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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.

TO REPORT AN ADVERSE DRUG REACTION

Online

1. Visit www.bpfk.gov.my.
2. Click on ADR Reporting and Product Complaints.
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

In This Issue:

Revatio® (sildenafil):

Safety Information on Paediatric Use for Pulmonary Arterial Hypertension

Revatio® (sildenafil): Safety Information on Paediatric Use for Pulmonary Arterial Hypertension

Background

Revatio® 20mg film-coated tablet (sildenafil citrate) is currently not approved in Malaysia for the treatment of paediatric pulmonary arterial hypertension (PAH) due to insufficient data on safety and efficacy. Healthcare professionals must consider whether the benefits of treatment with the drug are likely to outweigh its potential risks for each patient. The NPCB would like to alert healthcare professionals on results of a long-term clinical trial which showed increased risk of mortality with higher doses of Revatio® in paediatric patients with PAH.

Study data summary

In a long-term extension study of Revatio® for the treatment of PAH in paediatric patients with doses in the range of 10-80 mg three times a day (TID), an increased risk of mortality was observed among patients in the higher dose groups.

An independent Data Monitoring Committee (DMC) followed mortality trends across three dose groups (low, medium and high) since the completion of the pivotal trial in 2008. A total of 42 deaths were reported in the study, with an incidence of 9% in the low-dose group (5 of 55), 18% in the medium-dose group (13 of 74), and 24% in the high-dose group (24 of 100). Most deaths were assessed by the investigators to be associated with disease progression and none were assessed as causally related to study treatment.

Based on these data, the DMC unanimously concluded that, in the context of this clinical trial, the high dose of sildenafil was associated with a harmful effect on survival when compared to the low dose. They also expressed concern as to the potential dose-response relationship between increasing dose and mortality. Therefore, the DMC recommended immediate discontinuation of the 40 and 80 mg TID doses in the trial, as well as of the 20 mg TID dose in children with body weight ≤20 kg.

Local scenario

In Malaysia, Revatio® is the only registered product containing sildenafil citrate 20 mg. It was approved since the year 2007 for the treatment of adult patients with PAH with a recommended dose of 20mg TID (*please refer to the product package insert for full prescribing information*). The product is listed for the same indication in the Ministry of Health (MOH) Drug Formulary under category A* (to be initiated by consultants/ specialists for specific indications only).

All other registered products in Malaysia containing sildenafil citrate (25mg, 50mg and 100mg) are only approved for the treatment of erectile dysfunction.

Revatio® has been approved by the European Medicines Agency for the treatment of paediatric patients with PAH. The recommended dosing is 10mg TID (patients weighing ≤20kg) or 20mg TID (patients >20kg).

Although this indication is currently not approved in Malaysia, the Malaysian Clinical Practice Guidelines on the Management of Pulmonary Arterial Hypertension (June 2011) recommends sildenafil for the treatment of children with PAH.

Additionally, in 2013 alone, the Pharmacy Practice and Development Division, MOH, received 93 applications requesting approval from the Director General of Health for the use of Revatio® and Viagra® in paediatric patients with PAH. The applications were for the dose 0.3mg/kg 3-6 hourly, with duration of treatment ranging from 6 weeks up to 6 months.

The product registration holder is in the midst of updating the Malaysian package insert with warnings to highlight the evidence of increased mortality with increasing Revatio® dose in paediatric patients with PAH. In addition, a Direct Healthcare Professional Communication (DHPC) on this issue has been approved by NPCB on 7 October 2014 for distribution to healthcare professionals.

Adverse Drug Reaction Reports

As of 31 December 2014, the Drug Safety Monitoring Centre, NPCB has received a total of 47 reports related to sildenafil with 62 adverse events, mostly involving use for erectile dysfunction. The most commonly reported adverse event was medicine inefficacy (21 events, 34%). Other events reported include blurred vision, breathing difficulty, headache, nasal congestion, priapism, and palpitations.

One (1) report related to use in a paediatric patient with PAH. The patient, aged 7 days, was reported to have decreasing platelet count within one day of taking sildenafil 0.3mg/kg 6 hourly. This case was assigned MADRAC causality C3 (possibly-related to the drug).

Advice for Healthcare Professionals

- Use of sildenafil, particularly chronic use, is not recommended in children. An unexpectedly higher risk of mortality was found in paediatric patients taking a high dose of oral sildenafil citrate when compared to those taking a low dose.
- The maximum recommended dose of Revatio® for **adult** patients with PAH is 20 mg three times a day.
- All ADRs suspected to be related to sildenafil use should be reported to the Drug Safety Monitoring Centre, NPCB.

Reference:

Barst RJ, Ivy DD, Gaitan G, et al. (2012). *A randomized, double-blind, placebo-controlled, dose-ranging study of oral sildenafil citrate in treatment-naïve children with pulmonary arterial hypertension.* Circulation 125:324-334.