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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.
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:

Bromocriptine: Not to be Used Routinely for Lactation Suppression

Overview

Bromocriptine belongs to a group of medicines known as ergot alkaloids and is a dopamine receptor agonist. By mimicking some of the actions of dopamine, bromocriptine blocks the secretion of prolactin, hence preventing or suppressing breast milk production. Medicines containing bromocriptine were licensed in many European countries for lactation suppression after childbirth in women who are not breastfeeding. This indication is **not approved in Malaysia** as well as other countries such as the United States of America and Australia. However, the NPCB is aware that 'off-label' use of bromocriptine does occur.

Background of Safety Issue

In August 2014, the European Medicines Agency (EMA) issued an advisory that bromocriptine should not be routinely used to suppress lactation[1]. The advisory was based on a review of safety and efficacy data of bromocriptine, triggered by a rise in reports of rare but potentially serious or fatal side effects, particularly **cardiovascular** effects (such as heart attack and stroke), **neurological** side effects such as seizures, and **psychiatric** side effects (hallucinations and manic episodes).

In Europe, bromocriptine should only be used for stopping lactation when there are compelling medical reasons, such as the need to avoid further distress after the loss of the baby during or just after childbirth, or in mothers with HIV infection who should not breastfeed. It should not be used for relief of post-partum pain and engorgement which can be adequately treated with non-pharmacological intervention such as firm breast support, ice application, and simple analgesics.

EMA also concluded that bromocriptine use in general is **contraindicated** in patients with uncontrolled hypertension, hypertensive disorders of pregnancy (including eclampsia, pre-eclampsia or pregnancy-induced hypertension), hypertension post-partum and in the puerperium.

Local Scenario

In Malaysia, bromocriptine was first registered in May 1988, and currently there are four (4) products containing bromocriptine registered with the Drug Control Authority (DCA). These products are approved for the treatment of Parkinson's disease, prolactinomas, acromegaly, hyperprolactinaemia in men (prolactin-related hypogonadism), as well as menstrual cycle disorders and female infertility (including amenorrhoea with or without galactorrhoea).

Bromocriptine is listed in the Ministry of Health Formulary (FUKKM) under the prescriber category A/KK (only to be initiated by a Consultant/ Specialist/ Family Health Specialist) for treatment of hypogonadism, galactorrhea, and acromegaly.

Adverse Drug Reaction Reports

Since year 2000, NPCB has received **eight (8) ADR reports** involving bromocriptine, with 16 adverse events including nausea, vomiting, hallucination, alopecia, micturition disorder, and constipation.

In two of the reports, bromocriptine was used for the 'off-label' indication 'lactation suppression'. The first report involved a 34-year old woman who experienced nausea, vomiting and weakness 15 minutes after taking bromocriptine. The causality assigned by MADRAC was C2 (probably-related to drug). The second report was of a 32-year old woman with postpartum cardiomyopathy who developed eclampsia and ventricular tachycardia following use of bromocriptine for lactation suppression after an abortion. She recovered following treatment, and causality given was C3 (possibly-related).

Advice for Healthcare Professionals

- Bromocriptine should not be used for the routine suppression of lactation, nor for the relief of symptoms of post-partum pain and engorgement.
- Healthcare professionals are reminded to consider the existing warnings regarding cardiovascular, neurological and psychiatric concerns when prescribing bromocriptine to patients.
- Periodic monitoring of blood pressure is advisable in all patients treated with bromocriptine. If hypertension, severe headache, suggestive chest pain, or evidence of CNS toxicity occur, bromocriptine should be discontinued and the patient evaluated promptly.
- All ADRs suspected to be related to bromocriptine use should be reported to the NPCB.

Reference:

1. European Medicines Agency. Coordination Group for Mutual Recognition and Decentralised Procedures –Human (CMDh) endorses restricted use of bromocriptine for stopping breast milk production 21August 2014/EMA/441377/2014

Febuxostat: International Reports of Agranulocytosis and DRESS

Overview

Febuxostat is a non-purine selective inhibitor of xanthine oxidase which acts by decreasing serum uric acid. It was first marketed worldwide in 2009 and is indicated for the chronic management of hyperuricemia in patients with gout. It is not recommended for the treatment of asymptomatic hyperuricemia.

Currently, the mainstay therapy for chronic gout is allopurinol. However, the NPCB is aware of the safety issues pertaining to allopurinol, especially the large number of reports of severe adverse cutaneous drug reactions such as Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS).

While febuxostat is **not registered by the Malaysian DCA**, it has been purchased through special approval by the Director General (DG) of Health for use in patients with chronic tophaceous gout or gouty arthritis who cannot tolerate or are not responding to treatment with allopurinol.

Background of Safety Issue

Health Canada reported that since 2010, international cases of agranulocytosis and DRESS suspected of being associated with febuxostat have been identified. Thirteen (13) reports of agranulocytosis, and 14 reports of DRESS were noted in the WHO international ADR database (VigiBase®)*, out of 3,106 reports in total for febuxostat. The top adverse events reported were medication inefficacy (hyperuricaemia), rash and pruritus.

Besides the reports in the database, in 2013, two (2) cases of acute neutropenia in patients treated with febuxostat were published (Kobayashi *et al.*, 2013). The neutrophil count in both cases dropped to less than 1.5 x 10^9/L (normal range: ~1.5 - 8.0 x 10^9/L) during febuxostat therapy and returned to normal within 2 weeks of drug discontinuation. Both cases were reported to have a probable relationship between neutropenia and febuxostat.

Local Scenario

Since 2011, when the drug first stated being used in Malaysia, the NPCB has received **four (4) ADR reports** involving febuxostat, all of which were related to mild-moderate adverse cutaneous events. The ADRs reported were urticaria, pruritus, maculopapular rash, and photosensitive rash. All four cases were assigned causality C3 (possibly-related to the drug) as the patients were taking other concomitant drugs which could have contributed to the ADR.

Advice for Healthcare Professionals

- Patients on febuxostat should be monitored closely for ADRs to ensure any safety issues with this relatively new drug are identified as soon as possible.
- Counsel patients to immediately stop taking febuxostat and **report any early signs** of agranulocytosis or serious skin reactions such as fever, rash, sore throat, itching or photosensitivity.
- Discontinue therapy if there is a **derangement** in neutrophil count, lymphocyte count, haemoglobin, or liver function tests.
- Report to NPCB should any adverse events associated with febuxostat be suspected.

**The information comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases and it does not represent the opinion of the WHO.*