundice and hepatitis).

Subsequent to receiving the safety alert from the IMB, the DCA suspended the sale of nimesulide containing products at its 195th meeting in August 2007.

Having considered all of the available evidence, the European Medicines Agency (EMEA) in September 2007 concluded that the benefits of using nimesulide still outweigh the risks. However, the Committee for Medical Products for Human Use (CHMP) recommended that treatment with nimesulide should be limited to a maximum of 15 days with the pack size not more than 30 tablets per pack.

However, the IMB has decided to cancel the registration of all medicines containing nimesulide in Ireland, as did Switzerland. In other countries, such as the USA, Australia, Canada, Japan, United Kingdom and Sweden, nimesulide was never registered.

The DCA at its 199th meeting, after due consideration of the risk versus benefit assessment for nimesulide,

agreed with MADRAC's proposals as below:

a) To cancel the registration of products containing nimesulide.

b) Holders of all products are given a grace period of three (3) months from the date of DCA 199th meeting to recall their products from the market.

c) Products containing nimesulide will not be registered in the future.

References:

1) *Irish Medicine Board "Frequently Asked Questions Relating to suspension of Marketing of Nimesulide - Containing Medicinal Products For Oral Use".*

2) *Irish Medicines Board's Announcement, "Immediate Suspension of the Marketing of Medicines Containing Nimesulide.*

3) *European Medicen Agency Press Release, European Medicines Agency Recommends Restricted Use of Nimesulide - Containing Medicinal Products, 21st September 2007, available at http://www.emea.europa.eu*

LOCAL CASE REPORTS

PEDIACEL®

A 3-month old female child was vaccinated with a second dose of Pediacel® which contains DPT/ Polio/HIB on the 29 December 2006 at 9.50am. The child developed lethargy, poor feeding and intermittent crying with no fever in the afternoon of the vaccination day.

The child was only brought back to the clinic on the 30 December 2006 at about 4.20pm in near collapse condition. The child was pallor with perfusion of more than 3 seconds, heart rate of 100/min, poor pulse volume and poor lung function. She was resuscitated at the clinic but collapsed at 5.45pm. CPR was given for about one hour but unfortunately the child passed away at 6.45pm. Her body was sent to Hospital Kajang.

The post mortem was done in Hospital Kajang and the result shown that she died due to acute lymphocytic infiltration to the heart and mild viral endocarditis.

This report was sent to MADRAC on the 3 January 2007. The reporter also reported that the child was well prior to the 1st dose Pediacel®. MADRAC has classified this case as 'possible'.

DRUG EXPOSURE DURING PRENANCY - SODIUM VALPROATE

A 24-year old female patient with a medical history of generalized epilepsy secondary to arrested hydrocephalus was exposed to sodium valproate 200mg twice daily (Epilim®) during and before her pregnancy. Her concomitant medications included one multivitamin tablet daily and folic acid 5mg daily. She has been on sodium valproate since 2002. In 2004, she gave birth to a baby boy with sacral myelomeningocele.

According to the product information, there is a frequency of 1 to 2% associated with valproate use with neural tube defects such as myelomeningocele and spina bifida.

Reference:

1 MADRAC's database

For any query, complaint and reporting adverse drug reaction, please contact :

Adverse Drug Reaction Monitoring Centre
National Pharmaceutical Control Bureau
Ministry of Health
P.O. Box 319, Petaling Jaya
Selangor

Tel : 03 - 7957 3611
Fax : 03 - 7956 7151

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