ISSUE 3/2017, Vol. 35

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 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:

1. **Loperamide: Risk of Serious Cardiac Adverse Events with High Doses, Including Through Misuse**

2. **Thalidomide, Lenalidomide and Pomalidomide: Risk of Hepatitis B Reactivation, Herpes Zoster and Pulmonary Hypertension**

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

Loperamide: Risk of Serious Cardiac Adverse Events with High Doses, Including Through Misuse

About the drug

Loperamide is an antidiarrhoeal medicine which binds to opioid receptors in the gut, inhibiting the release of acetylcholine and prostaglandins. This reduces propulsive peristalsis and increases the intestinal transit time. Loperamide also increases anal sphincter tone, which reduces incontinence and urgency.

Background of Safety Issue

The NPRA received an alert from the **United States Food and Drug Administration (US FDA)** on the risk of **serious cardiac events**, including QT interval prolongation, *torsades de pointes*, other ventricular arrhythmias, cardiac arrest, syncope and death, associated with using higher than recommended doses of loperamide. This risk may be increased when high doses of loperamide are taken with certain drugs which **interact** with it (*see Advice for Healthcare Professionals*).

The US FDA adverse event database contained 48 reports of serious cardiac events associated with loperamide use, 31 of these resulting in hospitalisation, and ten (10) deaths. A total of 22 cases involved individuals who **intentionally misused** high doses of loperamide. While most of the cases involved patients who were taking high doses, in other cases, patients who were taking the recommended dose experienced increased loperamide levels due to interaction with other drugs. The US FDA is requiring labeling updates of all loperamide-containing products with warnings and information on this risk.

On 9 March 2017, the **European Medicines Agency's (EMA)** Pharmacovigilance Risk Assessment Committee (PRAC) recommended that all package inserts of products containing loperamide should be updated with information on the risk of cardiac events including QT prolongation and torsades de pointes, in association with overdose.

Local Scenario

There are currently 15 products containing loperamide registered with the Drug Control Authority (DCA).

Adverse Drug Reaction (ADR) Reports

Between year 2000 to December 2016, the NPRA has received 14 ADR reports with 29 adverse events suspected to be related to loperamide. More than half the adverse events (15 events, 52%) were related to skin disorders such as rash and pruritus. Other adverse events reported were anaphylaxis, shortness of breath, dizziness, dysaesthesia, face and mouth oedema, nausea, oculogyric crisis, stomatitis and throat tightness. To date, the NPRA has **not received** any reports of cardiac adverse events related to loperamide use.

A search of the WHO International ADR database* revealed 7,431 reports involving loperamide since year 1977. A total of 328 reports involved cardiac disorders such as ventricular tachycardia (60 reports), cardiac arrest (50), and *torsades de pointes* (46). *[*This 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.]*

In Malaysia, product registration holders will be required to update the package inserts of all products containing loperamide with warnings and safety information related to this risk.

Advice for Healthcare Professionals

- Be alert for individuals who may be intentionally abusing loperamide at high doses, or taking loperamide with other interacting drugs due to opioid addiction.
- Consider loperamide as a possible cause of unexplained serious cardiac events, such as QT interval prolongation, *torsades de pointes*, and cardiac arrest.
- Loperamide may **interact** with certain drugs resulting in increased loperamide blood levels (for example erythromycin, clarithromycin, cimetidine, gemfibrozil, ketoconazole, itraconazole, quinidine and ritonavir).
- Loperamide should be discontinued promptly if cardiotoxicity is suspected, and appropriate treatment initiated to manage and prevent cardiac arrhythmias or severe outcomes.
- **Counselling**: Patients must be informed of the risk of cardiac adverse events and reminded not to exceed the recommended dose.
- Please **report** all adverse events suspected to be related to the use of loperamide to the NPRA.

Thalidomide, Lenalidomide and Pomalidomide: Risk of Hepatitis B Reactivation, Herpes Zoster and Pulmonary Hypertension

Overview

Thalidomide was widely used in the late 1950s and early 1960s for the treatment of nausea in pregnancy, but was soon withdrawn due to its profound teratogenic effects. Almost four decades passed before studies demonstrated that thalidomide is useful for the treatment of leprosy and multiple myeloma. However, while thalidomide is effective, it is associated with dose-limiting toxicities including somnolence, constipation, neuropathy and increased incidence of venous thromboembolism (VTE), especially in combination with dexamethasone. Thus, thalidomide derivatives were developed, namely lenalidomide and pomalidomide. Currently, thalidomide is indicated for both multiple myeloma and erythema nodosum leprosum (ENL), whereas lenalidomide and pomalidomide are only indicated for multiple myeloma.

Background of Safety Issues

Cases of hepatitis B reactivation have been reported following treatment with thalidomide, lenalidomide and pomalidomide in patients who had previous history of hepatitis B virus (HBV) infection. Some cases of HBV reactivation progressed to acute hepatic failure and resulted in death.

Besides that, reactivation of varicella-zoster virus resulting in some cases of disseminated herpes zoster have been reported for both thalidomide and lenalidomide. There have also been post-marketing reports of herpes zoster with pomalidomide use.

In addition, thalidomide treatment has been linked to reports of pulmonary hypertension, in some cases fatal.

In agreement with regulatory agencies including the United Kingdom Medicines and Healthcare products Regulatory Agency (UK MHRA) and French National Agency for Medicines and Health Products Safety (ANSM), Dear Healthcare Professional Communication (DHPC) letters have been issued by the product registration holders for thalidomide, lenalidomide and pomalidomide to inform healthcare professionals of these safety risks.

Local Scenario

At present, one (1) product containing thalidomide (Domide®), eight (8) products containing lenalidomide (Revlimid®) and four (4) products containing pomalidomide (Pomalyst®) are registered in Malaysia.

Since year 2006 to December 2016, NPRA has received 105 ADR reports associated with these products (thalidomide: 20 reports with 47 adverse events; lenalidomide: 84 reports with 136 adverse events; pomalidomide: 1 report with 1 adverse event). The most reported adverse events were pneumonia, infection, bone pain, anaemia, decreased appetite, rash and pruritus. At the time of publication, there were no reports related to hepatitis B virus reactivation, herpes zoster and pulmonary hypertension received by the NPRA.

In Malaysia, the product registration holders, in agreement with NPRA, have issued DHPC letters with information on these safety issues. The local package inserts of Domide®, Revlimid® and Pomalyst® will be updated with the new information related to these safety issues.

Advice for Healthcare Professionals

- Hepatitis B virus status should be established before initiating treatment with thalidomide, lenalidomide and pomalidomide.
- A physician with expertise in the treatment of hepatitis B should be consulted for patients who test positive for HBV infection.
- Previously infected patients should be closely monitored for signs and symptoms of viral reactivation, including active HBV infection, throughout therapy.
- Patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease prior to initiating and during thalidomide therapy.
- Please **report** all adverse events suspected to be related to the use of these products to the NPRA.