MARCH 2017, No. 34

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 ADR Reporting.
3. Click to report as a healthcare professional and print out the ADR form.
4. Scan and submit the completed form via email to fv@npra.gov.my.

Mail

1. Print out and complete the ADR form available from our website.
2. Mail or fax to:
   The National ADR Monitoring Centre, Centre for Post Registration of Products, National Pharmaceutical Regulatory Agency, 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:

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

Interferon alfa & Interferon beta: Risk of pulmonary arterial hypertension (PAH)

Overview

Interferons are a group of glycoproteins that perform immunoregulatory, as well as antiviral and antineoplastic functions. Indications approved in Malaysia include treatment of multiple sclerosis, hepatitis, carcinoma, lymphoma, leukaemia and myeloma.

Background of Safety Issue

The European Medicines Agency (EMA) reviewed the risk of pulmonary arterial hypertension (PAH) with use of interferon alfa and interferon beta[1]. For interferon alfa, there were cases of PAH particularly in patients with known risk factors, such as portal hypertension, HIV infection and cirrhosis. The onset of PAH with interferon alfa was found to be several months after treatment initiation, while for interferon beta, the onset was several years after treatment initiation. Based on all available evidence, it was considered that a causal relationship between the use of interferons alfa and beta and the development of PAH cannot be excluded.

Health Canada carried out a safety review specifically on interferon beta, as the product information of interferon alfa already listed PAH as a possible adverse event[2]. Two (2) local cases of PAH possibly associated with interferon beta use were identified, both reporting a positive dechallenge when interferon beta treatment was withdrawn. A review of international reports revealed 136 cases of PAH in patients on interferon beta treatment. Health Canada concluded that there was a possible link between the use of interferon beta products and the risk of developing PAH, therefore the package inserts of all interferon products were required to be updated with this safety information.

Local Scenario

At present, there are 20 registered interferon alfa and four (4) registered interferon beta products in Malaysia. Interferon alfa comprises of four types, namely interferon alfa-2a, interferon alfa-2b, peginterferon alfa-2a, and peginterferon alfa-2b, whereas interferon beta is available as interferon beta-1a and interferon beta-1b.

Adverse Drug Reaction Reports

From year 2002 to January 2016, the NPRA has received 91 ADR reports with 204 adverse events associated with interferon alfa use. Seven (7) reports were related to the System Organ Class (SOC) Respiratory, Thoracic and Mediastinal Disorders, such as cough, difficulty in breathing, bloody sputum, nasal congestion and epistaxis.

For interferon beta, a total of 73 ADR reports with 137 adverse events were received by NPRA between 2002 to January 2016. Two (2) reports were associated with the SOC Respiratory, Thoracic and Mediastinal Disorders, namely difficulty in breathing and sneezing.

While there were no reports specifically on PAH, two (2) cases reported patients experiencing symptoms of PAH, namely chest pain (with use of peginterferon alfa-2a), as well as oedema and abdominal distension (with interferon beta-1b).

NPRA has reviewed this safety issue and released a directive [*Ruj: (6) dlm. BPFK/PPP/07/25 Jld. 1*] to mandate product registration holders of all products containing interferon alfa and beta to update the package inserts with information on the risk of PAH.

Advice for Healthcare Professionals

- All healthcare professionals are advised to **counsel and monitor** patients on interferon products for signs and symptoms of PAH, such as shortness of breath, persistent coughing, fatigue, chest pain, or swelling of the ankles, limbs and abdomen.
- Use particular caution when initiating treatment with interferon alfa for patients with **risk factors** such as portal hypertension, HIV infection and cirrhosis.
- All adverse events related to interferon products should be **reported** to the NPRA.

Fluconazole: Caution in use during pregnancy

Editor's Note: *This article highlights a safety signal which is currently under review by the NPRA. This potential safety issue is being investigated further to determine the final regulatory action. This article aims to increase awareness among healthcare professionals and stimulate ADR reporting, particularly of any reactions related to the safety issue below.*

Overview

Fluconazole is a triazole antifungal used for treatment and prevention of various fungal infections. While vaginal candidiasis occurs commonly during pregnancy, the use of oral fluconazole has been associated with increased risk of spontaneous abortion[3].

Background of safety concern

A study was conducted in Denmark on the possible association between oral fluconazole exposure during pregnancy and the risk of spontaneous abortion and stillbirth[3].

In this study, it was found that 147 spontaneous abortions occurred in 3,315 pregnancies exposed to fluconazole in weeks 7 through 22 (hazard ratio 1.48; 95% CI, 1.23-1.77), compared to 563 spontaneous abortions in 13,246 unexposed matched control pregnancies (hazard ratio 1.49; 95% CI, 1.27-1.75). A total of 21 stillbirths occurred in 5,382 pregnancies exposed to fluconazole from week 7 to birth (hazard ratio 1.32; 95% CI, 0.82-2.14), while 77 stillbirths occurred in the 21,506 unexposed matched pregnancies (hazard ratio 1.44; 95% CI, 0.94-2.21).

The study concluded that the use of oral fluconazole in pregnancy was associated with a statistically significant increased risk of spontaneous abortion compared with risk among unexposed women and those with **topical** azole exposure in pregnancy. While the increased risk of stillbirth was not statistically significantly, further investigation was recommended.

EMA has completed a review on this safety issue and recommended an update to the product information for **all formulations** of fluconazole-containing products with information on the risk of spontaneous abortion[4].

The United States Food and Drug Administration (US FDA) is currently evaluating the results from the study[5].

Local Scenario

In Malaysia, there are currently 40 registered products containing fluconazole. Fluconazole was first registered in 1989 and is approved for the treatment of cryptococcosis, systemic candidiasis, mucosal candidiasis, genital candidiasis, dermatomycosis and prevention of fungal infections in patients with malignancy [*please refer to product package inserts for full prescribing details].*

Adverse Drug Reaction Reports

Since year 2000 to July 2016, NPRA has received 149 ADR reports with 236 adverse events associated with fluconazole. The highest reported adverse events were maculo-papular rash, increased hepatic enzymes, and pruritus. At the time of this publication, there were no reports related to spontaneous abortion or stillbirth.

NPRA is currently reviewing this safety information to determine the appropriate risk minimisation action, if required. Until this review is completed, the NPRA advises cautious prescribing of oral fluconazole in pregnancy.

Advice for Healthcare Professionals

- Use **caution** in prescribing oral fluconazole in **pregnancy**.
- Consider **alternative treatment** options, such as clotrimazole for uncomplicated candidiasis.
- Please **report** any ADRs related to fluconazole use to the NPRA, particularly use in pregnancy.

References:

1. EMA (2015). PRAC recommendations on signals for update of the product information. EMA/PRAC/239532/2015.
2. Health Canada (2016). Summary Safety Review – Interferon beta products – Assessing the Potential Risk of Pulmonary Arterial Hypertension.
3. Mølgaard-Nielsen et al (2016). Association between Use of Oral Fluconazole during Pregnancy and Risk of Spontaneous Abortion and Stillbirth. JAMA 315(1):58-67.
4. EMA (2017). PRAC recommendations on signals. EMA/PRAC/68642/2017.
5. US FDA (2016). Drug Safety Communication: FDA to review study examining use of oral fluconazole (Diflucan) in pregnancy.