



Celgene Limited
1 Longwalk Rd
Stockley Park
Uxbridge
UB11 1DB
United Kingdom
Tel: +44(0)208 831 8300
Fax: +44(0)208 831 8301
www.celgene.com

06 May 2011

Direct Healthcare Professional Communication on the association between Thalidomide Celgene™ (thalidomide) and thromboembolism

Dear Healthcare Professional,

Celgene would like to inform you about important new safety information on Thalidomide Celgene (thalidomide).

Summary:

- Patients treated with thalidomide have an increased risk of arterial thromboembolism, including myocardial infarction and cerebrovascular events, in addition to the established risk of venous thromboembolism.
- Most patients presenting with venous or arterial thromboembolic events in association with thalidomide treatment have had identifiable risk factors for thromboembolism.
- Action should be taken to minimise all modifiable risk factors for thromboembolic events (e.g. smoking, hypertension and hyperlipidaemia).
- Healthcare professionals are advised to consider venous and arterial thrombotic risk and the need for thromboprophylaxis in the evaluation of patients suitable for treatment with thalidomide.

Healthcare professionals should also note the following regarding thromboembolism:

- The risk appears to be greatest during the first 5 months of therapy
- Thromboprophylaxis should be administered for at least the first 5 months of treatment, especially in patients with thrombotic risk factors in addition to multiple myeloma. Antithrombotic prophylactic measures should be prescribed after a careful assessment of the individual patient's underlying risk factors.
- Previous history of thromboembolic events and concomitant administration of erythropoietic agents or other agents such as hormone replacement therapy may increase the risk of thromboembolic events. These agents should be used with caution in multiple myeloma patients receiving thalidomide. A haemoglobin concentration above 12g/dL (7.5 mmol/L) in particular should lead to discontinuation of erythropoietic agents.

The content of this letter and the updates to the Thalidomide Celgene Product Information have been endorsed by the Committee for Medicinal products for Human Use (CHMP) and the Medicines and Healthcare Products Regulatory Agency (MHRA).

Additional information about arterial thromboembolic events

Thalidomide Celgene 50 mg hard capsules have been granted a European Marketing Authorisation for use in combination with melphalan and prednisone as first line treatment of patients with untreated multiple myeloma, aged ≥ 65 years, or those ineligible for high dose chemotherapy.

A recent review of the post marketing data showed that approximately one third of all thromboembolic reactions reported in association with thalidomide were arterial, most of which were myocardial infarction and cerebrovascular events (54.2% and 19.8%, respectively). The mechanisms involved in the physiopathology of arterial thromboses in patients treated with thalidomide are unknown.

Sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) of the Thalidomide Celgene Summary of Product Characteristics have been updated to reflect the newly identified risk of arterial thromboembolic reactions, including myocardial infarction and cerebral vascular events, and to advise on minimisation of modifiable risk factors for thrombosis.

Healthcare professionals should be aware that, due to the powerful human teratogenic effects of thalidomide and its important clinical risks, a Risk Management Plan has been implemented for thalidomide in agreement with the European Medicines Agency (EMA) and MHRA. This plan includes a **Pregnancy Prevention Programme** to avoid thalidomide exposure during pregnancy, the monitoring of other clinically important risks associated with thalidomide such as peripheral neuropathy and thromboembolism, and the provision of educational materials.

Call for Reporting

Suspected adverse reactions (and cases of suspected or confirmed pregnancy and foetal exposure) should be reported. Please report suspected adverse reactions with any medicine or vaccine to the MHRA through the Yellow Card Scheme online at www.yellowcard.co.uk.

Alternatively, prepaid Yellow Cards for reporting are available:

- upon request be mail: "FREEPOST YELLOW CARD"
- at the back of the British National Formulary (BNF)
- by telephoning the Commission on Human Medicines (CHM) free phone line: 0800-731-6789
- or by electronic download through the MHRA website (<http://yellowcard.mhra.gov.uk/downloads>)

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset and treatment dates.

In addition, adverse event report forms and pregnancy reporting forms are included in the Healthcare Professionals Information Pack and can also be found on www.celgene.co.uk. Completed forms should be forwarded to Celgene Drug Safety using the contact details below:

Celgene Limited
1 Longwalk Road
Stockley Park
Uxbridge
Middlesex
UB11 1DB
United Kingdom

Tel: 0808 238 9908

Fax: 08448 010 468

Email: drugsafetyuk@celgene.com

For further information please contact:

Celgene Limited
1 Longwalk Road
Stockley Park
Uxbridge
Middlesex
UB11 1DB
United Kingdom

Tel: 0844 801 0045

Fax: 0844 801 0046

Email: medinfo.uk.ire@celgene.com

Website: www.celgene.co.uk

Yours sincerely,



Dr Michael Thompson
Medical Director
Celgene Limited

Annex: Summary of Product Characteristics of Thalidomide Celgene (thalidomide) with changes highlighted