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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.

TO REPORT AN ADVERSE DRUG REACTION

Online

1. Visit http://npra.moh.gov.my.
2. Click on 'Report An Adverse Event'.
3. Click to report as a healthcare professional and choose 'Online Reporting'.
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 Pharmacovigilance Section,
   National Pharmaceutical Regulatory Agency (NPRA),
   Ministry of Health, Malaysia.
   Lot 36, Jalan Universiti,
   46200 Petaling Jaya, Selangor.

Telephone

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

Fax

03-7956 7151

In This Issue:

A bimonthly publication by the
National Pharmaceutical Regulatory Agency (NPRA), Malaysia.

Vemurafenib: Risk of Dupuytren's Contracture and Plantar Fascial Fibromatosis

Overview

Vemurafenib is the first approved drug for BRAF-mutant cancer[1]. The BRAF gene is a type of oncogene that instructs the body to make proteins. However, when the BRAF gene becomes mutated, normal cells can turn cancerous[2]. Vemurafenib acts by inhibiting kinase activity which results in tumour growth inhibition[3]. In Malaysia, vemurafenib is indicated in monotherapy for the treatment of adults with BRAF V600 mutation-positive unresectable or metastatic melanoma.

Background of the Safety Issue

Cases of Dupuytren's contracture have been reported with vemurafenib, characterised by thickening or appearance of visible cords in the palm of one or both hands which may cause tightening of the fingers inward. In most of the cases, the event persisted when treatment was maintained, while in cases where vemurafenib was either interrupted or discontinued, the majority of patients had improvement or resolution of symptoms. One patient with pre-existing Dupuytren's contracture experienced an exacerbation of the condition with vemurafenib use.

Plantar fascial fibromatosis is the thickening of deep tissues underneath the sole of the feet which can cause pain over time. Rare cases of mild and moderate plantar fascial fibromatosis were reported with vemurafenib use. Sequential involvement of the hands and feet was observed in one case[4,5].

Local Scenario

Currently, there is one (1) product containing vemurafenib (Zelboraf®) registered with the Drug Control Authority (DCA). Zelboraf® has been registered in Malaysia since the year 2013.

Adverse Drug Reaction Reports

The NPRA has received one (1) adverse drug reaction report[6] with two (2) adverse events associated with vemurafenib. The adverse events reported were rash and xerosis (abnormally dry skin). None of these adverse events were related to Dupuytren's contracture or plantar fascial fibromatosis.

A Direct Healthcare Professionals Communication (DHPC) letter has been issued to inform the healthcare professionals regarding the risk of developing Dupuytren's contracture and plantar fascial fibromatosis with the use of vemurafenib.

Advice to Healthcare Providers

- Dupuytren's contracture and plantar fascial fibromatosis suspected to be due to vemurafenib should be managed with temporary interruption or treatment discontinuation, as detailed in the current vemurafenib product information.
- All adverse events related to vemurafenib use should be reported to the NPRA.

References:

1. Bollag G., *et al* (2012). Vemurafenib: the first drug approved for BRAF-mutant cancer. Nature Reviews Drug Discovery; 11: 873-886.
2. United States National Library of Medicine. Genetics Home Reference. https://ghr.nlm.nih.gov/gene/BRAF [Accessed: July 2017].
3. Drugs.com (2017). Vemurafenib (https://www.drugs.com/ppa/vemurafenib.html). [Accessed: July 2017].
4. Palmoplantar fibromatosis/ Peyronie's disease with vemurafenib, DSR 1072145, Sep 2016 (CDS Vs 8.0).
5. Investigator's Brochure, RO5185426 (PLX4032) Zelboraf® (Vemurafenib), version 14, Dec 2016 (CDS Vs 8.0).
6. The National ADR Database, NPRA [Accessed: March 2017].

Leflunomide and Teriflunomide: Risk of Falsely Decreased Ionised Calcium Levels and Risk of Colitis

Overview

Leflunomide is a disease-modifying anti-rheumatic drug (DMARD) used in adults with active rheumatoid arthritis and psoriatic arthritis. It is a pyrimidine synthesis inhibitor that works by inhibiting dihydroorotate dehydrogenase. Teriflunomide is the active metabolite of leflunomide, which has been approved for use in the treatment of adults with relapsing-remitting multiple sclerosis (RRMS)[1].

Background of the Safety Issue

♦ **Risk of Falsely Decreased Ionised Calcium Levels**

Based on the available evidence in the European drug safety monitoring system, EudraVigilance, and in the literature, the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) has recommended product information updates to add warnings on the interference with determination of ionised calcium levels for both leflunomide and teriflunomide products. The measurement of ionised calcium levels may show falsely decreased values under treatment with leflunomide and/or teriflunomide, depending on the type of ionised calcium analyser used (e.g. blood gas analyser)[2].

♦ **Risk of Inflammation of the Colon (Colitis)**

Health Canada reviewed the risk of colitis associated with the use of teriflunomide following post-marketing reports of colitis, as well as a product information update of the closely-related drug, leflunomide, to include a new warning on colitis. Health Canada's review of the available information concluded that a link between teriflunomide-use and colitis could not be confirmed at this time, and the safety issue would continue to be monitored[3].

Local Scenario

At present, two (2) products containing leflunomide (Arava®) and one (1) product containing teriflunomide (Aubagio®) are registered in Malaysia since year 2000 and 2015, respectively.

Adverse Drug Reaction Reports

The NPRA has received 82 adverse drug reaction (ADR) reports[4] with 151 adverse events associated with leflunomide, and has not received any ADR reports related to teriflunomide.

At the time of this publication, there were no local reports of falsely decreased calcium levels or colitis associated with leflunomide and teriflunomide use. However, there were 13 local reports associated with leflunomide of adverse events which may be related to colitis, such as abdominal pain and diarrhoea.

NPRA has reviewed these safety issues and the local package inserts of Arava® and Aubagio® will be updated with this new safety information. As the association between teriflunomide-use and colitis could not be determined for the time being, NPRA will continue to monitor this safety issue.

Advice to Healthcare Providers

- Falsely low ionised calcium levels may be detected in patients under treatment with leflunomide or teriflunomide. In case of doubtful measurements, it is recommended to determine the total albumin adjusted serum calcium concentration.
- Colitis, including microscopic colitis, has been reported in patients treated with leflunomide. Patients on leflunomide treatment presenting unexplained chronic diarrhoea should undergo appropriate diagnostic procedures.
- Please report all adverse events suspected to be related to the use of leflunomide or teriflunomide to the NPRA.

References:

1. Wojtusik, A & Brett, F (2012). Teriflunomide: An Orally Administered Disease-Modifying Drug for the Treatment of Multiple Sclerosis. Formulary 47(3): 97-102.
2. European Medicines Agency (2017). PRAC recommendations on signals - Leflunomide; teriflunomide - Falsely decreased ionised calcium levels.
3. Health Canada (2017). Summary Safety Review - Aubagio (teriflunomide) - Assessing the potential risk of inflammation of the colon (colitis).
4. The National ADR Database, NPRA [Accessed: March 2017].