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Reaksi

DRUG SAFETY NEWS

Mission: This publication provides information and recommendations to healthcare professionals to enhance communication of drug safety updates, raise awareness of adverse drug reactions reported, and stimulate additional adverse drug reaction reporting.

This is a bimonthly publication by the Drug Safety Monitoring Centre, National Pharmaceutical Control Bureau (NPCB), Malaysia.

In This Issue:

TO REPORT AN ADVERSE DRUG REACTION

Online

1. Visit portal.bpfk.gov.my.
2. Click on 'ADR Reporting'.
3. Click to report as a healthcare professional online or via hardcopy.
4. Submit the form once completed.

Mail

1. Print out and complete the ADR form available from our website.
2. Mail or fax to:
   The Drug Safety Monitoring Centre, Centre for Post Registration of Products, National Pharmaceutical Control Bureau, Ministry of Health, PO Box 319, Jalan Sultan, 46730 Petaling Jaya, Selangor.

Telephone

03-7883 5400
(ext. 8460/ 8461/ 8463)

Fax

03-7956 7151

Testosterone Products: Possible Increased Risk of Heart Attack and Stroke

Overview

Testosterone replacement therapy is indicated for male hypogonadism related to certain medical conditions, including hypopituitarism and eunuchoidism.

Background of Safety Issue

The National Pharmaceutical Control Bureau (NPCB) initiated a review into the safety of testosterone-containing products following publication of some studies showing a possible increased cardiovascular risk. Though this risk has not been confirmed and low testosterone levels itself could increase the risk of heart problems, the European Medicines Agency (EMA) and the United States Food and Drugs Administration (US FDA) have implemented product information (PI) updates related to this issue. The US FDA cautions that the benefit and safety of the products have **not been established** for the treatment of **low testosterone levels solely due to aging.**

Local Scenario

There are currently six (6) products containing testosterone registered in Malaysia. The dosages forms include three intramuscular injections, two topical gels and one capsule.

Following this safety issue, all the registered products have updated their PIs with the following statement under 'Therapeutic Indications':

- Testosterone replacement therapy for male hypogonadism, when **testosterone deficiency** has been **confirmed by clinical features** and **biochemical tests**.

Additional warnings for patients with risk factors [severe cardiac, hepatic or renal insufficiency or ischaemic heart disease (IHD)] and advice on monitoring parameters have also been added to the PIs.

NPCB will continue to monitor the benefit-risk balance of testosterone products.

ADR Reports

Since year 2000, the NPCB has received **16 ADR reports** related to testosterone products with 28 adverse events. Almost all the reports were submitted by the product registration holders (PRHs) while one was from a university hospital.

Half the cases (8) reported medication inefficacy, while there were four (4) reports of patients experiencing lethargy, myalgia, and/or giddiness. Two (2) reports involved cardiovascular adverse events, namely **bradycardia** and **myocardial infarction**, however these lacked information such as patient age and time to onset of reaction. All the reports were given a causality of C3 (possibly-related to the drug).

Advice to healthcare providers:

- Testosterone replacement therapy should only be given when the hormone deficiency has been **confirmed by clinical features** and **biochemical tests**.
- **Regular monitoring** of testosterone levels, haemoglobin, haematocrit, liver function and blood lipid profile are recommended during treatment.
- Patients with severe **cardiac, hepatic, or renal insufficiency** or **IHD** may have severe complications (oedema with or without congestive heart failure) with testosterone therapy, in which case the treatment must be stopped immediately.
- Caution in patients with **hypertension**, as testosterone may cause an increase in blood pressure.
- There is limited experience on the safety and efficacy of the use of testosterone in **patients over 65 years** of age.
- The **misuse of androgens** to enhance ability in sports carries **serious health risks**.
- **Please report** any ADR related to testosterone to the NPCB.

Ivabradine: Risk of Cardiovascular Adverse Events

Overview

Ivabradine is approved in Malaysia for *[please refer to PI for full details]*:

(i) treatment of chronic heart failure;
(ii) symptomatic treatment of chronic stable angina in adults who are unable to take beta blockers, or in combination therapy for patients inadequately controlled with an optimal beta-blocker dose.

It lowers the heart rate by selective and specific inhibition of the cardiac pacemaker I_f current, which controls the spontaneous diastolic depolarisation in the sinus node. The cardiac effects are specific to the sinus node, slowing the heart rate without affecting cardiac contractility or ventricular repolarisation. The molecular subunits of the I_f channel are the hyperpolarisation-activated cyclic-nucleotide gated (HCN) channels. Some genetic alterations of this channel gene may be associated with the increased risk of bradycardia, arrhythmia and atrial fibrillation (AF).

Background of Safety Issue

A review into the safety of ivabradine was triggered by the preliminary results of the SIGNIFY clinical trial. The results of this trial showed a small but significant increase (3.4% vs 2.9% yearly incidence rates) in the combined **risk of cardiovascular death** or **non-fatal heart attack** with ivabradine compared with placebo, in patients with symptomatic angina. The study also revealed an increased risk of **bradycardia** (17.9% vs 2.1%) and **AF** (5.3% vs 3.8%) in participants taking ivabradine compared with placebo.

Local Scenario

There are currently two (2) products containing ivabradine registered in Malaysia since 2008 under the brand name Coralan®. Following this review, the product PIs have been updated with safety information to reduce the risk of cardiovascular adverse events.

Ivabradine is listed in the Ministry of Health Drug Formulary (FUKKM) under category A* (to be initiated by consultants for specific indications only).

ADR Reports

Since ivabradine was first registered in Malaysia, the NPCB has received **six (6) ADR reports** related to these products with 15 adverse events. **Two cases** reported patients suffering adverse **cardiovascular events** about one hour after taking ivabradine for angina. One patient suffered marked bradycardia (37 beats per minute- bpm), blurred vision and dizziness, while the second patient experienced palpitations with associated joint pain and tingling sensation. Both patients were taking concomitant medication which may have contributed to the adverse events, therefore the cases were assigned causality C3 (possibly-related to the drug).

Among the other adverse events reported for ivabradine were dyspepsia, nausea, shortness of breath, vomiting, and yellowish vision.

Advice to healthcare providers:

For the treatment of symptomatic angina:

- Ivabradine should only be started in patients with normal sinus rhythm and **heart rate ≥70 bpm**.
- Ivabradine use is **contraindicated** with **verapamil** or **diltiazem** (heart rate-reducing calcium channel blockers), and **strong CYP3A4 inhibitors** (for e.g. clarithromycin, ketoconazole, ritonavir).
- If there is **no improvement** or only limited improvement in symptoms of angina after 3 months of starting treatment, **discontinuation** of ivabradine should be considered.

Remember:

- Closely adhere to the **warnings and contraindications** related to ivabradine use.
- **Monitor** patients regularly for **atrial fibrillation** (AF). If AF develops during treatment, the benefit-risk balance of continued ivabradine treatment should be carefully reconsidered.
- Please **inform patients** of signs and symptoms of bradycardia, AF, and other documented cardiac adverse events. Advise them to contact their healthcare professional if any are suspected.
- If resting heart rate decreases **persistently below 50 bpm** or if the patient experiences symptoms of bradycardia, **down-titrate** the dose . The dose can be reduced to 2.5 mg twice daily if required.
- Ivabradine should be **stopped** if the resting heart rate remains below 50 bpm or symptoms of bradycardia persist.
- **Please report** any ADR related to ivabradine to the NPCB.