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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 (ADRs) reported, and stimulate additional adverse drug reaction reporting.

This is a bimonthly publication by the National Pharmaceutical Control Bureau (NPCB), Malaysia.

TO REPORT AN ADVERSE DRUG REACTION

Online

1. Visit http://bpfk.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@bpfk.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 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:

Epoeitin-associated PRCA: Current Scenario in Malaysia

Epoeitin-associated PRCA: Current Scenario in Malaysia

*This safety issue was previously featured in **Reaksi Drug Safety News March 2014** edition. The aim of this article is to provide updates on the current scenario in Malaysia and the impact of risk minimisation actions implemented since 2014.*

Introduction

Pure Red Cell Aplasia (PRCA) is a progressive, severe anaemia with sudden onset, characterised by an almost complete absence of red cell precursors from an otherwise normal bone marrow and very low reticulocyte count (< 10,000/mm^3), while all other cell lines are present and seem normal.

PRCA cases are often idiopathic, but may also be caused by underlying conditions (e.g. thymoma, myelodysplastic syndromes, leukemia, and viral infection such as parvovirus B19), or treatment with certain drugs (e.g. phenytoin, azathioprine, isoniazid).

Epoetin-associated PRCA is a rare adverse drug reaction (ADR) resulting from cross-reaction between anti-erythropoietin antibodies (AEAb) and endogenous erythropoietin. Erythropoietin stimulating agents (ESAs) have been known to cause PRCA since the early 1990's. Immunogenicity of ESAs can be influenced by many factors, such as **differences in protein structure** and in **glycosylation of the ESAs**, **storage conditions**, **patient associated variables**, as well as the **route of administration**, **frequency and duration of treatment**. PRCA that is caused by the administration of ESAs can be identified through AEAb testing.

Background

In 1998, an increase in the global incidence of ESA-related PRCA was observed with the subcutaneous use of Eprex® (epoetin alfa) in patients with chronic kidney disease (CKD). Investigations revealed the increased immunogenicity could be due to change of stabiliser, leaching from uncoated rubber stoppers, and breaks in the cold chain process. The prescribing information was revised to state that Eprex® should only be administered through the intravenous (IV) route in chronic renal failure patients and storage conditions should be strictly maintained.

Since 2013, the NPCB has been conducting targeted monitoring of ADR reports on suspected ESA-related PRCA. Every report received is reviewed and NPCB communicates with the respective product registration holder (PRH) to obtain information on bone marrow aspiration (BMA) and AEAb test results.

The risk minimisation measures proposed since 2014 include antibody testing by the PRH for all suspected PRCA cases, strict adherence to storage and handling procedures, recommended route of administration, and advice on patient monitoring.

Product Information

ESAs are generally approved for the treatment of anaemia in patients with chronic renal failure, concomitant chemotherapy, Human Immunodeficiency Virus (HIV) patients treated with zidovudine, and for erythropoiesis stimulation in certain procedures such as autologous blood donation or during surgery. In Malaysia, there are currently six (6) brands of ESAs (Table 1) approved by the Drug Control Authority (DCA), with a total of 33 products of various strengths.

