



## 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.  
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46200 Petaling Jaya, Selangor.

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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.

### In This Issue:

1. **Ketamine: Risk of Severe Liver Damage with Repeated and/or Prolonged Use at High Doses**
2. **Recombinant Human Erythropoietins: Risk of Severe Cutaneous Adverse Reactions (SCARs)**



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



# Ketamine: Risk of Severe Liver Damage with Repeated and/or Prolonged Use at High Doses

## Overview

Ketamine is an NMDA-receptor antagonist used for general anaesthesia and sedation<sup>1</sup>. It has anaesthetic and analgesic properties, depending on the dose administered. Ketamine is used in subanaesthetic doses for control of acute and chronic pain, especially severe forms with evidence of central sensitisation not well-controlled with other agents. It is usually combined with an opioid for acute pain<sup>2</sup>.

## Background of the Safety Issue

The French National Agency for the Safety of Medicines and Health Products (ANSM) published a Dear Healthcare Professional Communication (DHPC) letter on the risk of severe liver damage during repeated and/or prolonged use of high-dose ketamine.

Ten (10) cases of serious liver damage (cholestatic cholangitis), including four (4) which led to liver transplantation, have been reported to the ANSM since 2014. These may be linked to repeated or prolonged use of ketamine (between 1-5 months of continuous use) and at high doses in the management of severe pain (exceeding 100mg/day continuous over several days) or severe burns (200-400mg/hour in 3-6hours)<sup>3</sup>.

Healthcare professionals in France were reminded to follow the recommended dosage for palliative care practice at 0.5mg/kg/day (continuous IV infusion) with increments of 0.25mg/kg/day<sup>4</sup>. Treatment should be initiated by a team specialised in the management of pain or palliative care with close observation and monitoring, including liver function monitoring<sup>3,4</sup>.

## Local Scenario

In Malaysia, currently, there are two (2) products containing ketamine that have been registered. Indications approved in Malaysia include:

- Sole anaesthetic for diagnostic and surgical procedures that do not require skeletal muscle relaxation.
- Induction of anaesthesia prior to the administration of other general anaesthetic agents.
- As a supplement to low potency agents, such as nitrous oxide.
- May be used in children as intense analgesic for management of minor surgical and diagnostic procedures or repeated procedures, e.g. changing burn dressing.

## Adverse Drug Reaction (ADR) Reports

The NPRA has received a total of 24 reports with 34 adverse events related to ketamine. The most reported adverse event was tonic-clonic convulsions (5, 14.7%), followed by maculo-papular rash (3, 8.8%) and urticaria (3, 8.8%). To date, no case of liver damage has been reported to the NPRA.

## Advice for Healthcare Professionals

- Please comply with the recommended dosing for ketamine especially with repeated and/or prolonged use.
- Monitor patient's liver function closely if repeated and/or prolonged high dose of ketamine is used.
- Please report all adverse events suspected to be related to the use of ketamine to the NPRA.

# Recombinant Human Erythropoietins: Risk of Severe Cutaneous Adverse Reactions (SCARs)

## Overview

The hormone erythropoietin is essential for the formation of red blood cells. Recombinant human erythropoietins are indicated for the treatment of anaemia in patients with certain conditions, such as chronic renal failure or non-myeloid cancer patients who develop anaemia after chemotherapy<sup>5,6</sup>. [For full details of approved indications, please refer to the product package inserts].

## Background of the Safety Issue

In the European Union (EU), post-marketing reports of severe cutaneous adverse reactions (SCARs), in particular SJS and TEN, led to this safety signal being identified and analysed by the European Medicine Agency's Pharmacovigilance Risk Assessment Committee (PRAC)<sup>6</sup>.

All cases (including data from the EudraVigilance database and data from the marketing authorisation holders) were analysed for all recombinant human erythropoietins. This analysis concluded that severe cutaneous reactions including SJS and TEN can be considered a **class risk** for all recombinant human erythropoietins. The more severe reactions were reported with long-acting recombinant human erythropoietins, including cases with positive dechallenge and positive rechallenge. These severe cutaneous reactions were found to occur very rarely<sup>7</sup>.

## Local Scenario

There are currently 15 products containing recombinant human erythropoietins (darbepoetin alfa, epoetin alfa, epoetin beta, epoetin zeta and methoxy polyethylene glycol-epoetin beta) registered with the Drug Control Authority (DCA). Following review of this safety issue, product registration holders will be required to update the

package inserts of recombinant human erythropoietins in Malaysia with safety information related to this risk of SCARs.

## Adverse Drug Reaction (ADR) Reports

Between year 2000 to May 2017, the NPRA has received 213 ADR reports with 289 adverse events suspected to be related to recombinant human erythropoietins. The most commonly reported adverse events include rash, itching and pure red cell aplasia. To date, the NPRA has received one (1) report of SCARs related to recombinant human erythropoietins, where a 37-year-old female patient developed TEN (confirmed by skin biopsy) after the first dose of subcutaneous epoetin beta 2000 IU. The patient was treated with intravenous immunoglobulin for four days and her condition had improved at the time of reporting.

## Advice for Healthcare Professionals

- SCARs, some life-threatening or fatal, including cases of SJS and TEN have been reported in patients treated with recombinant human erythropoietins.
- Patients should be monitored and advised on the signs and symptoms of severe skin reactions when starting treatment with a recombinant human erythropoietin product.
- Patients should be instructed to stop recombinant human erythropoietin treatment and contact their doctor immediately if they develop:
  - ◇ flu-like symptoms including fever, tiredness, muscle and joint pain, followed by a widespread rash with reddening and blistering of the skin and oral mucosa, eyes, nose, throat, or genital area.

## References

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4. Afssaps (June 2010). Recommendation for good practice – rebound pain in an advanced palliative situation in adults. [http://ansm.sante.fr/var/ansm\\_site/storage/original/application/0f8ed3dd2a116934a6fe38cf56367eb8.pdf](http://ansm.sante.fr/var/ansm_site/storage/original/application/0f8ed3dd2a116934a6fe38cf56367eb8.pdf)
5. Jeikmann, W (2011). Regulation of Erythropoietin Production. J Physiol 589(6): 1251–1258.
6. Pharmacovigilance Risk Assessment Committee (2017). Minutes of the meeting on 6-9 February 2017.
7. The Medicines and Healthcare products Regulatory Agency (2017). Direct Healthcare Professional Communication - Recombinant human erythropoietins: Risk of severe cutaneous adverse reactions.