



DRUG SAFETY ALERT

July 2011

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

National Pharmaceutical Control Bureau, Ministry of Health Malaysia

In This Issue

The Drug Safety Alert is a newsletter published bimonthly by the Pharmacovigilance Section, National Pharmaceutical Control Bureau (NPCB). The objective is to provide advice regarding latest safety updates to healthcare professionals in a timely manner.

1. **Drospirenone-containing oral contraceptives (OC):** Possible increased risk of venous thromboembolism.
2. **Pioglitazone:** Suspension in France due to increased risk of bladder cancer
3. **Rituximab:** Fatal infusion-related reactions in rheumatoid arthritis.

To report an adverse drug reaction:

1. Visit <http://www.bpfk.gov.my>;
2. Click on "MADRAC (Adverse Drug Reactions)" on the left toolbar; and
3. Click on "Reporting Online".

Alternatively, please contact:

National Centre for Adverse Drug Reactions Monitoring
Centre for Post Registration of Products
National Pharmaceutical Control Bureau
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DROSPIRENONE-CONTAINING ORAL CONTRACEPTIVES (OC): POSSIBLE INCREASED RISK OF VENOUS THROMBOEMBOLISM

Recent publication of 2 studies that compared the risk of venous thromboembolism (VTE) in 2 groups of women – women taking OC containing drospirenone, and women taking OC containing levonorgestrel – in the *British Medical Journal* showed that:

- There is a **greater risk of VTE** (2 to 3 times greater) associated with OC containing drospirenone.
- The risk may be **similar** to the risk for OC containing **desogestrel** or **gestodene** (so-called third generation combined OC).

Drospirenone is a type of female sex hormone known as progestin (synthetic progestogen).

Previously published studies addressing the same issue had **conflicting findings**:

- 2 post-marketing studies required by FDA and EMA **did not report any difference in VTE risk** between OC containing drospirenone and OC containing levonorgestrel.
- 2 other publications in 2009 reported a **1.5 to 2-fold higher VTE risk** in women who use drospirenone-containing OC as compared to that in women who use levonorgestrel-containing OC.

In Malaysia

There are 2 combined OC containing drospirenone in Malaysia, i.e. Yasmin[®] (ethinylestradiol 0.03mg/drospirenone 3mg) and Yaz[®] (ethinylestradiol 0.02mg/drospirenone 3mg).

Since year 2007, 19 ADR reports had been received, of which 2 reports were related to VTE (ADR: deep vein thrombosis, pulmonary embolism).

Advice to Healthcare Professionals

- The risk of VTE with OC containing drospirenone is very small and comparable to any low-dose estrogen OC. Continue to **follow the recommendations** in package inserts when prescribing.
- All combined OC should be prescribed with **caution** to obese women (BMI >30), smoker, aged over 35 years, or those with a higher baseline risk of VTE for other reasons.
- Educate patients to recognise and **report** symptoms of VTE, e.g. unusual or persistent pain, redness or swelling in the legs, severe chest pain, sudden shortness of breath and sudden coughing for no apparent reason.

Reference:

<http://www.fda.gov/Drugs/DrugSafety/ucm257164.htm>

PIOGLITAZONE: SUSPENSION IN FRANCE DUE TO INCREASED RISK OF BLADDER CANCER

The French Medicines Agency (AFSSAPS) has **suspended** the use of pioglitazone-containing products in France based on a small, but statistically significant increased risk of **bladder cancer** in patients treated with pioglitazone. FDA has also announced that use of pioglitazone for **more than one year** may be associated with an increased risk of bladder cancer.

Pioglitazone belongs to the class of thiazolidinediones and is used in the treatment of type 2 diabetes mellitus.

In Malaysia

There are 5 pioglitazone products registered in Malaysia, under the brand name of Actos® and Piolet®. Pioglitazone is not listed in the MOH Drug Formulary, but can be obtained for use in the government institutions through approval from the Director-General of Health.

There is only 1 ADR report on pioglitazone since registration of Actos® in year 2005, of which patient experienced weight increase. She had then recovered and the causality assigned was C3 (possible).

Advice to Healthcare Professionals

- Do not use pioglitazone in patients with active bladder cancer.
- Use pioglitazone with caution in patients with a prior history of bladder cancer.
- Counsel patients to report any signs and symptoms that may be suggestive of bladder cancer, e.g. blood in the urine, urinary urgency, pain on urination or back / abdominal pain.

Reference:

http://www.afssaps.fr/var/afssaps_site/storage/original/application/4e293bcd0814c025b94d46d7502a0958.pdf

RITUXIMAB: FATAL INFUSION-RELATED REACTIONS IN RHEUMATOID ARTHRITIS

Four post-marketing cases of **fatal infusion-related reactions** have been received following the use of rituximab in rheumatoid arthritis (RA) patients. These reports originated from the US, UK, Venezuela and Algeria.

Rituximab is a monoclonal antibody used in the treatment of non-hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL) and RA.

Infusion-related reactions include fever, chills, difficulty breathing, tightness of chest and/or throat, upset stomach, rash and headache. **Deaths** within 24 hours of rituximab infusion have occurred. Approximately 80% of fatal reactions occurred with **first infusion**.

In Malaysia

There are 5 rituximab products registered in Malaysia, all under the brand name of MabThera®. Rituximab 500mg/50mL Injection is listed in the MOH Drug Formulary, under category A* (consultant/specialist for specific indication only).

There are 32 ADR reports on rituximab since year 2004, including 2 fatal cases (ADR: hepatitis B, renal failure acute; vomiting, abdominal pain,

breathing difficult). Signs and symptoms related to hypersensitivity or anaphylaxis have been reported in 26 cases.

Advice to Healthcare Professionals

- **Pre-medication**, including analgesic/anti-pyretic (e.g. acetaminophen) and antihistamine (e.g. diphenhydramine), should always be administered prior to infusion of rituximab for RA. 100mg IV methylprednisolone may also be completed 30 minutes prior to each infusion.
- Infusions should not be administered unless **resuscitation equipment** is easily and immediately available.
- If anaphylaxis or other serious hypersensitivity / infusion reaction occurs, administration of rituximab should be **stopped immediately**, and appropriate **medical management** (e.g. glucocorticoids, epinephrine, antihistamines, bronchodilators or oxygen) should be initiated.
- Patients with pre-existing cardiac conditions and those who experienced prior cardiopulmonary adverse reactions need to be **monitored closely**.

Reference:

http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2011/rituxan_6_hpc-cps-eng.php