

Wyeth Pharmaceuticals

Huntercombe Lane South
Taplow, Maidenhead
Berkshire, SL6 0PH
Tel: +44 (0)1628 604377
Fax: +44 (0)1628 666368

{Date}

{name, address}

IMPORTANT SAFETY INFORMATION**Direct Healthcare Professional Communication on the timing of and monitoring for hypersensitivity/infusion reactions associated with administration of Torisel® (temsirolimus) 25 mg/ml concentrate and diluent for solution for infusion**

Dear Sir/Madam

Summary

Hypersensitivity/infusion reactions (including some life-threatening and rare fatal reactions) have been associated with the administration of Torisel (temsirolimus). These include but are not limited to flushing, chest pain, dyspnoea, hypotension, apnoea, loss of consciousness, and anaphylaxis. The majority of these hypersensitivity/infusion reactions occurred with the first infusion, often within the first few minutes of the start of the infusion, although reactions with subsequent infusions have been reported.

This information has been approved for distribution by the European Medicines Agency (EMA) and the Medicines and Healthcare products Regulatory Agency (MHRA).

Advice for healthcare professionals:

- Carefully refer to the Summary of Product Characteristics (SPC) instructions for premedication, dilution and administration of the product
- Patients should be given intravenous diphenhydramine 25 – 50 mg (or similar antihistamine) approximately 30 minutes before the start of each dose of Torisel (temsirolimus)
- Patients should be closely monitored early during the infusion
- Appropriate supportive care should be readily available
- Torisel (temsirolimus) infusion should be interrupted in all patients with severe infusion reactions, and appropriate medical care administered

Doc ID: 50892
John Wyeth & Brother Limited
Registered in England No. 135937
Registered Office: Huntercombe Lane South
Taplow, Maidenhead, Berkshire, SL6 0PH



Incorporating: Wyeth Vaccines
Wyeth Biotechnology

- A benefit-risk assessment should be made prior to continuation of Torisel (temsirolimus) therapy in patients with severe or life-threatening reactions

The product information (SPC, see Annex) has been updated in line with this advice (see sections 4.4 and 4.8) and includes new advice on precautions advised when reinitiating infusion. A European Commission decision implementing this change is pending.

Further information

Torisel (temsirolimus) is indicated for first-line treatment of patients with advanced renal cell carcinoma who have at least three of six prognostic risk factors (see section 5.1 of the SPC). In the pivotal clinical trial¹ in renal cell cancer, 9% (18/208) of patients treated with Torisel (temsirolimus) 25 mg/ml concentrate and diluent for solution for infusion, experienced allergic reactions of any severity. In all clinical trials to date, about 1% of patients experienced serious hypersensitivity/infusion reactions, sometimes despite any premedication. We have received reports of hypersensitivity/infusion reactions in the post-marketing setting that are consistent with the clinical trial experience. One fatal hypersensitivity reaction has been reported to date in the post-marketing setting.

The majority of these hypersensitivity/infusion reactions occurred with the first infusion, often within the first few minutes of the start of the infusion, although reactions with subsequent infusions have been reported. Cases involved patients who received premedication, as described in the SPC. Therefore patients should be closely monitored early during the infusion and appropriate supportive care should be available. Torisel (temsirolimus) infusion should be interrupted in all patients with severe infusion reactions and appropriate medical care administered. A benefit-risk assessment should be done prior to the continuation of Torisel (temsirolimus) therapy in patients with severe or life-threatening reactions.

In agreement with the Committee for Medicinal Products for Human Use (CHMP), the Marketing Authorisation Holder will continue to monitor reports of hypersensitivity/infusion reactions in clinical trials and in the post-marketing setting.

On the basis of these findings, revisions to the SPC have been made (see Annex).

¹ Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, Interferon Alfa, or Both for Advanced Renal-Cell Carcinoma. N Engl J Med 2007; 356:2271-81.

Call for reporting

Physicians and other healthcare professionals are requested to be alert to adverse events following the infusion of Torisel (temsirolimus) and to report them to the MHRA by use of a Yellow card, which is available from MHRA, CHM Freepost, London SW8 5BR, or electronically via www.yellowcard.gov.uk. Suspected adverse reactions can also be reported to Wyeth Pharmacovigilance UK on 0845 367 0115, by fax on 0845 367 0600 or via e-mail to WATWADR@wyeth.com

Communication information

For more information please contact Wyeth UK Medical Information Department on 0845 367 0098 or by email to ukmedinfo@wyeth.com.

Yours faithfully

Dr Vignesh Rajah, MBBS, DCH, MRCP(UK), MBA
Medical Director
Wyeth Pharmaceuticals, UK
*Local representative for the Marketing Authorisation Holder,
Wyeth Europa Ltd*

Annex

Changes to SPC, and full SPC

Section 4.4 Special warnings and precautions for use

Addition of **bold** text:

Hypersensitivity/infusion reactions

Hypersensitivity/infusion reactions including anaphylactic reactions (including some life-threatening and rare fatal reactions), including and not limited to flushing, chest pain, dyspnoea, hypotension, apnoea, loss of consciousness, hypersensitivity and anaphylaxis, have been associated with the administration of temsirolimus (see section 4.8). These reactions can occur very early in the first infusion, but may also occur with subsequent infusions. Patients should be monitored early during the infusion and appropriate supportive care should be available. Temsirolimus infusion should be interrupted in all patients with severe infusion reactions and appropriate medical therapy administered. A benefit-risk assessment should be done prior to the continuation of temsirolimus therapy in patients with severe or life-threatening reactions.

*If a patient develops a hypersensitivity reaction during the TORISEL infusion, despite the premedication, the infusion must be stopped and the patient observed for at least 30 to 60 minutes (depending on the severity of the reaction). At the discretion of the physician, treatment may be resumed ~~with~~ **after** the administration of an H₁-receptor antagonist (such as diphenhydramine **or similar antihistamine**), ~~if not previously administered,~~ and/or a H₂-receptor antagonist (intravenous famotidine 20 mg or intravenous ranitidine 50 mg) approximately 30 minutes before restarting the TORISEL infusion. **Administration of corticosteroids may be considered; however, the efficacy of corticosteroid treatment in this setting has not been established.** The infusion may then be resumed at a slower rate (up to 60 minutes) **and should be completed within six hours from the time that TORISEL is first added to sodium chloride 9 mg/ml (0.9%) solution for injection.***

Because it is recommended that an H₁ antihistamine be administered to patients before the start of the intravenous temsirolimus infusion, temsirolimus should be used with caution in patients with known hypersensitivity to the antihistamine or in patients who cannot receive the antihistamine for other medical reasons.

Section 4.8 Undesirable effects

Addition of **bold** text:

*The most serious reactions observed with TORISEL are hypersensitivity/**infusion** reactions (**including some life-threatening and rare fatal reactions**), hyperglycaemia/glucose intolerance, infections, interstitial lung disease, hyperlipaemia, intracerebral bleeding, renal failure, bowel perforation, and wound healing complication.*