JANUARY 2017, No. 33

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 print out the ADR form.
4. Scan and submit the completed form via email to fv@npra.gov.my.

Mail

1. Print out 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 (NPRA), 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:

Eylea® vs. Zaltrap® (aflibercept): Same Active Ingredient, Different Safety Profiles?

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

Eylea® vs. Zaltrap® (aflibercept): Same Active Ingredient, Different Safety Profiles?

Introduction

Aflibercept acts as a soluble decoy receptor that binds to vascular endothelial growth factor A (VEGF-A), VEGF-B and placental growth factor (PlGF), with higher affinity than the native receptors. By acting as a ligand trap, aflibercept prevents binding of endogenous ligands to their cognate receptors, thereby inhibiting neovascularisation and vascular permeability[1,2].

In Malaysia, there are currently two (2) registered products containing different strengths of aflibercept, namely Eylea® and Zaltrap®. Both products have an identical molecular structure of aflibercept, but are administered through different routes.

While the **most common adverse reactions** documented for Eylea® involved ocular disorders (including conjunctival haemorrhage, eye pain, increased intraocular pressure, and cataract), the commonly reported adverse effects for Zaltrap® involved systemic reactions such as leucopenia, diarrhoea, neutropenia, and proteinuria.

Healthcare professionals are reminded of the **potential risk of medication error** between Zaltrap® and Eylea® due to the different routes of administration. Eylea® undergoes a different purification process and contains different buffer solutions that are less irritating when injected intravitreally in the eye[3]. The cancer drug, **Zaltrap®**, is administered through intravenous infusion, and is **contraindicated for intravitreal use** due to its hyperosmotic properties.

Table 1: Comparison of Eylea® and Zaltrap®

	Eylea® 40mg/ml Solution for Injection	Zaltrap® 25mg/ml Concentrate for Solution for Infusion
Route of administration	Intravitreal injection	Intravenous infusion
Indication(s)	• Neovascular (wet) age-related macular degeneration (wet AMD) • Visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO) • Visual impairment due to diabetic macular edema (DME) • Myopic choroidal neo-vascularisation (myopic CNV)	In combination with irinotecan/5-fluorouracil/folinic acid (FOLFIRI) chemotherapy for metastatic colorectal cancer (MCRC) that is resistant to or has progressed after an oxaliplatin-containing regimen.

Latest Safety Issues

(i) Zaltrap®: Risk of Osteonecrosis of the Jaw

Background of safety issue

In March 2016, the United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA) distributed a Dear Healthcare Professional Letter to remind healthcare professionals about the possible risk of osteonecrosis of the jaw (ONJ) associated with Zaltrap® use. Osteonecrosis of the jaw (ONJ) consists of progressive bone destruction in the maxillofacial region. Medication-related ONJ has been known to occur with the use of drugs including bisphosphonates, denosumab, and antiangiogenic agents (bevacizumab, sunitinib and sorafenib).

There have been eight (8) post-marketing cases of ONJ in patients treated with Zaltrap® reported worldwide. These patients also had other known risk factors for ONJ, namely concomitant bisphosphonate therapy, invasive dental procedures, or infection.

The mechanism by which Zaltrap® may increase the risk of ONJ is not fully known. However, it is an antiangiogenic agent and might therefore interfere with, and decrease, new capillary growth during wound healing at sites of physical trauma such as after dental procedures. Overall, although there are many known risk factors for ONJ, there is sufficient evidence to suggest that Zaltrap® may independently increase or contribute to this risk[4]. *Note:* **ONJ has not been identified as a risk for Eylea®.**

Local scenario

Zaltrap® has been registered in Malaysia since year 2014 and to date, the NPRA has received five (5) ADR reports related to this product. The reported adverse events include impaired healing, skin hyperpigmentation, back ache and hypertensive crisis. No ONJ case report associated with Zaltrap® has been received to date[5].

In agreement with NPRA, the product registration holder of Zaltrap® has issued a Direct Healthcare Professional Communication (DHPC) letter on this matter. The local package insert of Zaltrap® will be updated with the new information related to this safety issue.

Advice for Healthcare Professionals

- Cases of osteonecrosis of the jaw (ONJ) have been reported in cancer patients who have been treated with aflibercept (Zaltrap®).
- Patients who have previously or concomitantly received an intravenous bisphosphonate may be at particular risk.
- Before starting treatment, consider whether a dental examination and any appropriate preventive dentistry are needed.
- Avoid invasive dental procedures, where possible, in patients being treated with Zaltrap® who have previously received, or are currently receiving, an intravenous bisphosphonate.
- During treatment, advise patients to: maintain good oral hygiene; receive routine dental check-ups; and to report any oral symptoms such as dental mobility, pain, or swelling.
- Please report suspected adverse drug reactions related to Zaltrap® to the NPRA.

(ii) Eylea®: Potential Risk of Systemic Toxicity

Background of safety issue

In May 2016, Health Canada published its review on the risk of systemic toxicity associated with Eylea®. The review was triggered by three (3) scientific studies which observed that following injection into the eye, Eylea® is removed from the bloodstream slower than alternative products, and this could possibly lead to systemic toxicity.

The review found that there was **not enough evidence to conclude that Eylea® is associated with a greater risk of systemic adverse effects**. The potential for experiencing some adverse effects in areas of the body other than the eye is already mentioned in the Canadian product package insert for Eylea®[6].

Local scenario

Since Eylea® was first registered in Malaysia in 2013, the NPRA has received **eight (8) ADR reports** related to Eylea®. The adverse events reported included local side effects such as increased intraocular pressure as well as systemic adverse events such as cerebrovascular accident, congestive cardiac failure, chest pain, and myocardial infarction[5].

Advice for Healthcare Professionals

- Healthcare professionals should consider the potential systemic and ocular risk-benefit balance of Eylea® before treatment is started.
- Closely monitor the patients for adverse effects that may occur in the immediate or subsequent periods after administration of the drugs, especially when they have underlying comorbidities and other risk factors.
- All healthcare professionals are encouraged to report suspected adverse drug reactions related to Eylea® to the NPRA.

References:

1. Eylea® Package Insert, Malaysia [version: June 2014].
2. Zaltrap® Package Insert, Malaysia [version: June 2014].
3. Trichonas G & Kaiser PK (2013). Aflibercept for the Treatment of Age-Related Macular Degeneration. Ophthalmol Ther 2(2): 89–98.
4. Medicines and Healthcare Products Regulatory Agency (2016). Drug Safety Update: Aflibercept (Zaltrap®): Minimising the Risk of Osteonecrosis of the Jaw.
5. The National Adverse Drug Reaction database, NPRA. [Accessed: December 2016]
6. Health Canada (2016). Summary Safety Review: EYLEA (aflibercept)- Assessing the Risk of Side Effects Outside the Eye (systemic side effects).