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Tuesday, June 19, 2007

Dear Healthcare Professional,

We wish to inform you about important aspects in the clinical use of Revlimid® ▼ (lenalidomide) which has now received market authorisation for the treatment, in combination with dexamethasone, of multiple myeloma patients who have received at least one previous therapy.

### **Pregnancy Prevention Programme**

Lenalidomide is structurally related to thalidomide, which is a known human teratogenic active substance. If lenalidomide is taken in pregnancy, a teratogenic effect cannot currently be ruled out. Lenalidomide is therefore contraindicated for use in pregnancy. It is also contraindicated in women of childbearing potential unless all the conditions of the lenalidomide Pregnancy Prevention Programme are met.

Multiple Myeloma is a disease of a predominantly elderly population. However, women of childbearing potential could be part of the patient population. We wish to draw your attention to the conditions of the Pregnancy Prevention Programme that must be complied with in this small specific patient population.

### **Lenalidomide Prescription Authorisation and Pharmacy Registration**

Celgene Ltd has agreed with the Medicines and Healthcare Products Regulatory Agency (MHRA) to implement a series of measures to minimise the risk of adverse events to patients and in particular the risk of foetal exposure.

Lenalidomide should only be prescribed by consultants or specialist registrars with appropriate experience in managing haematological malignancy. Specialists wishing to prescribe must confirm their understanding of the Pregnancy Prevention Programme and the Summary of Product Characteristics (SPC) for Revlimid® by signing a Lenalidomide Prescription Authorisation form which must accompany the prescription or be part of it.

In order to be able to dispense lenalidomide, pharmacies must first register with Celgene Ltd by agreeing to comply with the obligations of the Pregnancy Prevention Programme and to implement the prescription authorisation form.

Celgene Ltd will not authorise distribution of lenalidomide to pharmacies not registered with the Company.

### **Non-promotional Educational Materials**

In addition to the SmPC for healthcare professionals and Patient Information Leaflet (PIL) for patients, the Company has also made available a Healthcare Professional Information Pack for lenalidomide. The pack contains key information about minimising the risk of adverse events from lenalidomide and reducing the risk of foetal exposure through the Pregnancy Prevention Programme. In addition it contains several memory aids and tools including patient brochures to assist in managing your patients. These non-promotional packs are available for yourself or your staff from any Celgene representative or from the Company Medical Information Dept at the address below.

### **Women of childbearing potential**

All women of childbearing potential must:

- Receive counselling regarding the potential teratogenicity of lenalidomide and the need to avoid pregnancy
- Use one effective method of contraception for 4 weeks before therapy, during therapy, during dose interruptions and 4 weeks after therapy has finished, unless the woman commits to absolute and continued abstinence confirmed on a monthly basis.
- Have a medically supervised negative pregnancy test once she has been established on contraception for 4 weeks, at 4 weekly intervals during therapy and 4 weeks after the end of therapy.

The following can be considered to be examples of effective methods of contraception:

- Implant
- Levonorgestrel-releasing intrauterine system (IUS)
- Medroxyprogesterone acetate depot
- Tubal sterilisation
- Sexual intercourse with a vasectomised male partner only; vasectomy must be confirmed by two negative semen analyses
- Ovulatory inhibitory progesterone-only pills (i.e., desogestrel).

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking lenalidomide and dexamethasone, combined oral contraceptive pills are not recommended.

Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of lenalidomide should occur within a maximum of 7 days of the prescription.

Section 4.4 of the enclosed SPC provides further guidance on the definition of a woman of childbearing potential, counselling, effective contraception and pregnancy testing.

**In the event of exposure to lenalidomide during pregnancy**

If pregnancy does occur in your patient whilst she is receiving lenalidomide, treatment must be stopped and the patient be referred to a physician specialised or experienced in teratology for evaluation and advice. You are also requested to notify Celgene Ltd of all such occurrences and notify the MHRA using the yellow card scheme.

Celgene Ltd should be notified using the Pregnancy Capture Form located in the Healthcare Professional Information Pack or available from the Company's drug safety department.

**Men**

It is not currently known if lenalidomide is present in semen. Therefore all male patients should use condoms throughout treatment duration, during dose interruption and for 1 week after cessation of treatment if their partner is of childbearing potential and has no contraception.

**All patients**

Patients should be instructed never to give lenalidomide to another person and all unused capsules should be returned to the pharmacist.

Patients should not donate blood or semen during therapy or for 1 week following the discontinuation of lenalidomide.

**Myelosuppression**

The major dose-limiting toxicities of lenalidomide are neutropenia and thrombocytopenia.

A complete blood count, including white blood count monitoring with differential count, platelet count, haemoglobin and haematocrit should be performed at baseline and every week for the first 8 weeks of treatment and then monthly thereafter.

In the pivotal Phase III studies, grade 4 neutropenia occurred in 5.1% of patients in the lenalidomide/dexamethasone arm compared to 0.6 % in the placebo/dexamethasone arm.

Grade 4 febrile neutropenia episodes were however observed infrequently (0.6% in the lenalidomide/dexamethasone arm compared to 0.0% in the placebo/dexamethasone arm).

Grade 3 and Grade 4 thrombocytopenia occurred in 9.9% and 1.4% respectively in the lenalidomide/dexamethasone treated patients compared to 2.3% and 0.9% in placebo/dexamethasone patients.

A dose reduction may be required.

In the case of neutropenia, the physician should consider the use of growth factors in patient management.

Co-administration of lenalidomide with other myelosuppressive agents should be undertaken with caution.

Guidance on dose reduction is provided in Section 4.2 of the attached SPC.

### **Venous thromboembolism**

The combination of lenalidomide and dexamethasone is associated with an increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients with multiple myeloma.

Concomitant administration of erythropoietic agents or previous history of DVT may also increase the thrombotic risk in these patients.

Prophylactic antithrombotic medications are recommended especially in patients with additional thrombotic risk factors. The decision to take antithrombotic prophylactic measures should be made after careful assessment of an individual patient's underlying risk factors.

Section 4.4 of the enclosed SPC provides further information.

### **Initial dosing in patients with renal failure**

Lenalidomide is eliminated predominantly by renal excretion.

Initial starting doses should be reduced in patients with creatinine clearance below 50 ml/min.

Guidance on initial dosing in patients with renal failure is provided in Section 4.2 of the enclosed SPC.

### **Hypothyroidism**

Cases of hypothyroidism have been reported and monitoring of thyroid function should be considered.

### **Peripheral neuropathy**

Lenalidomide is structurally related to thalidomide, which is known to induce severe peripheral neuropathy. At this time, the neurotoxic potential of lenalidomide associated with long term use cannot be ruled out.

**For further information please contact:**

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The content of this communication has been approved by the Committee for Medicinal Products for Human Use (CHMP) and the Medicines and Healthcare products Regulatory Agency (MHRA).

Yours faithfully,



**Dr Nick Broughton  
Medical Director  
Celgene UK and Ireland**

**Date: 19<sup>th</sup> June 2007**