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Severe liver toxicity associated with temozolomide (Temodal®)

Dear Healthcare Provider,

Merck Sharp & Dohme (MSD) in agreement with the European Medicines Agency (EMA) and the Irish Medicines Board (IMB) would like to inform you of the following:

Summary

- **Cases of hepatic injury, including fatal hepatic failure, have been reported in patients receiving temozolomide.**
- **Liver toxicity may occur several weeks or more after initiation of treatment or after temozolomide discontinuation.**
- **Liver function tests should be performed**
  - **prior to treatment initiation. If abnormal, the decision to initiate temozolomide treatment should carefully consider the benefits and risks for the individual patient;**
  - **after each treatment cycle.**
- **For patients on a 42 day treatment cycle, liver function tests should be repeated midway during this cycle;**
- **For patients with significant liver function abnormalities the benefits and risks of continuing treatment should be carefully considered.**

Background
Temodal® is indicated for the treatment of:

- Adult patients with newly-diagnosed glioblastoma multiforme concomitantly with radiotherapy (RT) and subsequently as monotherapy treatment.
- Malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy in children from the age of three years, adolescents and adult patients.

Safety concern

A review of serious, including fatal, cases of hepatotoxicity reported for temozolomide worldwide was recently performed. In total, 44 cases of hepatic injury, including fatal hepatic failure were identified in patients receiving temozolomide. These cases of fatal hepatic failure were reported with an approximate onset of 42 to 77 days following initiation of treatment with temozolomide. Non-fatal cases of liver toxicity were also reported with variable times to onset up to 112 days. The product label for temozolomide already documents hepatotoxicity, but does not include fatal hepatocellular injury and hepatic failure, or specific recommendations for monitoring liver function.

As a consequence of this review, the product information for temozolomide (Temodal®) is being updated across the EU in line with the summary recommendations above.

Call for reporting

Please report suspected adverse events with the use of temozolomide in accordance with your national reporting system. Healthcare professionals are asked to report any suspected adverse reactions via Pharmacovigilance Section, Irish Medicines Board, Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517; Website: www.imb.ie; e-mail: imbpharmacovigilance@imb.ie

Company contact point

If you have any questions or require additional information regarding the use of temozolomide, please call MSD on 01 2998700.

Yours sincerely,

Dr. Colm Galligan MB MSc MBA MFPM

Medical Director

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