Table 1: Erythropoietin Stimulating Agents registered in Malaysia

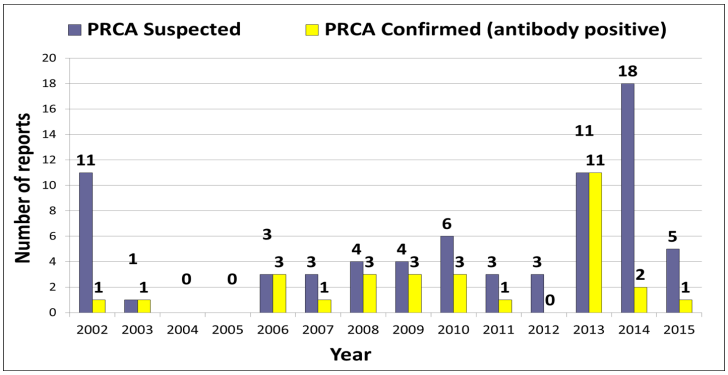
Product Name	Active ingredient	Year of Registration with DCA	Product Registration Holder
Eprex®	Epoetin alfa	1996	Johnson & Johnson (M) Sdn. Bhd.
Recormon®	Epoetin beta	2002	Roche (M) Sdn. Bhd.
Mircera®	Pegylated epoetin beta	2008	Roche (M) Sdn. Bhd.
Binocrit®	Epoetin alfa **(biosimilar to Eprex®)**	2011	Novartis (M) Sdn. Bhd.
NESP®	Darbepoetin alfa	2011	Smart Medicine Sdn. Bhd.
EPO STADA®	Epoetin zeta **(biosimilar to Eprex®)**	2015	Inno Bio Ventures Sdn. Bhd.

Local ADR Reports

Since 2002, the National ADR Monitoring Centre has received **210 reports** with **221 adverse events** related to ESAs.

The majority of the reports involved Blood and Lymphatic system disorders (135 reports, 64.3%), such as decreased haemoglobin, PRCA, and anaemia. There were 78 reports (37%) associated with suspected PRCA, all related to the use of Eprex® or Recormon®. It was found that 30 cases (22%) tested positive for AEAb, and of these, almost all (27 cases; 90%) involved the subcutaneous (SC) route of administration.

Graph 1: Malaysian ESA-related PRCA reports (2002-2015)



The sudden increase in number of reports for **2013** was investigated, but no specific cause was identified.

In 2014, NPCB received 18 ESA-related PRCA reports, of which **two (2)** had performed AEAb testing and received **positive** confirmation of PRCA. One case involved IV administration, and one involved the SC route. Four (4) reports tested negative for AEAb, while PRCA was ruled out in another two (2) cases as the low haemoglobin was confirmed to be due to gastrointestinal bleeding.

The remaining 10 reports in 2014 did not have a confirmation of PRCA as the AEAb testing was not carried out due to various complications, such as patients' illnesses, insufficient facilities to collect and store specimens, and lack of information on BMA test and retics results.

In 2015, a total of five (5) ESA-related PRCA reports were received, with **one (1) PRCA confirmation** through AEAb testing. Two reports tested negative for AEAb, while the remaining two (2) reports are still under follow-up.

This 72% decrease in the number of reports received from 2014 to 2015 may partly be a result of the risk minimisation steps implemented. However, under-reporting of ADR cases cannot be ruled out.

Issues of Concern

- More than 90% of the ADR reports were submitted by the PRHs, and many of these **reports lacked vital information** on the patient, product, as well as brand-switching. It is hoped that healthcare professionals in hospitals and haemodialysis centres will play an active role in reporting cases of suspected PRCA to the NPCB.
- **Storage procedures** of ESAs may not be strictly adhered to from hospital to end-users, including the home transportation system.

Conclusion

NPCB will continue to monitor this safety issue. All healthcare professionals are reminded to adhere to the **guidelines** issued by the Pharmaceutical Services Division recently (***Garis Panduan Pemantauan Keselamatan Produk ESAs dan Pelaporan Kesan Advers PRCA***) available at http://www.pharmacy.gov.my/v2/ms/dokumen/garis-panduan-pemantauan-keselamatan-produk-erythropoietin-stimulating-agents-esas-pelaporan-kesan.html

Advice for Healthcare Professionals

- Treatment with ESAs must be **initiated** under supervision of **experienced physicians** for the approved indications only.
- Storage conditions listed in the product package inserts must be strictly adhered to. ESAs must always be **stored between 2-8°C**.
- Patients on regular haemodialysis with **IV access available**: use IV administration of ESAs
- **Please report** all ADRs suspected to be related to ESA use to the National ADR Monitoring Centre, NPCB.