January 27, 2012

Guido RASI, Executive Director, EMA (guido.rasi@ema.europa.eu)

Dear Sir,

We have had reports from several European countries (the UK, Spain, France) that the label on eribulin (Halaven®), a new drug recently authorized via a centralized process by the European Medication Agency for metastatic or locally advanced breast cancer may lead to errors in dosing.

Authorization for this medication was based on results of global study in phase III EMBRACE (*Eisai Metastatic Breast Cancer Study Assessing Treatment of Physician's Choice Versus E7389*)[1], in which a dose of 1.4 mg/m^2 of eribulin mesylate was used (that is, the dose was expressed in terms of salt).

In the USA, this medication was registered in 2010 as a solution for injection. Strength was expressed on the label also in terms of eribulin mesylate. It was marketed in 2 mL vials which contained a 1 mg dose of eribulin mesylate.

In Europe, however, the dose for this medication is expressed in terms of eribulin base, following European guidelines with several discrepancies regarding some national translations. The label for the same vial as marketed in the US indicates: 0.44 mg/mL, 2 mL. Below that it states: "*Each 2 mL vial contains 0.88 mg of eribulin (in the form of mesylate)".* The way this label is written could lead one to believe that the quantity given is for eribulin mesylate.

In our opinion, there is a risk of dosing errors occurring when this medication is used because of confusion between "salt" and "base." If the professionals did not know about this divergence in the form of expressing the dose, and used the dose from the pivotal trial, as is frequently done, they might think that the dose of 1.4 mg/m2 corresponded to the amount indicated on the label. Besides, when the professionals who prepare the medication read the label on it, they could easily believe that the 0.88 mg was eribulin mesylate instead of eribulin base. As a result they would prepare a higher dose than they should.

The IMSN feels that the dosing indication for a medication should always be expressed in terms of base, and accordingly, the European guideline would be correct. The pity in this case is that this guideline is not in harmony with the guidelines in all other countries, which would avoid a large number of problems. Nevertheless, it also considers that the label authorized for use in Europe should be modified to contain the following text:

"Each 2 mL vial contains 0.88 mg of eribulin (**equivalent to 1 mg of eribulin mesylate**)."

In this way, there would be no ambiguities when health care professionals read the label.

The prevention of medication errors related to labeling and packaging is one of the fields of concentration of the IMSN. In this sense, when one of the medication error centers of the IMSN receives and analyzes reports arising from problems with labeling and packing of a new medicinal product, it shares that information with other centers so that they may work together to disseminate recommendations designed to reduce the risk of reoccurrence.

Thus, on behalf of the European members of the IMSN, I would appreciate it if you would investigate this matter and modify the Halaven label.

Thank you very much for your attention to this matter.

Sincerely,

Michael R. Cohen, RPh, MS, ScD (hon), FASHP
Chairperson, IMSN

[1] Cortés J, O´Shaughnessy J, Loesch D, Blum JL, Vahdat LT, Petrakova K, on behalf of the EMBRACE investigators. Eribulin monotherapy versus treatment of physician´s choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet. 2011; 377: 914-23.